NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Premeeting briefing: Atezolizumab for treating locally advanced or metastatic urothelial carcinoma – STA

This slide set is the premeeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the committee meeting.

Metastatic urothelial carcinoma

Disease background

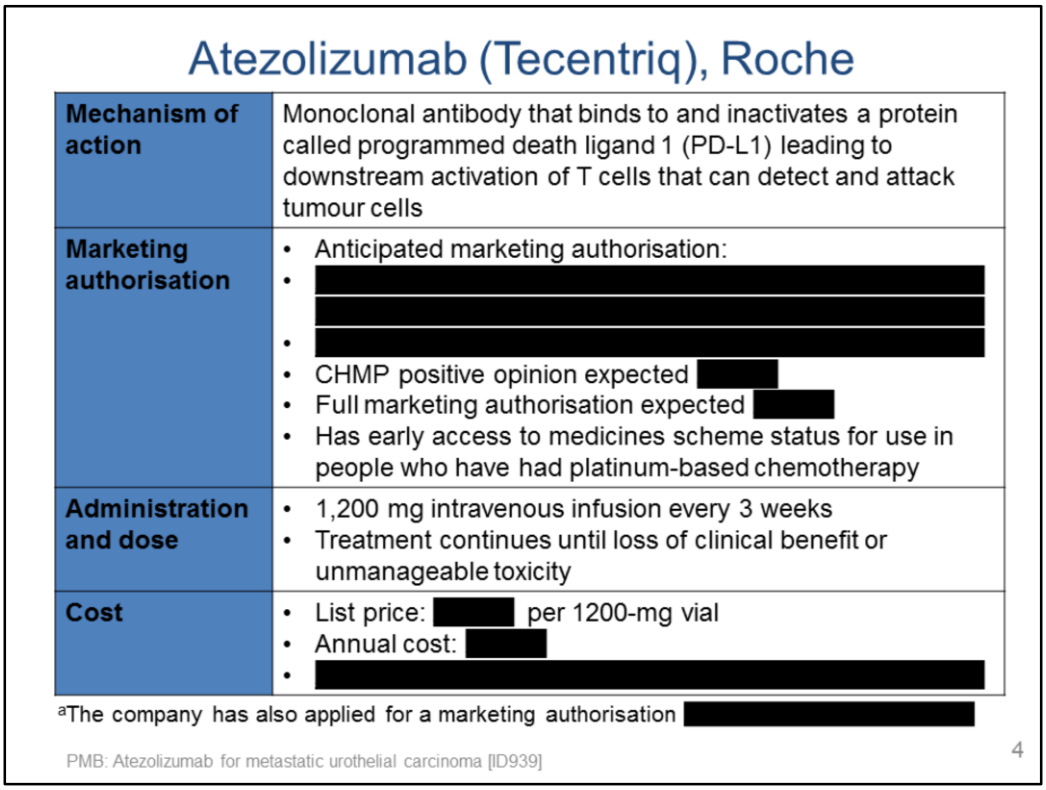
- There are around 10,100 new cases of bladder cancer in the UK each year, resulting in 5,400 deaths
- 90% of bladder cancers are urothelial carcinomas
  - remainder are squamous cell bladder cancers (5%) and adenocarcinomas of bladder (1–2%)
- 90–95% of urothelial carcinomas develop in bladder
  - tumours can also originate in renal pelvis, urethra or ureter as these are also lined by urothelial cells
- 55% of new cases occur in people 75+, ~75% in men
- 5-year survival rate for metastatic disease ~6%

Source ERG report pages 19, 21, company submission page 40-42, 46

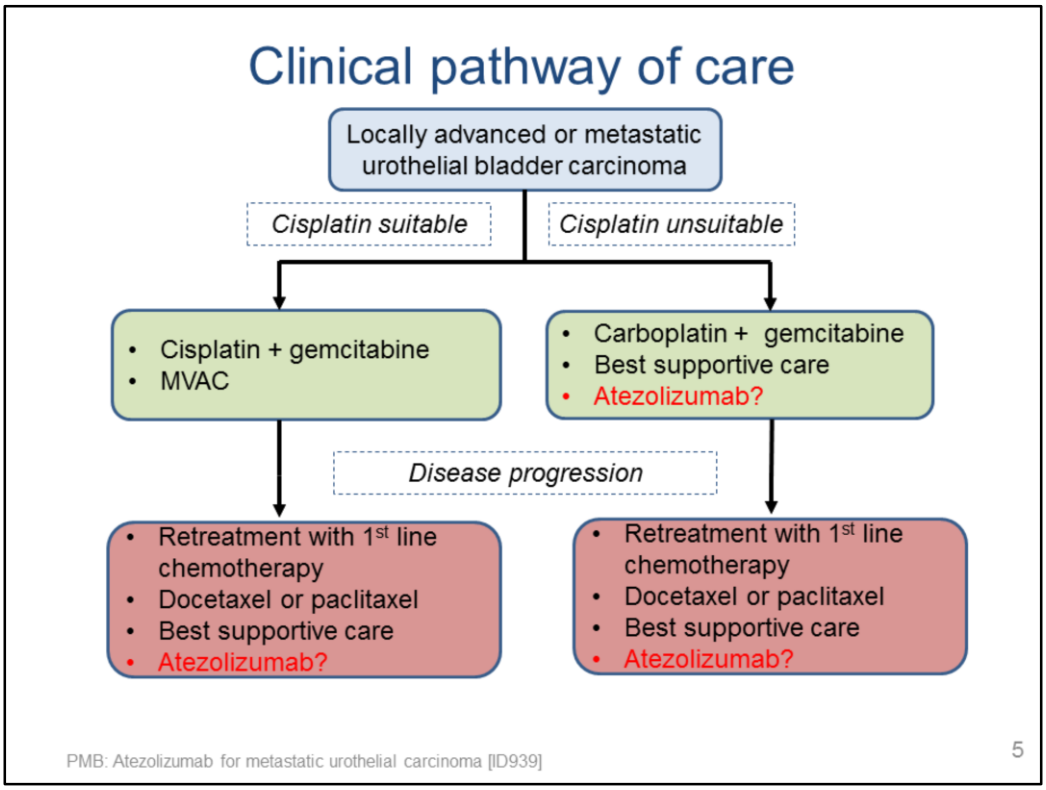
Impact on patients and carers

- Symptoms include: haematuria (blood in urine), pain at site of primary tumour or metastatic disease, increased frequency, urgency and pain associated with urination
- Awareness is low as it is often not discussed
- Older age of diagnosis means many people have co-morbidities which can affect treatment decisions
- Cisplatin is unsuitable for some people as it can be very damaging for the kidneys, so there is an urgent need for alternative therapies
- Response rates to current treatments and quality of life are poor
- Prolonging life, improved quality of life and complete response are important outcomes for people with the disease

Source: company submission section 3.2 and 3.3



EAMS indication is "Treatment of adult patients with locally advanced or metastatic urothelial carcinoma after disease progression following one prior platinum-containing chemotherapy regimen regardless of its setting (neoadjuvant, adjuvant, or metastatic)"



MVAC is high dose methotrexate, vinblastine, doxorubicin and cisplatin plus granulocyte-colony stimulating factor

Decision Problem - **population**

NICE scope	Company submission	Company rationale
Adults with locally advanced or metastatic urothelial carcinoma: • Whose disease has progressed after prior chemotherapy • For whom cisplatin-based chemotherapy is unsuitable	• Populations based on IMvigor 210 trial: – 1st line, cisplatin-based chemotherapy is unsuitable – 2nd line, disease progression after platinum-based chemotherapy • 2nd line population includes people for whom cisplatin is unsuitable and who have had platinum-based chemotherapy; they are separated in scope	• Treatment patterns and response rates for people having 2nd line therapy do not differ based on suitability of cisplatin • Comparators are the same

Decision Problem - **comparators**

NICE scope	Company rationale	ERG comment
1. Cisplatin-based chemotherapy unsuitable: • Gemcitabine + carboplatin • ~~Best supportive care~~	• People having BSC 1st line must be unable/unwilling to have any active therapy including atezolizumab • No data; no comparison possible	• Atezolizumab likely to have better safety profile than chemotherapy and may be option for some people unable/unwilling to have chemotherapy
2. Disease progressed after platinum-based chemo; 3. Cisplatin-based chemotherapy unsuitable, disease progressed after platinum-based therapy: • ~~Retreatment with 1st line platinum-based therapy~~ • Docetaxel, paclitaxel • Best supportive care	• Retreatment with 1st line therapy is an option for a small number of people and not standard care in England • No data; no comparison possible	• Reasonable approach given limited evidence base
~~Red~~ = in scope but not in company's submission		

Trial evidence – IMvigor 210, single-arm trial

	IMvigor 210
Description	• Multicentre (3 UK), open-label, single-arm, phase II • Cohort 1: previously untreated, unsuitable for cisplatin-based chemotherapy (n=119) • Cohort 2: disease progression after platinum-based chemotherapy (n=310)
Eligibility criteria	• People with locally advanced or metastatic urothelial carcinoma Cohort 1: • ECOG≤2 • No prior chemotherapy, unsuitable for cisplatin Cohort 2: • ECOG≤1 • Disease progression following treatment with at least 1 platinum containing regimen (≥2 cycles)
Outcomes	1º: Independent review-facility assessed objective response rate (ORR), according to RECIST criteria 2º: Overall survival, progression-free survival, duration of response

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Note:

Cohort 1 included 5 UK patients and cohort 2 had 17

Unsuitability for for cisplatin-based chemotherapy defined as:

- Impaired renal function (30<EGFR<60 mL/min) – most common reason (70% of patients)
- Hearing loss (of 25 dB)
- Grade≥2 peripheral neuropathy (i.e. sensory alteration or parasthesis)
- ECOG performance score of ≥2

See section 4.11.3 of company submission for more information

IMvigor 210 – Baseline characteristics

		Cisplatin unsuitable (1st line)	Previous chemotherapy (2nd line)
Male		81%	78%
Age: median (range) **≥80 years**		73 (51–92) 21%	66 (32–91) 7.7%
ECOG performance status score		0 = 38% 1 = 42% 2 = 20%	0 =38% 1 = 62%
Visceral metastasis		66%	78%
Tumour site	**Bladder/urethra**	71%	77%
	Renal pelvis/ureter	28%	22%
Prior therapy	**Cisplatin-based**	15%	73%
	Carboplatin-based	1%	26%
	Number of prior therapies (for metastatic disease)	0 = 98% 1 = 2%	0 = 18% 1 = 39% 2 = 21% ≥3 = 22%

Source: company submission table 29

15% of the patients in cohort 1 (cisplatin unsuitable) received prior cisplatin therapy. The CS states that this is likely to be due to treatment with cisplatin in the neoadjuvant setting, and following progression patients are subsequently deemed cisplatin ineligible at the time of selecting first-line treatments in the metastatic setting.

ERG comment on baseline characteristics

- 20% of patients for whom cisplatin is unsuitable (1st line population) had ECOG = 2, 66% visceral metastases and 21% liver metastases
  - reflects population with poor prognostic factors
- 43% of patients who had previous chemotherapy (2nd line population) had ≥2 regimens for metastatic disease
  - heavily pre-treated population
- High proportion primary tumour site renal pelvis or ureter (28% and 22%) compared with 5–10% in clinical practice
  - more likely to be invasive at diagnosis and have worse prognosis than those in the bladder
- Few UK patients (n=22), but ERG's clinical adviser believes trial population generalisable to those with advanced or metastatic bladder cancer in England

IMvigor 210 – results

	Cisplatin unsuitable (1st line) n=119	Previous chemotherapy (2nd line) n=310
Primary analysis	**6 month follow-up**	**6 month follow-up**
Objective response rate, % (95% CI)	19.3 (12.66 – 27.58)	15.1 (11.3-19.6)
Updated analysis	**15 month follow-up**	**20 month follow-up**
Objective response rate, % (95% CI)	22.7 (15.52 – 31.27)	15.8 (11.9 – 20.4)
-historical controls ORR	*10.0*	*10.0*
Median PFS, months (95% CI)	2.7 (2.1 – 4.2)	2.1 (2.1 – 2.1)
Median OS, months (95% CI)	15.9 (10.4 – not estimable)	7.9 (6.7 – 9.3)
12 month survival, % (95% CI)	57.2 (48.2 – 66.3)	36.9 (31.4 – 42.3)
Median treatment duration (range)	15 weeks (0 – 102 weeks)	12 weeks (0 – 104 weeks)

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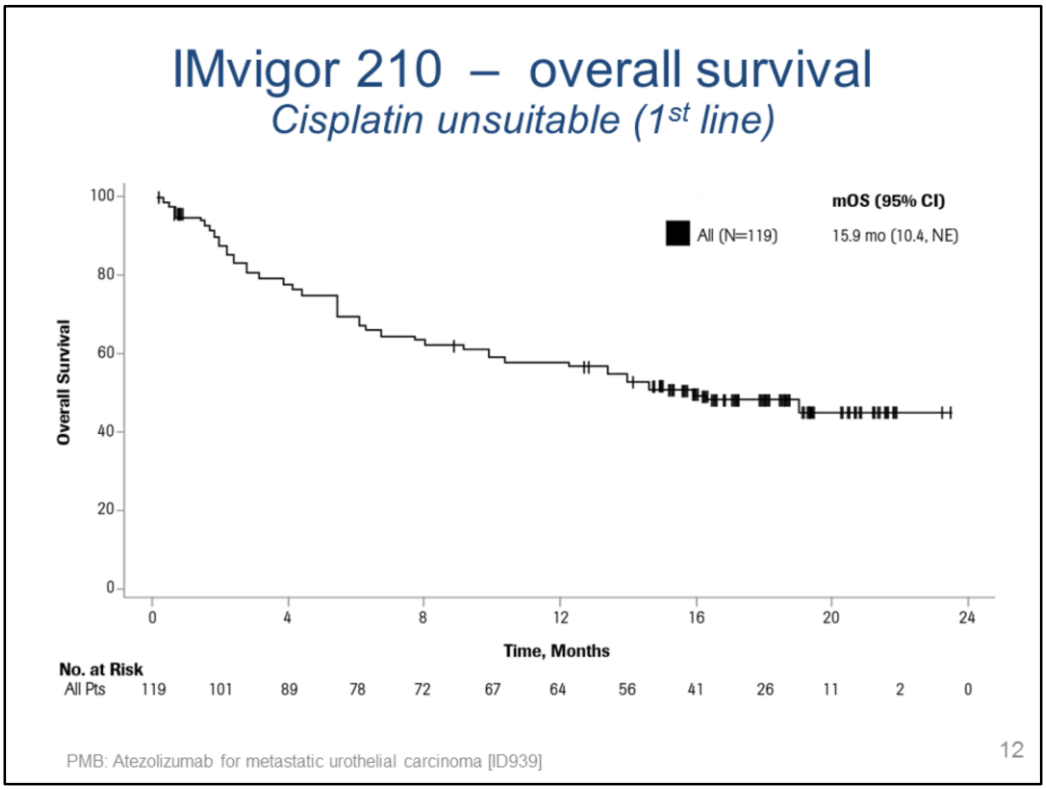
Source: company submission table 30, 31, 32, 33, 34, 36, 38, 39

- Cisplatin unsuitable: Primary efficacy results – September 2015 (minimum 6 month follow-up for all patients), updated analyses – July 2016 (minimum 15 month follow-up for all patients, median follow-up 17.2 months)

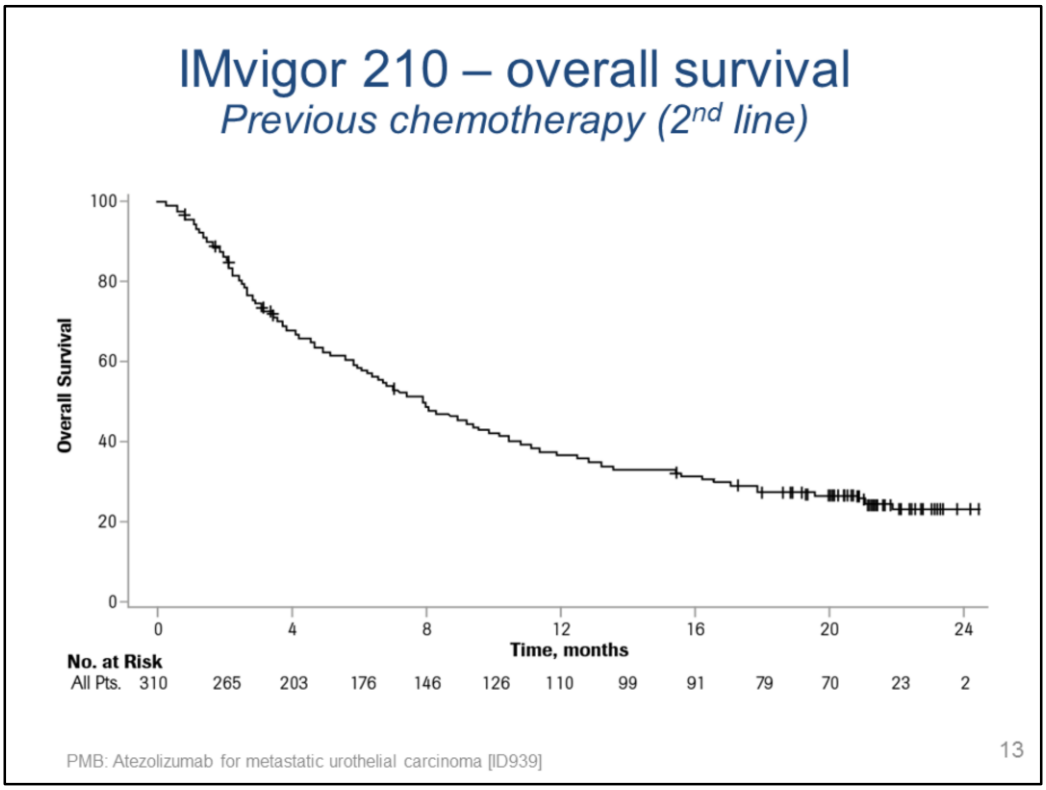
- Previous platinum-based chemotherapy: Primary efficacy results – May 2015 (minimum 6 month follow-up for all patients), updates analyses – July 2016 (minimum 20-month follow-up for all patients, median follow-up 21.1 months)

- All results reported in table above are from the independent review facility assessment of outcomes

- The company compares the objective response rate to historical controls, for which the ORR is 10% for both the 1st line and 2nd line populations



Source: company submission figure 19



Source: company submission figure 21

IMvigor 210 – PD-L1 subgroups

Cisplatin unsuitable (1st line) – 6 month follow-up			
	All patients (n=119)	**PD-L1 expression ≥5% (n=32)**	**PD-L1 expression ≥1% (n=80)**
ORR % (95% CI)	19.3 (12.66 – 27.58)	21.9 (9.28 – 39.97)	18.8 (10.89 – 29.03)
Complete response % (95% CI)	5.0 (1.87 – 10.65)	3.1 (0.08 – 16.22)	3.8 (0.78 – 10.57)

Previous chemotherapy (2nd line) – 6 month follow-up			
	All patients (n=311)	**PD-L1 expression ≥5% (n=100)**	**PD-L1 expression ≥1% (n=208)**
ORR % (95% CI)	15.1 (11.3 – 19.6)	27.0 (18.6 – 36.8)	18.3 (13.3 – 24.2)
Complete response % (95% CI)	3.9 (2.0 – 6.6)	8.0 (3.5 – 15.2)	5.3 (2.7 – 9.3)

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Source company submission tables 30 and 34

PD-L1 status is determined by the proportion of tumour area occupied by PD-L1 expressing tumour-infiltrating immune cells (% IC) of any intensity. PD-L1 expression on IC was evaluated based on 3 scoring levels: IC0 (<1%), IC1 (≥1% but <5%), IC2/3 (≥5%)

Indirect treatment comparison

- No comparative efficacy data for atezolizumab
- Company conducted simulated treatment comparison using cox regression
  - key prognostic factors identified and atezolizumab individual patient data used to predict atezolizumab outcomes for comparator trials
  - effectively building an atezolizumab 'arm' into each trial
- Network meta-analysis constructed linked together through atezolizumab 'arms'
- Network meta-analysis used fractional polynomial model
  - allows analysis of outcomes at multiple time-points
  - company believes proportional hazards assumption likely to be violated (based on appraisals of immunotherapies in melanoma and lung cancer) so traditional survival models not appropriate

Indirect treatment comparison

Prognostic factors

- Company identified 4 characteristics which predict clinical outcomes:
  - age (≥65 years)
  - gender (male)
  - performance status (ECOG≥1 or Karnofsky ≤90%)
  - presence of liver metastases at baseline
- Comparator studies all reported ≥3 factors
  - for missing data, company imputed values by generating random values

ERG comment on simulated treatment comparison

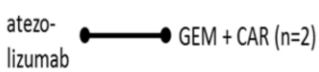
- Fundamental assumption: all prognostic factors have been included in the analysis
  - company only included up to 4 which may limit how well the simulated atezolizumab arms match the comparator arms
  - re-treatment interval could have been considered
  - age and performance status important but correlated
- Selection of the prognostic factors is not well-justified
  - e.g. no empirical evidence for age cut-off at ≥65 years
- Method of imputing missing data and multiple errors and inconsistencies add to uncertainty

- The ERG cross-checked the company's values for the proportion of patients in each trial with a particular prognostic factor with the original publications and found some discrepancies. At clarification stage, the company stated that the errors would not affect the overall results, but the ERG believes that they add to the uncertainty. See page 56/57 of the ERG report for more information.

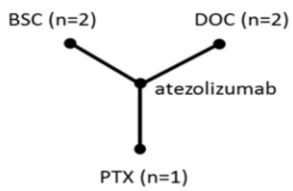
Network meta-analysis (NMA)

- Outcomes: overall survival, 12-month survival, objective response rate, progression-free survival
  - only overall survival used in the economic model

Network for overall survival
Cisplatin unsuitable (1st line)



Network for overall survival
Previous chemotherapy
(2nd line)



Included studies

Cisplatin unsuitable (1st line)

	Bamias et al.	De Santis et al.	IMvigor 210
Description	Single arm, phase II, n=34	RCT, n=119	Single arm, phase II, n=119
Intervention of interest	Gemcitabine + carboplatin	Gemcitabine + carboplatin	Atezolizumab
Age ≥65 years	94%	65%	83%
Gender (male)	82%	76%	81%
Performance status	ECOG ≥2: 68%	ECOG ≥1: 83%	ECOG ≥1: 62%
Liver metastases	-	17%	21%
Study results			
Median PFS	4.4 months	5.8 months	2.7 months
Median OS	9.8 months	9.3 months	15.9 months

- Not reported

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Source: company submission, table 17; ERG report: table 18

Note:

For, age ≥65 years the data here are not reported in the primary studies and are values imputed by the company.

For performance status ≥1 the value of 68% given for Bamias is for PS≥2. The value for PS≥1 would be higher than 68% but is not precisely calculable.

Included studies

Previous chemotherapy (2nd line)

	Bellmunt et al.	Choueiri et al.	Kim	Lee et al.	Noguchi et al.	IMvigor 210
Description	RCT, n=117	RCT, n=75	Single-arm, n=31	Single-arm, n=37	RCT, n=41	Single-arm, n=310
Intervention of interest	BSC	Docetaxel + placebo	Docetaxel	Paclitaxel*	BSC	Atezolizu-mab
Age ≥65	44%	46%	46%	17%	50%	59%
Gender	78%	68%	77%	78%	80%	78%
Performance status ≥1	69%	53%	100%	62%	20%	62%
Liver mets.	-	38%	32%	30%	-	31%
Study results						
Median PFS	-	1.6 months	1.4 months	2.7 months	1.8 months	2.1 months
Median OS	4.6 months	7.0 months	8.3 months	6.5 months	4.1 months	7.9 months

- Not reported
* Polyethoxylated caster oil-free, polymeric micelle formulation

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Source: company submission, table 17; ERG report, table 19

Note:

For, age ≥65 years the data here are not reported in the primary studies and are values imputed by the company.

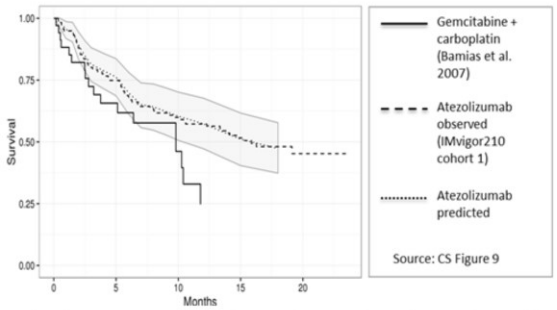
ERG notes that only relevant study found for paclitaxel used a polymeric micelle formulation and it is unclear whether this formulation would have similar effectiveness and tolerability compared to standard paclitaxel chemotherapy.

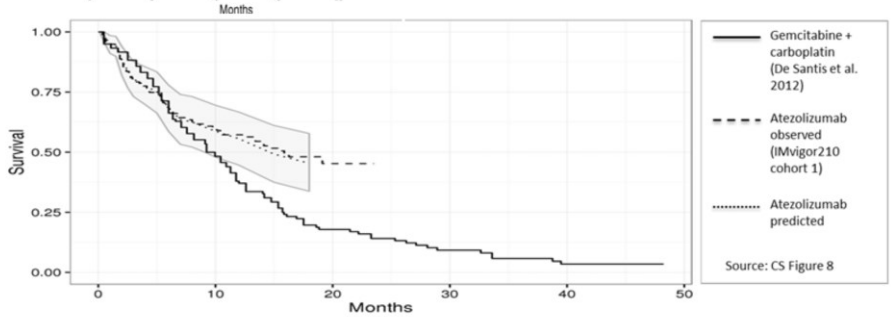
ERG comment on network meta-analysis

- Hard to assess heterogeneity of included studies (e.g. prior therapies not consistently reported)
- Results are presented as log-hazard function curves and their intercept and slope because hazard ratio varies over time
  - company provides no guidance on clinical interpretation of these parameters or discussion of clinical effectiveness results from the NMA
- The NMA produced clinically implausible results: PFS not used in model and the company caps hazard ratios for overall survival to obtain plausible results
- No sensitivity analyses to test robustness of the simulated treatment comparison or NMA methods, adding to uncertainty

NMA results – cisplatin unsuitable (1st line)

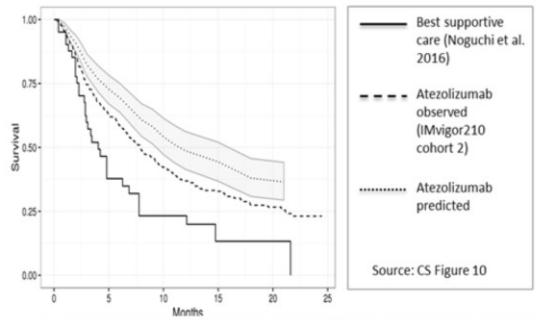
gemcitabine + carboplatin, overall survival

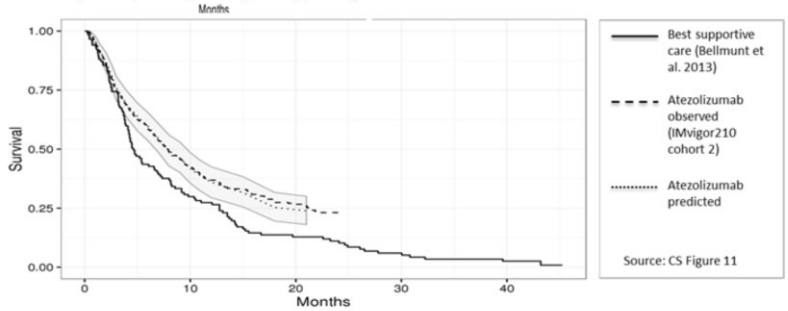




NMA results – previous chemotherapy (2nd line)

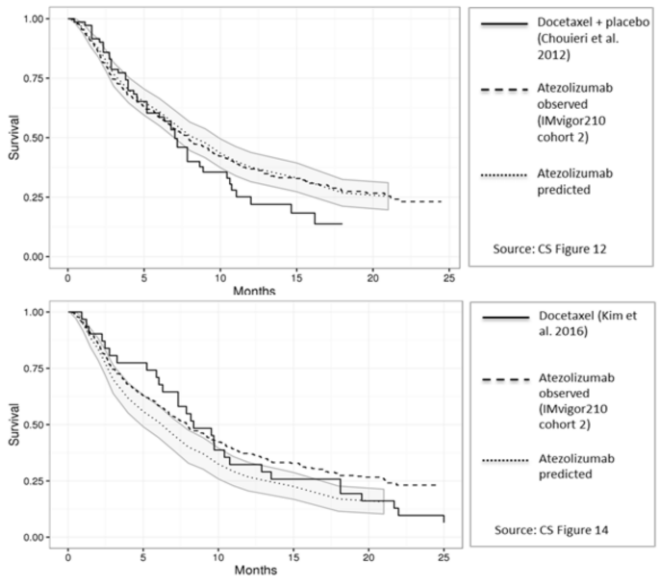
BSC, overall survival



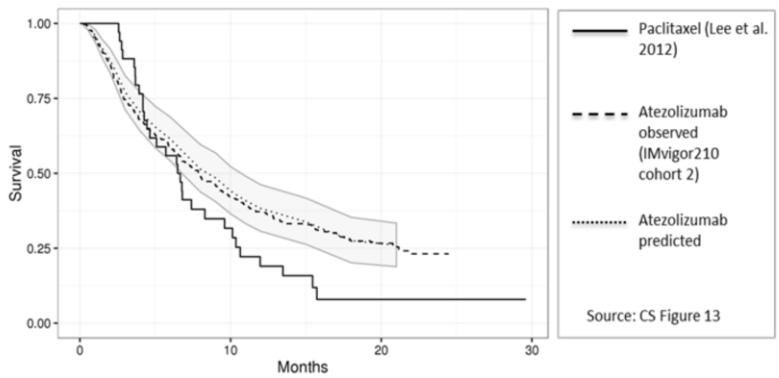


NMA results – previous chemotherapy (2nd line)

docetaxel, overall survival



NMA results – previous chemotherapy (2nd line)
paclitaxel, overall survival



Adverse events

- Most commonly reported treatment-related adverse events in IMvigor 210 were
  - cisplatin unsuitable: fatigue (30%), diarrhoea (12%) and pruritus (11%)
  - previous platinum-based chemotherapy: fatigue (31%), nausea (27%), pyrexia (22%), vomiting (19%), arthralgia (18%), pruritus (12%), rash (12%), decreased appetite (11%) and chills (11%).

On-going trials

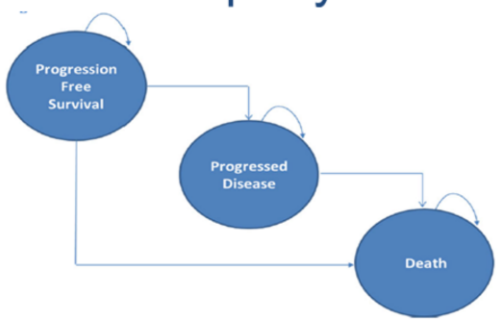
- IMvigor 211
  - phase III, open-label RCT (n=932)
  - previously treated metastatic urothelial carcinoma
  - atezolizumab compared with investigator's choice of vinflunine, docetaxel or paclitaxel
  - estimated completion date: November 2017
- IMvigor 130
  - phase III, double-blind RCT (n=1,200)
  - previously untreated metastatic urothelial carcinoma
  - Arm A: atezolizumab monotherapy
  - Arm B: atezolizumab + gemcitabine + carboplatin
  - Arm C: gemcitabine + carboplatin
  - estimated completion date: July 2020

Key issues – clinical effectiveness

- Decision problem:
  - is BSC a comparator for people for whom cisplatin is unsuitable?
  - is re-treatment with 1st line chemotherapy a comparator for the 2nd line population?
  - is it appropriate to consider only one 2nd line population, regardless of whether people could have cisplatin as 1st line therapy?
- Quality of evidence
  - no comparative atezolizumab trial data
  - how reliable is the simulated treatment comparison? Does the company account for all of the important prognostic factors?
  - how reliable is the network meta-analysis? Are the included studies sufficiently homogeneous?
- How effective is atezolizumab?

Cost-effectiveness

Company's economic model



Populations modelled
People for whom cisplatin is unsuitable and have had no previous treatment
People whose disease has progressed after previous platinum-based chemotherapy

- 20 year time horizon, NHS/PSS perspective, 3.5% discount rate
- Weekly cycle length with half-cycle correction
- Treatment with atezolizumab, paclitaxel and docetaxel continues until disease progression or discontinuation due to adverse events
- Treatment with gemcitabine + carboplatin is given for the number of cycles specified in the summary of product characteristics

Overview of sources of clinical inputs

Outcome	Intervention	Comparators		
1st line	**Atezolizumab**	**Gemcitabine + carboplatin**		
PFS	Extrapolation from IMvigor 210	Assumption: PFS of gemcitabine + carboplatin = PFS of atezolizumab		
OS	Mix cure rate model (data from IMvigor 210 and Life tables)	Results from NMA with capped HR		
2nd line	**Atezolizumab**	**BSC**	**Docetaxel**	**Paclitaxel**
PFS	Extrapolation from IMvigor 210	Use of proportional hazards model (HR from NMA)	Assumption: PFS of gemcitabine +carboplatin = PFS of atezolizumab	
OS	Mix cure rate model (data from IMvigor 210 and Life tables)	Results from NMA with capped HR		

Source: ERG report table 25

Clinical inputs: progression-free survival

- Atezolizumab: PFS extrapolated from IMvigor 210 by fitting generalised gamma distribution to Kaplan–Meier curves for both populations
- Gemcitabine + carboplatin: PFS assumed to be equivalent to atezolizumab
- Docetaxel and paclitaxel: PFS assumed to be equivalent to atezolizumab
  - Company rationale: KEYNOTE-045 trial reported non-significant hazard ratio of 0.98 for PFS, pembrolizumab vs. blended comparison docetaxel, paclitaxel, vinflunine for metastatic urothelial carcinoma
- BSC: proportional hazard ratio of 1.12 vs. atezolizumab from company network meta-analysis

ERG comments on PFS modelling

- Generalised gamma appears to fit the atezolizumab data well
- Company explores alternative distributions, but these had little effect on the ICER
- Assuming equal efficacy of atezolizumab and comparators for PFS (company approach) vs. using hazard ratios from network meta-analysis produces similar ICERs

See table 93 and 94 of company submission for alternative PFS distributions

See table 26 of ERG report for ICERs using hazard ratios from NMA

Clinical inputs: overall survival

- Atezolizumab: observed survival in IMvigor 210 adjusted for background mortality and extrapolated using generalised gamma distribution
- Gemcitabine + carboplatin: hazard ratio from NMA
  - company noted that this increased linearly over time, producing clinically implausible results
  - hazard ratio capped at 8 months (median follow-up in the Bamias et al. study), with proportional hazards assumed beyond this point
- Docetaxel, paclitaxel and BSC: hazard ratios from NMA capped at 21.16 months (median follow-up in atezolizumab study), proportional hazards assumed beyond this point

ERG comments on OS modelling

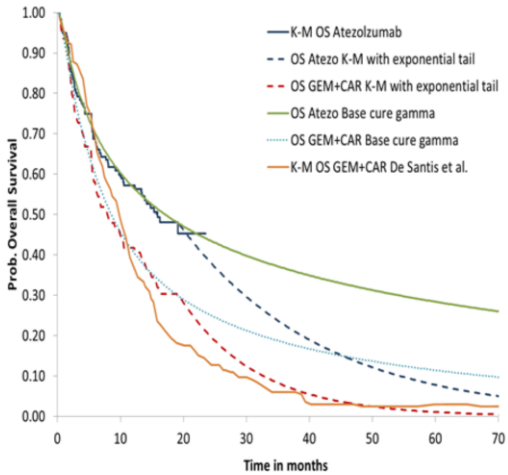
- Atezolizumab extrapolation corresponds well with observed data
- Company does not provide any sensitivity analyses for the choice of parametric distribution or varying the treatment effect of atezolizumab
- Inconsistent time points used for capping hazard ratios
- Using capped network meta-analysis results in model adds to uncertainty
- No sensitivity analyses varying atezolizumab treatment effect
- ERG exploratory analyses assess:
  - the effect of equalised time points for capping the hazard ratios
  - varying the change in hazard ratio over time (to avoid the need to cap the hazard ratios)
  - varying the atezolizumab treatment effect (using the upper and lower bounds of the confidence interval for the hazard ratio intercept)

See section 4.4, page 126 and 127 for details of these exploratory analyses

ERG exploratory analyses: OS extrapolation

Cisplatin unsuitable (1st line)

- Company uses gamma distribution for atezolizumab and comparator extrapolations, as it fits atezolizumab data well
- Follow-up in gemcitabine + carboplatin trial (De Santis) longer than atezolizumab
  - exponential distribution fits De Santis better than gamma
- ERG: more reasonable to use individual Kaplan–Meier curves from atezolizumab and comparator trials with tails extrapolated using exponential function

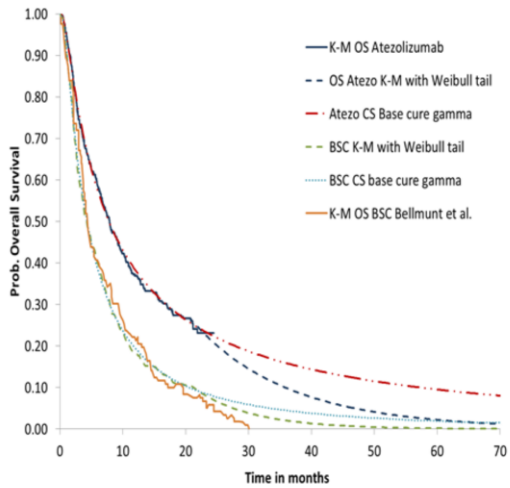


Source: ERG report figure 21

ERG exploratory analyses: OS extrapolation

Previous chemotherapy (2nd line)

- Company uses gamma distribution for atezolizumab and comparator extrapolations as it fits atezolizumab data well
- Of comparator trials, BSC (Bellmunt) has largest number of patients and longest follow-up
  - Weibull distribution fits BSC data better than gamma
- ERG: more reasonable to use individual Kaplan–Meier curves from atezolizumab and comparator trials with tails extrapolated using Weibull function



Source: ERG report, figure 22

Clinical inputs: time to treatment discontinuation

- Company used data from IMvigor 210 for atezolizumab, extrapolated using generalised gamma function as trial still on-going
- Gemcitabine + carboplatin given for 6 cycles (as detailed in summary of product characteristics)
- For docetaxel and paclitaxel, progression-free survival used as a proxy for time on treatment
- ERG comments:
  - same distribution used to extrapolate atezolizumab discontinuation for both populations, but Weibull for 1st line and log-logistic for 2nd line provide a better fit

Health-related quality of life

- No health-related quality of life data collected in IMvigor 210
- Company used values from a study of vinflunine
- ERG comment:
  - same utility value on-treatment for atezolizumab and comparators counter-intuitive due to adverse events of chemo
  - people off-treatment after atezolizumab would not have a lower utility than on-treatment because of treatment related adverse events

	Company choice		ERG choice	
	Atezolizumab	**Comparators**	**Atezolizumab**	**Comparators**
On-treatment	0.75	0.75	0.75	0.71
Off-treatment	0.71	0.75	0.75	0.75

- No adverse event disutility included in model

Source: ERG report table 45

Company's cost-effectiveness results

list price, deterministic analyses

Cisplatin unsuitable (1st line)					
	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Gemcitabine + carboplatin	£18,106	1.35	£59,106	1.34	£44,158
Atezolizumab	£77,211	2.69			

Previous chemotherapy (2nd line)					
	Total		Incremental		Pairwise ICER atezolizumab vs. comparator
	Costs	QALYs	Costs	QALYs	
BSC	£4,836	0.55	£67,032	0.68	£98,208
Docetaxel	£9,439	0.76	£62,430	0.47	£131,579
Paclitaxel	£16,606	0.71	£55,262	0.53	£104,850
Atezolizumab	£71,868	1.23	-	-	-

PMB: Atezolizumab for metastatic urothelial carcinoma [ID939]

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Source: company submission, tables 73, 74

- Paclitaxel is dominated by docetaxel (higher costs, lower QALYs)

- The company provides probabilistic results but notes "Results of the PSA should be interpreted with caution, as they are unlikely to be reliable. The high level of uncertainty in the fractional polynomial model and prediction model provides a skewed output for OS. This subsequently impacts other model outputs."

Company's cost-effectiveness results
with PAS, deterministic analyses

Cisplatin unsuitable (1st line)

	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Gemcitabine + carboplatin	[redacted]	1.35	[redacted]	1.34	[redacted]
Atezolizumab	[redacted]	2.69			

Previous chemotherapy (2nd line)

	Total		Pairwise vs. Atezolizumab			ICER: incremental
	Costs	QALYs	Inc. costs	Inc. QALYs	ICER	
BSC	[redacted]	0.55	[redacted]	0.68	[redacted]	-
Docetaxel	[redacted]	0.76	[redacted]	0.47	[redacted]	[redacted]
Paclitaxel	[redacted]	0.71	[redacted]	0.53	[redacted]	[redacted]
Atezolizumab	[redacted]	1.23	-	-	-	[redacted]

PMB: Atezolizumab for metastatic urothelial carcinoma [ID939]

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Source: company PAS submission

Company base case probabilistic analysis (1st line) - **with PAS**

Company base case probabilistic analysis (2nd line) - **with PAS**

Company's sensitivity and scenario analyses

- Company: probabilistic results unlikely to be reliable due to high level of uncertainty in fractional polynomial and prediction models
- Deterministic sensitivity analyses: ICER most sensitive to atezolizumab cost, on- and off-treatment utility values
- Scenario analyses:
  - atezolizumab PFS as proxy for time on treatment increases ICER for 1st line population and decreases ICERs for the 2nd line population
  - decreasing atezolizumab off-treatment utility value from 0.71 to 0.5 increases ICERs for both populations

List price	ICER vs. gem+carbo	ICER vs BSC	ICER vs. docetaxel	ICER vs. paclitaxel
Base case	£44,158	£98,208	£131,579	£104,850
Atez. time on treatment = PFS	£64,365	£78,028	£102,982	£78,727
Off-treatment utility value: 0.5	£69,252	£120,299	£159,492	£131,530

See section 5.8.1 of the company submission for the probabilistic sensitivity analyses

See section 5.8.3 of the company submission for the scenario analyses. Results are reported in tables 93 and 94

ERG exploratory analyses and preferred analysis

list price, deterministic analyses

	Cisplatin unsuitable	Previous chemotherapy (2nd line)		
	ICER vs. gemcitabine	ICER vs BSC	ICER vs. docetaxel	ICER vs. paclitaxel
Company base case	£44,158	£98,208	£131,579	£104,850
OS: K-M + exponential tail	£101,711	-	-	-
TTD: Weibull	£42,683	-	-	-
OS: K-M + Weibull tail	-	£153,806	£287,175	£176,090
TTD: log-logistic	-	£133,035	£180,213	£149,491
ERG preferred utility values	£43,317	£99,409	£127,528	£101,654
ERG preferred analysis	£93,948	£166,805	£288,247	£180,901

Source: ERG report tables, 40, 41, 48, 49

ERG exploratory analyses and preferred analysis
with PAS, deterministic analyses

	Cisplatin unsuitable	Previous chemotherapy (2nd line)		
	ICER vs. gemcitabine	ICER vs BSC	ICER vs. docetaxel	ICER vs. paclitaxel
Company base case	[redacted]	[redacted]	[redacted]	[redacted]
OS: K-M + exponential tail	[redacted]	-	-	-
TTD: Weibull	[redacted]	-	-	-
OS: K-M + Weibull tail	-	[redacted]	[redacted]	[redacted]
TTD: log-logistic	-	[redacted]	[redacted]	[redacted]
ERG preferred utility values	[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred analysis	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		

*Paclitaxel dominated by docetaxel

Source: ERG PAS analysis appendix tables 2,3,5,6,7

ERG preferred analysis probabilistic analysis (1st line) - **with PAS**

ERG preferred analysis probabilistic analysis (2nd line) - **with PAS**

ERG exploratory analyses not included in preferred analysis – **list price**

	ICER vs. gem+carbo	ICER vs BSC	ICER vs. docetaxel	ICER vs. paclitaxel
Base case	£44,158	£98,208	£131,579	£104,850
Treatment effect varied: lower bound	£191,793	Atez. Dominated	Atez. Dominated	Atez. Dominated
Treatment effect varied: upper bound	£33,432	£79,017	£87,990	£68,427
HR capped at 8 months	-	£97,397	£310,395	£107,514
HR capped at 21.16 months	£35,764	-	-	-
Slope parameters varied: no capping	£47,505	£99,417	£193,686	£101,835

Source ERG report tables 42, 43 and 44

End of life criteria

		From modelling		From literature
		Mean (months)	Median (months)	Median (months)
Cisplatin unsuitable (1st line)				
Short life expectancy	**Atezolizumab**	55.3	17.1	15.9
	Gem + carboplatin	25.1	8.5	9 – 10
Extension to life		30.2	8.6	>6
Previous chemotherapy (2nd line)				
Short life expectancy	**Atezolizumab**	22.7	7.9	7.9
	Docetaxel	12.9	7.6	7 – 8
	Paclitaxel	12.2	5.3	6.5
	BSC	9.4	4.4	4 – 5
Extension to life		9.8 – 13.3	0.3 – 3.5	0 – 4

PMB: Atezolizumab for metastatic urothelial carcinoma [ID939] 50

Source: company submission, table 47

Company argues that mean overall survival results better reflects outcomes

- due to the shape of the treatment response and long survival tail, median results do not capture the survival gains with atezolizumab

Survival values from the literature come from the trials included in the NMA: Gemcitabine + carboplatin, Bamias et al and De Santis et al; BSC, Bellmunt et al. and Noguchi et al.; docetaxel, Choueiri et al. and Kim; paclitaxel, Lee et al. (see also slides 19 and 20).

Innovation and equality

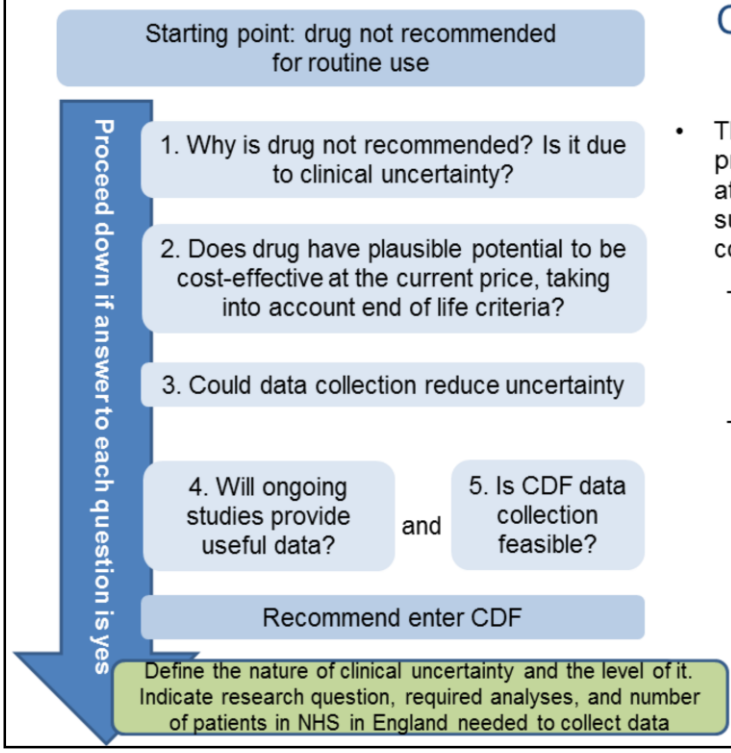
- First immunotherapy for locally advanced or metastatic urothelial carcinoma
  - pembrolizumab also being assessed by NICE for same indication (does not yet have marketing authorisation)
- Early access to medicine scheme designation
  - (for population 2: previous platinum-based chemotherapy only)
- No additional benefits not captured in the QALY highlighted by company
- No equality issues identified during scoping or in submissions

Key issues – cost effectiveness (1)

- Which overall survival extrapolations are most appropriate?
  - company: gamma distribution for atezolizumab and all comparators
  - ERG: Individual Kaplan-Meier curves for all therapies with exponential tail (cisplatin unsuitable population) and Weibull tail (previous platinum-based chemotherapy population)
- Are the hazard ratios from the network meta-analysis suitable for decision-making, given that they had to be capped to provide plausible results?
- Which distribution should be used for time to treatment discontinuation?
  - company: gamma for both populations
  - ERG: Weibull (cisplatin unsuitable population), log-logistic (previous platinum-based chemotherapy population)

Key issues – cost effectiveness (2)

- Which utility values should be used?
  - company lower value for atezolizumab off-treatment than on-treatment
  - ERG lower value for comparators on-treatment than atezolizumab
- Are the end-of-life criteria met?
  - should mean or median overall survival be used?
- What are the most plausible ICERs?



Cancer Drugs Fund

- The company have proposed that atezolizumab would be suitable for CDF consideration:
  - uncertainty in clinical efficacy because of lack of head-to-head trial
  - clinical uncertainty could be reduced with results from the ongoing IMvigor 211 trial (for previous chemotherapy population) and IMvigor 130 trial (for cisplatin unsuitable population)

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Authors

- **Ross Dent**
  Technical Lead
- **Ian Watson**
  Technical Adviser
- with input from the Lead Team (**Rebecca Harmston, Sumithra Maheswaran** and **David Meads**)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of atezolizumab within its marketing authorisation for treating locally advanced or metastatic urothelial carcinoma in people whose disease has progressed after prior chemotherapy or for whom cisplatin-based chemotherapy is unsuitable.

Background

Urothelial carcinoma is cancer of the transitional cells which form the inner lining of the bladder, urethra, ureter, or renal pelvis. Transitional cell cancer (TCC) of the renal pelvis and ureter is rare and in the UK accounts for only about 7 out of 100 kidney cancers, and is 4 times less common in the ureter. Urothelial carcinoma is most common in the bladder, and accounts for 90% of bladder cancers[1].

Transitional cell cancers can be split into papillary carcinomas and flat carcinomas. Papillary carcinomas often grow towards the centre of the bladder, without going into deeper layers (non-invasive) but sometimes these can grow deeper into the bladder wall and are more likely to spread (invasive). Flat carcinomas do not grow toward the hollow part of the bladder and remain in the inner layers (non-invasive). Other types of bladder cancers include squamous cell carcinoma (beginning in thin flat cells) and adenocarcinoma (beginning in cells which make and release mucus and other fluids). These types of bladder cancer arise as a result of chronic irritation and inflammation.

There were 10,300 diagnoses of bladder cancer in 2013, accounting for 1 in every 30 new cases of cancer each year[2, 3]. Overall incidence is 11.4 per 100,000 and is more common in men than women (3:1)[2]. The majority of cases are in those over the age of 60 but can also affect young people too[3, 4]. Smoking is major factor in the cause of bladder cancer[4].

Patients with metastatic or advanced urothelial cancer may receive treatment with surgery and/or radiotherapy. Chemotherapy may be given before (neoadjuvant) or after surgery and/or radiotherapy in an attempt to improve cure rates. If the urothelial cancer is too advanced for surgery/radiotherapy or has recurred after these treatments, chemotherapy can be used to improve quality of life and survival. NICE guideline NG2 recommends cisplatin-based

regimens (such as gemcitabine plus cisplatin or accelerated methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF]) for untreated disease or after one prior therapy. In addition, carboplatin plus gemcitabine maybe considered for untreated disease and carboplatin or gemcitabine plus paclitaxel may be considered after one prior therapy. For people whose disease has progressed after platinum-based chemotherapy, a taxane such as docetaxel or paclitaxel may be given. Vinflunine is not recommended for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy (NICE technology appraisal 272).

The technology

Atezolizumab (Tecentriq, Roche) is a humanised, anti-programmed cell death ligand-1 (PD-L1) monoclonal antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Atezolizumab does not currently have a marketing authorisation in UK for treating metastatic urothelial carcinoma after treatment with chemotherapy. It is being studied in a phase III clinical trial in adults with locally advanced or metastatic urothelial cancer that has progressed following a platinum-containing regimen, compared to vinflunine, paclitaxel, or docetaxel. It is also being studied in a phase II single arm clinical trial in adults with untreated or cisplatin-ineligible disease, and in adults who have previously received a platinum-containing therapy.

Intervention(s)	Atezolizumab
Population(s)	Adults with locally advanced or metastatic urothelial carcinoma: • Whose disease has progressed after prior chemotherapy • For whom cisplatin-based chemotherapy is unsuitable

Comparators	People with locally advanced or metastatic urothelial carcinoma for whom cisplatin-based chemotherapy is unsuitable: • Gemcitabine plus carboplatin • Best supportive care People whose disease has progressed after platinum-based chemotherapy: • Retreatment with 1st line platinum-based chemotherapy (only for people whose disease has had an adequate response) • Docetaxel • Paclitaxel • Best supportive care People for whom cisplatin-based chemotherapy is unsuitable, and whose disease has progressed after platinum-based therapy: • Retreatment with gemcitabine plus carboplatin (only for people whose disease has had an adequate response) • Docetaxel • Paclitaxel • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract. (2013) NICE technology appraisal guidance 272. Reviewed November 2015. Decision to transfer to static list. **Related Guidelines:** Bladder cancer: diagnosis and management (2015) NICE guideline NG2. Improving outcomes in urological cancers (2002) NICE cancer service guidance. Published September 2002. **Related Interventional Procedures:** Laparoscopic cystectomy NICE interventional procedure guidance 287. Published February 2009. Electrically-stimulated intravesical chemotherapy for superficial bladder cancer NICE interventional procedure guidance 277. Published November 2008 Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer NICE interventional procedure guidance 235. Published October 2007. **Related Quality Standards:** Bladder cancer NICE quality standard. Published December 2015 **Related NICE Pathways:** Bladder cancer (2015) NICE Pathway
Related National Policy	Department of Health (2014) NHS outcomes framework 2015-2016 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-

	2020 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy

References

1. Transitional cell cancer, Cancer Research UK. Accessed September 2016

2. Bladder Cancer statistics, Cancer Research UK. Accessed July 2016

3. Bladder Cancer, Patient UK. Accessed July 2016

4. The facts about Bladder cancer, Action Bladder Cancer UK. Accessed July 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma [ID939]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Atezolizumab (Roche) Patient/carer groups • Action Bladder Cancer UK • Black Health Agency • Bladder & Bowel Foundation • Cancer 52 • Cancer Black Care • Cancer Equality • Fight Bladder Cancer • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Pelican Cancer Foundation • Penny Brohns UK • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • Bladder and Bowel Foundation • British Association of Urological Nurses • British Association of Urological Surgeons	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord Healthcare (carboplatin, docetaxel, gemcitabine, paclitaxel) • Actavis UK (docetaxel, gemcitabine, paclitaxel) • Dr Reddy's Laboratories (docetaxel) • Eli Lilly (gemcitabine) • Hospira (carboplatin, docetaxel, gemcitabine, paclitaxel)

Consultees	**Commentators (no right to submit or appeal)**
• British Geriatrics Society • British Gynaecological Cancer Society • British Institute of Radiology • British Psychosocial Oncology Society • British Society of Urogynaecology • British Uro-Oncology Group • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society • Urology Foundation • University College London Hospitals NHS Foundation Trust <u>Others</u> • Department of Health • NHS England • NHS Newbury and District CCG • NHS Sheffield CCG Welsh Government	• Medac (docetaxel, gemcitabine, paclitaxel) • Sanofi (docetaxel) • Seacross Pharmaceuticals (docetaxel) • Sun Pharmaceuticals UK Ltd (carboplatin, gemcitabine) • Peckforton Pharmaceuticals (paclitaxel) <u>Relevant research groups</u> • Cochrane Prostate Diseases and Urologic Cancers Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Urothelial Cancers Research Group, Leeds Institute of Cancer & Pathology <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma after prior chemotherapy and patients who are considered cisplatin-ineligible

Company evidence submission

18th January 2017

File name	Version	Contains confidential information	Date
Atezolizumab mUC evidence submission [ID939]	**V1**	**Yes**	**18th January 2017**

Contents

Abbreviations

1L	First-line
2L	Second-line
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AIC	Akaike information criterion
AQoL	Assessment of quality of life
AR	Adverse reaction
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUA	American Urological Association
BCG	Bacillus Calmette–Guérin
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CE	Conformité Européene
CADTH	Canadian Agency for Drugs and Technologies in Health
CCOD	Clinical (data) cutoff date
CCT	Non-randomised controlled clinical trials
CDR	Common drug reviews
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRUK	Cancer research UK
CSR	Clinical study report
CT	Computed tomography
CTLA	Cytotoxic-T-lymphocyte-associated antigen
DARE	Database of Abstracts of Reviews of Effects
DCR	Disease control rate
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DIC	Deviance information criterion
DOR	Duration of response
DVT	Deep vein thrombosis
EAMS	Early Access to Medicines Scheme
EAU	European Association of Urology
ECCO	European Cancer Congress
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European public assessment report

ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMUC	European Meeting on Urologic Cancers
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence review group
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FE	Fixed effects
FFPE	Formalin-fixed paraffin-embedded
FP	Fractional polynomial
GC	Gemcitabin plus cisplatin
GEM	Gemcitabin
GFR	Glomerular filtration rate
GP	General practitioner
GU	Genitourinary
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare resource group
HS	Health state
HSUV	Health state utility values
HTA	Health technology assessment
IC	Immune cell
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
iDCC	Independent data coordinating centre
iDMC	Independent data monitoring committee
IFU	Information for use
IHC	Immunohistochemistry
IL	Interleukin
INAHTA	International network for agencies of HTA
INV	Investigator
IPD	Individual patient data
IRF	Independent review facility
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IUO	Investigational use only
IV	Intravenous
KM	Kaplan Meier
LFT	Liver function test
LYG	Life years gained
MAA	marketing authorisation application
MAIC	Match-adjusted indirect comparison
M-CAVI	Methotrexate, carboplatin, vinblastine
MHRA	Medicines and Healthcare products Regulatory Agency

MIBC	Muscle-invasive bladder cancer
MRI	Magnetic resonance imaging
mUC	Metastatic urothelial carcinoma
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NA	Not applicable
NAC	Neoadjuvant chemotherapy
NCCC	National Collaborating Centre for Cancer
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NHS	National Health Service
NHSEED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NIHR	National Institute of Health Research
NMA	Network meta-analysis
NMIBC	Non−muscle-invasive bladder cancer
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
OOB	Out-of-bag
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patients access scheme
PASLU	Patient access scheme liaison unit
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PICO	Patient, problem or population; Intervention; Comparison, control, or comparator; Outcome
PIM	Promising innovative medicine
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSS	Personal social services
PTX	paclitaxel
QALY	Quality-adjusted life year
QLQ	Quality of Life Questionnaire
QoL	Quality of life
QWB	Quality of well-being scale
RC	Radical cystectomy
RCT	Randomised controlled trial
RE	Random effects
RECIST	Response evaluation criteria in solid tumors
RR	Response rate

SAE	Serious adverse events
SD	Stable disease
SE	Standard error
SEER	Surveillance, epidemiology and end results program
SF	Short form
SG	Standard gamble
SITC	Society for immunotherapy of cancer
SLD	Sum of the longest diameter of the target lesions
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	Standard of care
SmPC	Summary of product characteristics
STA	Single technology appraisal
STC	Simulated treatment comparison
TC	Tumour cell
TCC	Transitional cell carcinoma
TCCU	Transitional cell carcinoma of the urothelial tract
TCGA	The Cancer Genome Atlas
TIR	Time in response
TNF	Tumour necrosis factor
TTO	Time trade off
TTP	Time to progression
TURBT	Transurethral resection of bladder tumours
UBC	Urothelial bladder cancer
UC	Urothelial carcinoma
UK	United kingdom
ULN	Upper normal limit
UNK	Unknown
US	United States
UTI	Urinary tract infection
VAS	Visual analogue scale
VAT	Value added tax
VFL	Vinflunine
VHR	Very high risk

Tables and figures

1 Executive summary

Urothelial carcinoma (UC) describes cancer deriving from the cells which line the bladder wall and the ureters. The bladder is the predominant location for UC, but tumours can originate in the renal pelvis, urethra, or ureter, which are also lined by urothelial calls. There are a number of well-known risk factors for the development of UC, including increased age, smoking, and some industrial chemicals.

Bladder cancer is the tenth most common cancer in the UK. In 2014 there were 10,063 new cases in the UK, and 5,369 deaths were attributable to bladder cancer.

As early symptoms of bladder cancer are often detectable to patients, they present to healthcare services early resulting in prompt diagnosis. Patients with early UC are highly treatable; however there is a high risk of recurrence. Thus, while early diagnosis rates continue to increase, there is still a need for effective treatments for metastatic or advanced UC (mUC).

Current UK Practice

Only two new drug treatments have become available for the treatment of mUC in the last two decades, neither of which have shown an improvement in overall survival (OS) vs. standard of care. Both are non-specific cytotoxic agents that give rise to the toxicities typical of chemotherapy.

For patients who are fit enough, chemotherapy is the main treatment option. As mUC is incurable with current treatments, the aim of these is to prolong life and palliate or alleviate symptoms.

For patients with adequate renal function, and who are otherwise physically fit, cisplatin based therapy is the preferred first-line treatment option. However up to 50% of patients are not eligible for treatment with cisplatin. NICE recommends treatment with gemcitabine in combination with carboplatin for these patients.

Despite first-line treatment, the majority of patients will experience disease progression and may require second line therapy. Vinflunine is the only medicine specifically approved in the EU for use after failure of prior platinum-containing chemotherapy. Following appraisal by NICE, vinflunine was not recommended for

use in England. As there are no other licensed second-line therapies, there is a wide variety of practice in the UK. An independent survey of UK clinical practice determined monotherapy taxane based therapy as the typical treatment option (Lamb et al., 2014). Weekly paclitaxel is recommended by the London Cancer Alliance guidelines (London Cancer Alliance, 2013), and UK expert clinical advisors confirmed this, and three weekly docetaxel are the most frequently used second-line treatments. A proportion of patients will also be ineligible for chemotherapy in the 2L setting, and as such rely on best-supportive care (BSC) to alleviate symptoms.

Unmet need

Although multiple treatment options are available for earlier stages of bladder cancer, advanced metastatic disease remains an area of extremely high unmet need. This is particularly true in the second-line setting where no treatment has been shown to improve survival. Vinflunine, the only licensed therapy for second-line treatment, was not recommended by NICE in 2013. As such there is an urgent need for effective treatments for patients who have failed first line therapy, or are ineligible for cisplatin based therapy.

Atezolizumab

Atezolizumab is an immunotherapy – a class of treatments designed to upregulate patients own immune system to fight tumours. A monoclonal antibody, atezolizumab is the first of these therapies which specifically binds to and inactivates a protein called programmed death ligand 1 (PD-L1). This leads to the activation of T cells which can detect and attack tumour cells. UC is an attractive target for systemic immune therapy – the earliest stages of the disease respond well to topical immunotherapy with BCG and the tumour carries a high frequency of genetic mutations – a hallmark of immune responsiveness.

Atezolizumab is given at a dose of 1200mg intravenous (IV) infusion, every 3 weeks.

Efficacy with atezolizumab

The efficacy of atezolizumab has been demonstrated in a large phase II clinical trial, IMvigor 210. This single arm study included two cohorts of patients:

- Cohort 1: first-line patients, unfit for cisplatin-based chemotherapy (n=119)
- Cohort 2: patients whose disease has progressed during or following a prior platinum-based chemotherapy regimen (either containing cisplatin or carboplatin) (n=310)

The primary analysis for cohort 1 was in September 2015, and for cohort 2 in May 2015. The most recent data cut was in July 2016 for both cohorts. At this time median OS was 15.9 months (95% CI, 10.4 to NE) for cohort 1, and 7.9 months (95% CI, 6.7–9.3) for cohort 2.

For the primary efficacy endpoint, objective response rates (ORR) were compared to historical controls, for which the ORR is10% in both the 1L and 2L settings. In the July 2016 data cut, 22.7% (95% CI: 15.52, 31.27) of patients in cohort 1, and 15.8% (95% CI: 11.9, 20.4) of patients in cohort 2 had an OR - defined as a complete or partial response (at least 30% decrease in the sum of the target lesions) to atezolizumab.

The phase II study was designed to additionally explore the outcomes for patients based on their PD-L1 expression level on tumour-infiltrating immune cells (ICs). Clinically meaningful and statistically significant levels of ORR were observed across all levels of IC expression, and as benefit is observed across all subgroups of patients, regulatory approval has been sought (and is anticipated) for the entire population.

The IMvigor 210 study demonstrated that for those patients who do respond, disease remissions tends to be very long lasting – much more so than those achieved with conventional chemotherapy – both in patients with locally advanced or mUC after prior chemotherapy (cohort 2), and in newly diagnosed patients who are considered cisplatin ineligible (cohort 1).

On-going studies for atezolizumab in mUC

The clinical development programme of atezolizumab includes 2 phase III, randomised controlled trials in mUC (Clinicaltrials.gov, 2016b). The 2L+ IMvigor 211 study (NCT02302807) compares atezolizumab to an investigator choice chemotherapy of vinflunine, paclitaxel or docetaxel, in patients who have progressed

on prior chemotherapy. Study results are anticipated in 2017. The 1L IMvigor 130 study (NCT02807636) investigates atezolizumab with or without gemcitabine + carboplatin, compared to gemcitabine + carboplatin. Results are anticipated in 2020. These studies will provide comparative data for atezolizumab vs. treatments relevant to clinical practice in England and Wales.

These on-going studies include key outcomes of interest for cost-utility analysis – OS, PFS, time on treatment, response rates, adverse effects of treatment and health-related quality of life (HRQoL). Both studies collect HRQoL directly from atezolizumab treated patients, in the form of the EQ5D health questionnaire.

Table 1: Clinical development programme for atezolizumab in mUC

Study name	Atezolizumab arm(s)	Comparator	Data availability
IMVigor211	Atezolizumab 1200mg	Investigator choice vinflunine, docetaxel or paclitaxel	2017
IMvigor 130	Atezolizumab 1200mg	Gemcitabine + carboplatin	2020
	Atezolizumab 1200mg with gemcitabine + carboplatin		

Anticipated role of atezolizumab in English clinical practice

There is a high unmet need in the treatment of mUC due to the lack of effective and tolerable therapies. Atezolizumab offers significant clinical promise, and is anticipated to provide a step change in the management of UC. As such, it is expected that atezolizumab would be used in both patient populations, should NICE recommend it for use in mUC.

Indirect treatment comparison

The clinical promise atezolizumab offers patients with mUC, coupled with the high therapeutic need and limited efficacy of existing treatments, has allowed regulatory filing to be based on a single arm, phase II clinical trial. This provides the opportunity for earlier patient access to this innovative treatment option. However, the limitation of this accelerated regulatory approval is non-availability of comparative data, which will be provided by ongoing comparative trials. This is particularly challenging for decision analysis, in which the incremental benefit of therapies vs. standard of care is the basis of decision making.

A consequence of the limited therapeutic research in mUC is a lack of controlled trial evidence for the current standards of care, used as comparators in this appraisal. This adds additional challenge when comparing these mostly single arm studies to the single arm evidence for atezolizumab, as well as when extrapolating these data to a life-time horizon.

Until such time as controlled, phase III data are available, in order to conduct cost-effectiveness analysis it was necessary to compare to comparators via an indirect treatment comparison. With single arm studies, a connected network was not available. Rather than conduct naïve comparisons of treatment arms across studies, a prediction model was built, which adjusted for key prognostic factors in the study populations. This allowed a connected network to be built, and network meta-analysis was conducted.

Cost effectiveness analysis

A cost-utility analysis was conducted to determine the cost-effectiveness of atezolizumab in mUC as compared to the standard of care. For patients who are cisplatin ineligible (1L), the relevant comparator is gemcitabine + carboplatin. For patients having failed prior chemotherapy (2L), paclitaxel is the most relevant comparator in England. Additional comparators docetaxel and BSC were also included in the 2L setting.

A three-state partitioned survival model was built, with a 20 year time horizon. Clinical inputs for the model were derived from IMvigor 210, and the results of the indirect treatment comparison. The model takes the perspective of NHS England,

and is consistent with the NICE reference case and broadly consistent with the final scope of the appraisal.

Utility data are not available from the IMvigor 210 study. Data will become available with the phase III studies. Until these data are available, it was necessary to use utility values from prior mUC HTA appraisals.

The base-case incremental cost-effectiveness ratios (ICERs) comparing first line treatment of atezolizumab to gemcitabine + carboplatin, is £44,158. ICERs in second line are £131,579 versus docetaxel, £104,850 versus paclitaxel and £98,208 versus BSC.

Cancer Drugs Fund

Atezolizumab is an innovative treatment option in mUC. In June 2014, the United States Food and Drug Administration (FDA) recognised the potential of atezolizumab in mUC by granting it “breakthrough therapy designation” (FDA, 2016). In the UK, the MHRA awarded atezolizumab “Promising Innovative Medicine” (PIM) status in April 2016; a positive opinion for an Early Access to Medicine Scheme (EAMS) is anticipated in January 2017.

Whilst the IMvigor 210 study demonstrates the clinical benefit of atezolizumab in mUC patients, Roche recognises the current evidence base makes certainty in decision analysis challenging. Compounding this is the extremely weak evidence base for existing treatments in mUC, with a paucity of comparative trials. This creates challenges for the accurate estimation of the treatment effect of comparators, and subsequently determining the relative efficacy to atezolizumab.

The lack of clinical research in mUC extends to HRQoL and utility research. There are few quantitative data relating specifically to the impact of the disease and its symptoms on patients’ quality of life. Sensitivity analyses demonstrated that patient utility is a driver of the atezolizumab economic model.

Much of this uncertainty will be resolved with the availability of controlled, phase III trials. The atezolizumab clinical development programme in mUC includes 2 phase III studies, as described in (Clinicaltrials.gov, 2016b, Clinicaltrials.gov, 2016a).

These studies will provide comparative evidence (vs. relevant comparators) in both atezolizumab mUC treatment populations considered in this submission: 2L and 1L cisplatin ineligible patients In addition, these trials will also provide evidence on HRQoL outcomes for atezolizumab and comparators, reducing the requirement for assumptions in any future cost-utility analysis.

In light of the clinical promise of atezolizumab, and the desire for effective treatment options in clinical practice, Roche proposes atezolizumab be made available for patients via the Cancer Drugs Fund. This interim funding solution will provide patients access to this important new medicine until availability of phase III clinical trial data, which will resolve the most significant uncertainties. Roche do not propose collection of data additional to that which will become available from the existing phase III studies.

Advice sought from NICE confirmed no additional details regarding data collection or proposed Commercial Access Agreements are required within this submission dossier; we understand these will be subject to ongoing discussions, should NICE recommend atezolizumab for use within the Cancer Drugs Fund.

External Expert Input

Expert clinical advisory panel

An expert advisory board was convened to provide feedback on the appraisal compartors, model structure, OS extrapolation methodology and clinical plausibility of results, resource use and utility inputs. The panel consisted of consultant oncologists specialising in the management of patients with mUC, many of whom have experience of atezolizumab from clinical trials. The panel was selected based on their significant clinical and research experience.

Twelve expert clinical advisors were consulted, including four Professors. At the one-day meeting, invited experts were briefed on the economic model structure and sources of key data inputs; their comments were recorded and taken into account in the subsequent development of the model.

Expert Health Economist advisory panel

A panel of experienced health economists and clinicians (both UK and non-UK based) were consulted during the development and validation of the economic model, most recently at a one-day meeting in November 2016. Feedback was requested on the potential approaches to the assessment, including specific focus on the methodology used in comparison of single-arm clinical trials.

1.1 Statement of decision problem

The appraisal is consistent with the reference-case and broadly in-line with the final NICE scope.

Not all comparators in the final scope have been included within the submission. The approach to comparators taken in the appraisal has been ratified by the previously described expert clinical advisor panel, and is described below.

First-Line (1L) cisplatin ineligible patients

Comparators included in the final appraisal scope for 1L were: gemcitabine plus carboplatin, or best supportive care (BSC). Expert advice confirmed all mUC patients who are willing and able to receive therapy, would receive a 1L treatment option. Those patients receiving BSC are unable, or unwilling to receive any active treatments, and represent a small minority. As such, these patients would also be unable or unwilling to receive atezolizumab. BSC has never been assessed as part of a clinical trial in the first line setting, meaning it is also not possible to conduct any comparison for atezolizumab to BSC as 1L options in cisplatin-ineligible patients.

Second Line (2L+)

Expert clinical advisors confirmed paclitaxel is the most relevant comparator for 2nd line (or more) treatment of mUC in England and Wales. This is consistent with London Cancer Alliance guidelines, and is also reflected by recruitment of patients into the IMvigor 211 study. This study includes pre-specified investigator chemotherapy choice for the control arm. Taxane choice for patients recruited from the UK is heavily weighted towards paclitaxel [redacted] vs. docetaxel [redacted]

The appraisal scope separates 2L patients into those eligible, and those ineligible, for cisplatin. However, expert advisors confirmed the comparators for these 2 populations are consistent: docetaxel, paclitaxel and BSC. The treatment patterns and response rates are not anticipated to be different for patients based on their eligibility for cisplatin and receiving 2L treatment. As such these 2 populations are combined into a 2nd line or more (2L+) cohort within the appraisal submission.

Both 2L populations listed in the scope include the comparator ‘Retreatment with 1st line chemotherapy (only for people whose disease has had an adequate response)’. Expert clinical advice confirmed this is an option only for a very small proportion of patients, and is not considered standard of care within England. Additionally this treatment option has not been the subject of a systematic clinical evaluation. As such this is not included as a comparator in the appraisal.

1.1.1 The decision problem

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with locally advanced or metastatic urothelial carcinoma: • Whose disease has progressed after prior chemotherapy • For whom cisplatin-based chemotherapy is unsuitable	Adults with locally advanced or metastatic urothelial carcinoma: • Whose disease has progressed after prior chemotherapy • For whom cisplatin-based chemotherapy is unsuitable	n/a
Intervention	Atezolizumab	Atezolizumab	n/a
Comparator (s)	1. People with locally advanced or metastatic urothelial carcinoma for whom cisplatin-based chemotherapy is unsuitable: • Gemcitabine plus carboplatin • Best supportive care 2. People whose disease has progressed after platinum-based chemotherapy: • Retreatment with 1st line platinum-based chemotherapy (only for people whose disease has had an adequate response) • Docetaxel • Paclitaxel • Best supportive care 3. People for whom cisplatin-based chemotherapy is unsuitable, and whose disease has progressed after platinum-based therapy: • Retreatment with 1st line platinum-	1. People with locally advanced or metastatic urothelial carcinoma for whom cisplatin-based chemotherapy is unsuitable: • Gemcitabine plus carboplatin 2. People whose disease has progressed after platinum-based chemotherapy; or people for whom cisplatin-based chemotherapy is unsuitable, and whose disease has progressed after platinum-based therapy: • Docetaxel • Paclitaxel • Best supportive care	Expert advice received from clinicians managing the treatment of UK mUC patients confirmed the comparators addressed in the submission represent current clinical practice in England and Wales. The excluded comparators have not been subject to systematic clinical evaluation of patient outcomes in their respective populations.

	based chemotherapy (only for people whose disease has had an adequate response) • Docetaxel • Paclitaxel • Best supportive care		
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	n/a
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for comparator technologies will be taken into account.	As per reference case	n/a
Subgroups to be considered	None identified	None identified	n/a
Special considerations including issues related to equity or equality	None identified	None identified	n/a

1.2 Description of the technology being appraised

Table 3: Technology being appraised

UK approved name and brand name	Atezolizumab. EMA and FDA approved brand name: Tecentriq®
Marketing authorisation/CE mark status	EMA, centralised procedure, full submission made. Awaiting CHMP opinion
Indications and any restriction(s) as described in the summary of product characteristics	Anticipated marketing authorisation: *Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible* The initial Marketing Authorisation Application also seeks approval for use of atezolizumab in the following indication: *Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy [NICE ID 970].*
Method of administration and dosage	1,200 mg administered intravenously every three weeks. Initial dose is administered over 60 minutes. If tolerated all subsequent infusions may be administered over 30 minutes It is recommended patients are treated with atezolizumab until loss of clinical benefit, or unmanageable toxicity.

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FDA, Food and Drug Adminstration; NICE, National Institute for Health and Care Excellence

1.3 Summary of the clinical effectiveness analysis

Evidence for the clinical effectiveness and safety profile associated with the use of atezolizumab has been demonstrated with a large phase II trial, with supportive evidence from a phase I study. There are two ongoing phase III trials.

IMvigor210 is a multicentre, single arm, Phase II trial examining the effectiveness of atezolizumab at a dose of 1200mg intravenously administered every 3 weeks in two cohorts of patients with inoperable locally advanced or mUC; those unfit for platinum-based chemotherapy (n=119, cohort 1) and those previously treated with platinum-based chemotherapy (n=310, cohort 2) . The primary analysis for objective response rates (ORR) in cohort 2 was on the 5th May 2015, and for cohort 1 on the 14th September 2015; the most recent data cut-off in both cohorts is 4th July 2016.

For patients in cohort 1 at the July 2016 data-cut (15-month follow-up), ORR was 22.7% (95% CI: 15.52, 31.27) in all comer patients, with 19 of 27 (70%) responses ongoing (Balar et al., 2016b). After 17.2 month median follow-up duration, the median PFS was 2.7 months (95% CI 2.1–4.2) in all patients (Balar et al., 2016b) and the median OS was 15·9 months (95% CI, 10.4 to NE) (Balar et al., 2016b). The adverse event profile was similar to those seen with other immunotherapy treatments, with treatment-related Grade 3-4 AEs reported in 16.0% of patients, the most common of which (≥ 2.5%) were fatigue, ALT increased, and AST increased (Balar et al., 2016b).

Patients in cohort 2 experieced an ORR at the July 2016 datacut (20-month follow-up) of 15.8% (95% CI: 11.9–20.4) (Balar et al., 2016b). PFS was similar across cohorts at 2.1 months (95% CI 2.1,2.1) (F. Hoffmann-La Roche Ltd, 2016b). Median OS was 7.9 months (95% CI 6.7-9.3), with a 12 month OS rate of 36.9% (31.4-42.0) (Loriot et al., 2016).

Treatment-related Grade 3-4 AEs were reported in 18.1% of patients, the most common of which (≥ 1.0%) were fatigue, ALT increase, AST increase, hypertension, lymphocyte count decrease, and pneumonitis (F. Hoffmann-La Roche Ltd, 2016b). There were no treatment-related Grade 3-4 AEs reported at a rate of ≥2.5% in cohort 2.

The responses observed in IMvigor 210 represent significant improvements as compared to current available therapies for locally advanced and mUC patients. Atezolizumab presents a favourable benefit-risk profile, when considered against historical controls (single agent chemotherapy) in a population with a high unmet medical need. Durable responses were observed with atezolizumab, including subsets of heavily pre-treated patient populations with pre-defined poor prognostic factors. It is this durability of response, already seen with immunotherapies for other cancers such as melanoma, but not with conventional treatments for UC, that marks out atezolizumab as a step-change in the treatment of this disease.

An indirect treatment comparison (ITC) was required for comparison to all comparators. With single arm studies, a connected network was not available. Rather than conduct naïve comparisons of treatment arms across studies, a

prediction model was built, which adjusted for key prognostic factors in the study populations. This allowed a connected network to be built. As proportional hazards are likely to be violated with the availability of comparative data for atezolizumab in mUC, a fractional polynomial network meta-analysis (NMA) was conducted. This accounts for varying hazard over time, and does not assume proportionality between arms.

An extremely small number of studies provide evidence for PFS and OS within the NMA, those studies being of limited size and quality. Results of the ITC are therefore subject to uncertainty, given the limitations of data feeding into the NMA.

1.4 Summary of the cost-effectiveness analysis

The cost-utility analysis was implemented in line with the reference case, to determine the incremental-cost-effectiveness-ratio (ICER) for atezolizumab in mUC, as compared to standards of care in current clinical practice. Two de novo models were developed to evaluate the cost-effectiveness of atezolizumab as: a 1L treatment in cisplatin-ineligible patients, and; a 2L treatment after prior chemotherapy. Three-state partitioned survival models were built, and included health-states for progression-free-survival, progressed disease and death. A 20 year time horizon was used to capture life-time costs and benefits, with discounting applied at 3.5% for costs and effects.

Clinical inputs for the model were derived from IMvigor 210 for atezolizumab, and the results of the ITC for comparators. Incorporation of the ITC results into the economic analysis was challenging, with the analysis projecting clinically implausible PFS and OS estimates. The adjustments made to avoid these scenarios may overestimate the treatment effect for comparators. This uncertainty is largely a result of the evidence base available at time of submission, which is limited to single arm studies. This uncertainty will be resolved with the availability of controlled phase III data.

The model expressed treatment effect in QALYs. Costs for all therapies included drug cost, administration cost, resource use, and adverse event management. Time-to-treatment discontinuation data were available for atezolizumab. For comparators these data were not publicly available, as such PFS was used as a

proxy for treatment duration, consistent with the approach used in other oncology appraisals.

Atezolizumab provided 3.74 life-years in 1L, an increase of 1.91 compared to gemcitabine + carboplatin. In 2L, atezolizumab was projected to provide 1.69 life-years, an additional 0.73 as compared to paclitaxel – the most relevant 2L comparator for English clinical practice. Despite the conservative approach employed for the assessment of comparative effectiveness, these results demonstrate the significant survival benefit that atezolizumab is expected to provide over current treatment options.

In 1L, atezolizumab provides an incremental gain of 1.34 QALYs over gemcitabine + carboplatin. In 2L, 0.53 QALYs are gained over paclitaxel. In the absence of robust HRQoL data in mUC, the utility values for all therapies were assumed equal whilst patients are on treatment. This is a conservative approach, as it does not account for the expected disutility associated with the tolerability profile of chemotherapy. The utility value for patients' off-treatment was identical regardless of their allocated treatment prior to discontinuation. As such, any QALY gain provided by atezolizumab over comparators is derived from extending time in PFS or extending patient life.

The base-case incremental cost-effectiveness ratios (ICERs) comparing first line treatment of atezolizumab to gemcitabine + carboplatin, is £44,158 (Table 4). ICERs in second line are £131,579 versus docetaxel, £104,850 versus paclitaxel and £98,208 versus BSC (Table 5).

Executive Summary Conclusion

Atezolizumab has proven clinical benefit over historical controls, and is anticipated to provide significant benefit over currently available therapies. Critically, for responding patients, it delivers the type of long-lasting disease remissions not seen with conventional therapy for mUC but increasingly seen as typifying effective immunotherapies, such as those recently approved by NICE for the treatment of melanoma and lung cancer. This hypothesis will be fully resolved with availability of phase III data in 2017 for 2L and 2020 for 1L. However, due to data limitations on

the current evidence for atezolizumab and relevant comparators, the cost-utility analysis is uncertain for relative treatment effects, and utility of patients with mUC. Considering the high unmet need, and clinical promise of atezolizumab, Roche proposes atezolizumab should be available for mUC patients via the Cancer Drugs Fund. This interim funding solution will provide patients access to this important new medicine until availability of phase III clinical trial data, which will resolve the most significant uncertainties.

Table 4: Incremental cost-effectiveness results (1L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£77,211	3.74	2.69				
Gemcitabine + carboplatin	£18,106	1.84	1.35	£59,106	1.91	1.34	£44,158
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 5: Incremental cost-effectiveness results (2L+)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£71,868	1.69	1.23				
Docetaxel	£9,439	1.04	0.76	£62,430	0.65	0.47	£131,579
Paclitaxel	£16,606	0.96	0.71	£55,262	0.73	0.53	£104,850
BSC	£4,836	0.75	0.55	£67,032	0.94	0.68	£98,208
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

2 The technology

2.1 Description of the technology

Brand name: Tecentriq®

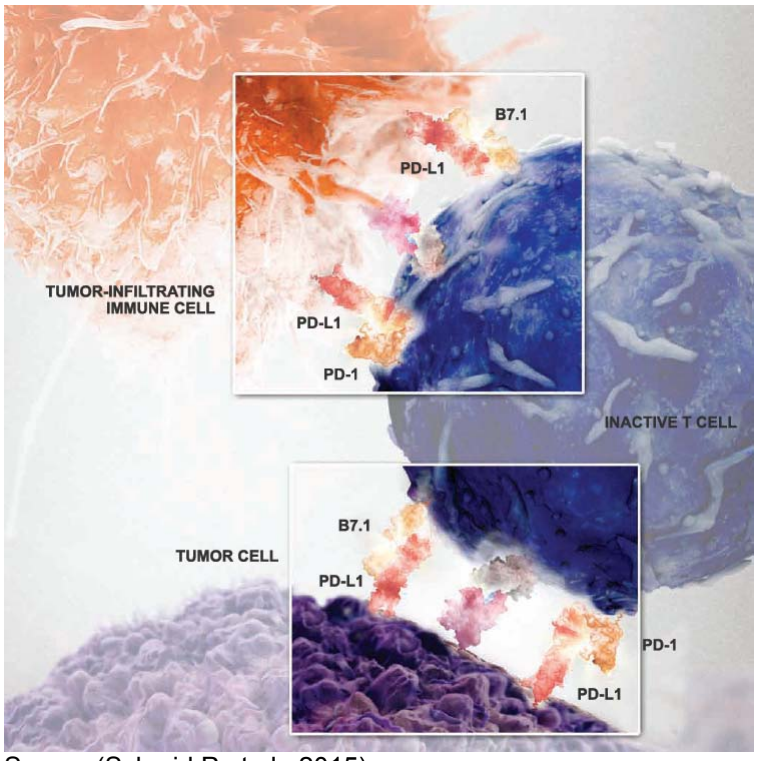
Generic name: atezolizumab

Therapeutic class: anatomical therapeutic chemical (ATC) code: not yet confirmed

Overview of atezolizumab: Atezolizumab is a monoclonal antibody that binds to and inactivates a protein called programmed death ligand 1 (PD-L1), which leads to downstream activation of T cells that can detect and attack tumour cells (F. Hoffmann-La Roche Ltd, 2016a)

PD-L1 is an immune checkpoint protein expressed on both tumour cells (TC) and tumour-infiltrating immune cells (IC) (Meng et al., 2015). PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1) to inhibit T-cell proliferation, cytokine production and cytolytic activity and thus restrict tumour cell killing (Chen and Mellman, 2013, Herbst et al., 2014, Schmid P et al., 2015).

Figure 1: PD-L1 is expressed on tumour cells



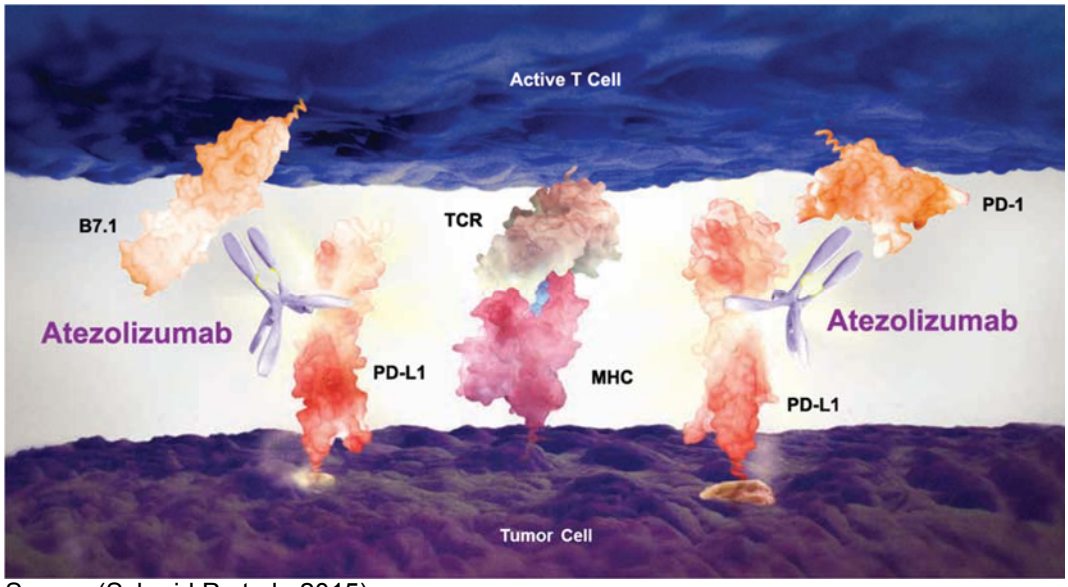
Source:(Schmid P et al., 2015)

Overexpression of PD-L1 in tumour cells has been associated with poor prognosis in patients with several cancers (Thompson et al., 2006, Hamanishi et al., 2007, Hino et al., 2010, Mu et al., 2011). Therefore interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway represents an attractive strategy for anti-tumour response (Chen and Mellman, 2013, Ohaegbulam et al., 2015).

Programmed death-ligand 2 (PD-L2) is an alternative ligand that can bind to PD-1 if PD-L1 is inhibited (Herbst et al., 2014). Based on this, targeting PD-L1 rather than targeting PD-1 preserves the PD-L2/PD-1 interaction, and potentially avoids autoimmune reactions in healthy tissue (Harshman et al., 2014).

Atezolizumab is a humanised IgG1 monoclonal antibody which binds directly and selectively to PD-L1 on the surface of TC and IC, preventing it from binding to PD-1 and B7.1 (Inman et al., 2016). This prevents down-regulation of T-cell activity while allowing for the priming of new T cells. Atezolizumab does not cause antibody-dependent cell-mediated cytotoxicity (ADCC) as it is FcγR-binding deficient, therefore it cannot bind to Fc receptors on phagocytes (Herbst et al., 2014, Inman et al., 2016). This is important because PD-L1 is heavily-expressed by T cells and other leukocytes and binding of a monoclonal antibody to their cell membrane could result in ADCC-mediated depletion of tumor-specific T cells; an event which could worsen antitumor immunity rather than improving it(Inman et al., 2016).

Figure 2: Mechanism of action of atezolizumab – atezolizumab inhibits binding of PD-L1 to PD-1 and B7.1



Source:(Schmid P et al., 2015)

2.2 Marketing authorisation/CE marking and health technology assessment

An application for EU Marketing Authorisation was made for Atezolizumab on 20th April 2016. Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in [redacted], with regulatory approval expected in [redacted].

Indication wording has been submitted; however this may be modified following comments from the CHMP:

- Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible
- Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy

The draft SmPC is included in appendix 8.1. As noted in the draft summary of product characteristics (SmPC), this medicine will be contraindicated to people who demonstrate hypersensitivity to atezolizumab or to any of the excipients below:

- L-Histidine
- Glacial Acetic Acid
- Sucrose
- Polysorbate 20
- Water for injections

The CHMP opinion has not yet been received, therefore the European Public Assessment Report (EPAR) is not available. As such, information regarding key regulatory issues, or special conditions of marketing authorisation is not yet available.

2.2.1 Current availability of atezolizumab

Atezolizumab will be routinely available once Marketing Authorisation is received.

Atezolizumab is anticipated to be available in the UK under an Early Access to Medicines Scheme (EAMS), by February 2017. The EAMS indication is: "Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma treated with a single chemotherapy regimen for inoperable, locally advanced or metastatic disease". Access for new patients via the EAMS will cease once marketing authorisation is received.

On 18th May 2016, atezolizumab was given accelerated Food and Drug Administration (FDA) approval in the U.S. for patients with locally advanced or metastatic UC whose disease has worsened during or following platinum-containing chemotherapy, or within 12 months of receiving platinum chemotherapy either before (neoadjuvant) or after (adjuvant) surgical treatment (U.S. Food & Drug Administration, 2016).

Atezolizumab in mUC has also received regulatory approval in Kuwait and South Korea.

2.2.2 HTA for atezolizumab

The National Institute for Health and Care Excellence (NICE) health technology assessment (HTA) submission for atezolizumab in non-small cell lung cancer will be submitted on 16th February 2017 (ID970).

It is anticipated submissions will be made for both indications to the Scottish Medicines Consortium (SMC). Timelines will follow the usual SMC process.

2.3 Administration and costs of the technology

Please see Table 6 below for details of administration and costs for atezolizumab.

Table 6: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate). Clear, colourless to slightly yellowish liquid. One vial of 20ml concentrate contains 1,200 mg atezolizumab, corresponding to a concentration before dilution of 60 mg/mL.	Draft SmPC
Acquisition cost (excluding VAT) *	The list price for atezolizumab is not yet confirmed with the Department of Health. The proposed list price for atezolizumab is £3807.69 per 1200mg vial	Draft SmPC
Method of administration	Intravenous infusion Administered over 60 minutes for initial infusion. . If tolerated subsequent infusions may be administered over 30 minutes.	Draft SmPC
Doses	1200mg	Draft SmPC
Dosing frequency	Every 3 weeks	Draft SmPC
Average length of a course of treatment	It is recommended patients remain on treatment until loss of clinical benefit or unmanageable toxicity.	Draft SmPC
Average cost of a course of treatment	The proposed list price for atezolizumab results in a cost per cycle of £3807.69	Draft SmPC
Anticipated average interval between courses of treatments	Atezolizumab is administrated once every 3 weeks, until loss of clinical benefit	Draft SmPC
Anticipated number of repeat courses of treatments	Patients should remain on treatment until loss of clinical benefit	Draft SmPC
Dose adjustments	Decision on dose adjustments for management of adverse events is at the prescriber discretion. Dose modification advice for specified Adverse Drug Reactions are available within the draft SmPC.	Draft SmPC
Anticipated care setting	Atezolizumab must be administered under the supervision of a qualified healthcare professional.	Draft SmPC

SmPC, summary of product characteristics

2.4 Changes in service provision and management

No negative service impact is anticipated through introduction of atezolizumab as a treatment option in England and Wales.

The anticipated indication for atezolizumab is for the treatment of patients with mUC. It will enter the treatment pathway at a point which patients have received their full

diagnosis and associated tests, and no additional tests are required to initiate atezolizumab treatment. Therefore, the addition of atezolizumab as a treatment option for these patients is not considered an additional cost or resource burden regarding investigations or tests.

Treatment with atezolizumab should only be initiated and supervised by qualified healthcare professionals. As such it is anticipated treatment will be in specialist secondary, or tertiary care centres only. Current therapies available for patients are administered via IV infusion, by qualified healthcare professionals. The atezolizumab SmPC does not specify any additional monitoring which may be required during treatment, as compared to the current standard of care. Monitoring and dose delays may be required to manage certain adverse events. However this is not considered additional resource as compared to established clinical practice in England and Wales, where the current standard of care – cytotoxic chemotherapy – is associated with significant morbidity and some treatment related mortality.

2.5 Innovation

Targeting T cell receptors to modulate the immune response and target cancers has been gaining momentum over recent years, starting with Cytotoxic-T-lymphocyte-associated antigen (CTLA)-4 inhibition, for which ipilimumab is indicated in advanced melanoma(Bristol Myers Squibb, 2016). More recently PD-1 inhibition is indicated in advanced melanoma, advanced non-small cell lung cancer (NSCLC), advanced renal cancer and classical Hodgkin lymphoma(Bristol Myers Squibb, 2017, Merck Sharp and Dohme, 2016). As the first drug developed within these T cell modulators, ipilimumab has the longest survival follow up, with 1,861 melanoma patients treated in a pooled analysis. The three year survival rate was 21% with an apparent plateau in the survival curve at three years, which extended up to 10 years in some patients (Schadendorf et al., 2015). This provides substantial credibility to the durability of such immunomodulatory mechanisms.

Many tumour types, including UC, express PD-L1 either on the tumour cells themselves or on immune cells that are infiltrating the tumour, and this is often associated with aggressive tumour behaviour(Inman et al., 2016, Nakanishi et al., 2007). The PD-1 receptor and its ligand, PD-L1, comprise one of the main immune

checkpoint pathways that downregulate immune activity (Inman et al., 2016). Rather than mistakenly recognising tumour cells as part of the normal human body and being deactivated when they come into contact with tumour cells via the PD-1-PD-L1 checkpoint, they remain active and detect, attack, and destroy tumour cells. By exposing tumour cells to the immune system and utilising the body's own immune system in this way, responses can be both complete and durable in some patients.

No such immunomodulatory therapies are yet available for UC. Atezolizumab is expected to be the first available in this indication, and inhibits PD-L1, the ligand within the PD-1-PD-L1 checkpoint. This is distinct from PD-1 inhibition which is thought to block the interaction with both PD-L1 and PD-L2. In contrast, PD-L1 binds not only to PD-1 but also to B7.1, another T cell costimulatory molecule, whilst not binding to PD-L2. These additional interactions are thought to have additional anti-tumour activity. The B7.1 appears to function uniquely to inhibit T cell responses, and so inhibition of B7.1 further augments the anti-tumour response (Butte et al., 2007). PD-L2 has been demonstrated in pre-clinical models to preferentially enhance T helper (TH)1 responses whilst allowing suppression of tumour-promoting TH2 responses. Theoretically, leaving this intact should further enhance the anti-tumour responses (Chen et al., 2012). These additional interactions may not be realised by targeting PD-1 alone (Chen et al., 2012).

In comparison to conventional chemotherapy, atezolizumab exploits evolutionary mechanisms which, once activated, can maintain responses in some patients. Recent chemotherapeutic advances in bladder cancer have only demonstrated gains in PFS, with no change in OS for these patients. As will be discussed further in Section 0, outcomes in UC have been generally poor with limited therapeutic options and poor quality of life for patients who progress to more advanced disease. Only two new drug treatments have become available for the treatment of advanced bladder cancer in the last two decades – in the first line gemcitabine plus cisplatin replaced the older MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen on the basis of better tolerability, although it improved neither overall or progression-free survival nor response rate(Sun Pharma, 2016). Whilst at second-line, vinflunine was approved in 2009 despite its failure to improve OS compared with supportive care alone, and was subsequently not recommended for use by

NICE(Pierre Fabre Ltd, 2015, National Institute for Health and Care Excellence, 2013). The approval of these two agents by the EMA on the basis of modest benefits is indicative of the extent of the unmet therapeutic need in this area. In comparison, and as demonstrated with earlier immunomodulatory agents in other cancers, early trials already demonstrate promising survival gains, with atezolizumab represents a step change in the management of bladder cancer.

In June 2014, the United States FDA recognised the potential of atezolizumab in this area by granting it “breakthrough therapy designation” for the treatment of patients previously treated for mUC who are PD-L1 positive (FDA, 2016). This designation is granted to potential new drugs for serious or life-threatening disease where early clinical evidence suggests the drug may demonstrate substantial improvement compared with existing therapies, and was created to expedite development and review time of these therapies.

In the UK the MHRA awarded atezolizumab “Promising Innovative Medicine” (PIM) status in April 2016, and by February 2017 positive opinion for an Early Access to Medicine Scheme (EAMS) is anticipated to be received. The EAMS will be conducted for atezolizumab in “the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after disease progression following one prior platinum-containing chemotherapy regimen regardless of its setting (neoadjuvant, adjuvant, or metastatic)” indicating that they felt the treatment offered significant advantages over existing treatment options in an area of high unmet therapeutic need.

Observing only the end-points traditionally used in oncology trials (ORR, PFS), immunotherapy advantages over traditional chemotherapy may appear modest. However, in those patients who develop a response, these responses are demonstrating durability, with the potential for long-term survival. Durable responses have been observed with atezolizumab in UC, including subsets of heavily pre-treated with pre-defined poor prognostic factors, who in the phase I trial have demonstrated a 2 year OS rate of 30.3%.(F. Hoffmann-La Roche Ltd, 2014) As a class of drugs, immunotherapies have been recognised to demonstrate ongoing

survival advantages to patients which have been considerably higher than historical standards with chemotherapy.

Atezolizumab represents a new paradigm in cancer treatments in mUC. As the first immunotherapy in mUC, atezolizumab represents a clinically significant innovative therapeutic option for the treatment of patients, which will provide significant positive impact on patients' lives.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease Background

Bladder cancer is the tenth most common cancer in the UK. In 2014, there were 10,063 new cases of bladder cancer in the UK, and 5,369 deaths were attributable to bladder cancer (CRUK, 2017a) (CRUK, 2017b). The most common subtype is urothelial carcinoma (UC) (90%), the majority of the remainder being squamous cell bladder cancer (5%) and adenocarcinoma of the bladder (1-2%) (CRUK, 2017d). Patients are classified according to the stage of disease; early non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC) or metastatic cancer.

Urothelial carcinoma – historically more commonly termed transitional cell carcinoma (TCC) – describes cancer deriving from the cells which line the bladder wall and the ureters. The bladder is the predominant location for UC, but tumours can also originate in the renal pelvis, urethra, or ureter, which are also lined by urothelial cells.

There are a number of well-known risk factors for bladder cancer, including increasing age, smoking, and some industrial chemicals(Burger et al., 2013, Ploeg et al., 2009). Bladder cancer is primarily a disease of the elderly, with around half of all new cases of bladder cancer occurring in people aged 75 and over (CRUK, 2017c). Since the 1970's it is reported that the incidence of bladder cancer has decreased by 27% in the UK (CRUK, 2017a), a trend mirrored across Western countries and thought to be attributable to the changing habits of cigarette smoking, and a reduction in exposure to industrial chemicals (Ploeg et al., 2009).

3.2 Course and prognosis

The most common early symptom of bladder cancer is haematuria, which is experienced by approximately 80% of people with bladder cancer (Mullassery, 2010). Other symptoms include increased frequency and urgency of urination and pain when passing urine. Because these symptoms are usually highly visible to the patient themselves, patients will often present early to the healthcare services, which means that bladder cancer is often diagnosed early (Kaufman et al., 2009, American Cancer Society, 2015).

Most patients presenting with bladder cancer will be diagnosed initially with NMIBC, cancer that involves the urothelium, or the connective tissue layer (lamina propria) that connects the surface lining to the main muscle coat. This form is highly treatable, but has a high risk of recurrence (National Collaborating Centre for Cancer, 2015 , Kaufman et al., 2009). Up to 45% of patients with NMIBC will eventually progress to MIBC (Sylvester et al., 2006), and 20–50% of patients with MIBC will eventually progress to metastatic disease (Feifer et al., 2011, Mak et al., 2014, Millikan et al., 2001).

Global data suggests the 5 year survival rate for localised NMIBC is 69%, dropping to 34% for those with regional spread, and 6% for metastatic disease (Howlader et al., 2011). Metastatic disease remains incurable with currently available therapies. The average life expectancy for mUC is 14-15 months in patients who are suitable for optimum systemic treatment and 8 months without treatment(Guancial et al., 2015, Sonpavde et al., 2010). This submission concerns the use of atezolizumab in locally advanced and metastatic disease.

3.3 Burden of illness

Symptoms at the time of diagnosis have been discussed earlier in this section. Ongoing symptoms related to bladder cancer can occur in some patients, the most significant of which include bleeding from the bladder and pain at the site of the primary tumour, or sites of metastatic disease. In addition, increased frequency and urgency of urination and pain when passing urine can also occur.

There is limited quantitative information relating specifically to the impact of the disease and its symptoms on patients' quality of life (QoL), as opposed to the impact of interventions, especially surgical interventions in the earlier disease setting. In addition, there is no single QoL tool that is used preferentially in bladder cancer (Gerharz et al., 2005).

In a prospective study of 60 genitourinary cancer patients, bladder cancer sufferers were found to have the highest depression and anxiety levels (Rispoli et al., 2005). In addition, the advanced age of many patients means they often have multiple comorbidities and pre-existing impairments of activities of daily living which can have an impact on treatment decisions (Guancial et al., 2015). For those patients who have progressed from earlier stages of disease, these symptoms are often superimposed on the long term issues arising from surgical interventions such as cystectomy. 20-50% of these patients will progress to metastatic disease despite these interventions (Feifer et al., 2011, Mak et al., 2014, Millikan et al., 2001).

For those patients who have disease which progresses despite available treatments (including chemotherapy in the metastatic setting), intractable bleeding from the bladder is one of the most serious terminal complications for patients with bladder cancer. This can be difficult to manage, and may require hospitalisation for ongoing management. Patients with severe haematuria are often elderly and already extremely frail (National Collaborating Centre for Cancer, 2015).

In summary, there is a paucity of data demonstrating the impact of mUC and their treatments, especially in the metastatic setting, on quality of life

3.4 Unmet medical need

The lack of tolerable and effective treatment options for patients with mUC, and especially of approved options offering any proven survival benefit in the second line setting, is widely recognised.

3.4.1 Untreated metastatic disease

In the metastatic setting, the mainstay of treatment is chemotherapeutic regimens. These will be discussed in more detail in section 3.5 but are not universally applicable to all UC patients. It is widely recognised only 50% of patients are eligible

for cisplatin based doublet chemotherapy, which is considered to be the standard of care for first line therapy. UC is largely a disease of the elderly and patients may be ineligible due to age- and disease-associated decline in their performance status, renal function, and other comorbidities including hearing loss. Smoking is recognised to be a risk factor for UC, often with additional co-morbidities, including pulmonary or cardiovascular disease, which leads to an accelerated deterioration in renal function (de Vos and de Wit, 2010). There has been recognition of this disconnect between the recommended treatments and the number of ineligible patients for some time, and although trials have been designed specifically for these patients 'unfit' for cisplatin based chemotherapy, there is still a high unmet need (Galsky et al., 2011). With current practice, these patients would typically receive carboplatin based chemotherapy regimens in the first line setting, with a median overall survival of 9.3 months (De Santis et al., 2012).

3.4.2 Relapsing metastatic disease

Regardless of whether they received cisplatin or carboplatin, nearly all patients experience disease progression after first-line chemotherapy and require second-line therapy. Vinflunine is the only approved therapy in the second line setting in the EU, although it has not been recommended for use in the NHS. It has not been shown to significantly improve overall survival compared with BSC alone. (National Institute for Health and Care Excellence, 2013). Since this time, no further advances in treatment have been made, and vinflunine remains the only licenced drug in this indication. No other strong evidence of benefit exists to guide treatment decisions in the second line setting (Witjes et al., 2014, Bellmunt et al., 2014).

There is a pressing need for improved treatments for mUC, particularly for untreated patients unable to receive cisplatin and universally in the second line setting.

3.5 Clinical pathway of care

3.5.1 A summary of first and second line treatments in mUC

First-line treatment

For patients who are fit enough, chemotherapy is the main treatment option for advanced or mUC. Metastatic UC is incurable with currently available treatments and the aim of chemotherapy in this context is to prolong life and palliate or alleviate symptoms (National Collaborating Centre for Cancer, 2015) . In the first-line setting for patients who are otherwise physically fit (ECOG-PS 0 or 1) and have adequate renal function (typically defined as a glomerular filtration rate [GFR] of 60 ml/min/1.73m2 or more), NICE recommend offering a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [dose-dense] methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] in combination with granulocyte-colony stimulating factor) (National Institute for Health and Care Excellence, 2015b). These recommendations are based on results from a randomised trial of gemcitabine + cisplatin vs MVAC in 405 patients with incurable locally advanced or metastatic bladder cancer. Median OS in the 1L setting was 14 months for gemcitabine + cisplatin vs 15.2 months for MVAC (hazard ratio [HR], 95% CI 1.09; 0.88-1.34). However, both regimens were characterized by high rates of grade 3-4 anaemia (27.1% vs 17.8%), thrombocytopenia (57.1% vs 20.8%) and neutropenia (70.9% vs 82.2%). In addition, neutropenic sepsis occurred in 11.9% of patients in the MVAC arm.

For patients not eligible for cisplatin, but who may benefit from systemic therapy, NICE recommends offering carboplatin in combination with gemcitabine. This is estimated to be up to 50% of patients in the first line setting (De Santis et al., 2009). Given the recognised need to establish a treatment standard in patient unfit for therapy with cisplatin, the EORTC Study 30986 was conducted. This was a randomised trial in 238 patients unfit for cisplatin-based chemotherapy, comparing the carboplatin based regimens; gemcitabine and carboplatin or methotrexate, carboplatin and vinblastine (M-CAVI)(De Santis et al., 2012). After a median of 4.5 years follow-up there were no differences in overall survival (9.3 months vs 8.1 months, HR 0.94, 95% CI 0.72 to 1.02) and progression-free survival (HR 1.04, 95%

CI 0.8 to 1.35) between the two treatments. Gemcitabine + carboplatin produced a lower rate of severe acute toxicity than M-CAVI (9% vs. 21%). There were no differences between treatments for changes in HRQoL from baseline to end of cycle 2, although mean scores were not reported and there was less than 50% completion rate after the baseline assessment. Gemcitabine + carboplatin became the recommended standard of care following this trial based mainly on its improved toxicity profile (De Santis et al., 2012). Regardless of treatment in the first line setting, most patients experience disease progression and may require second-line therapy, subject to eligibility (Bellmunt et al., 2013).

Second-line treatment

Vinflunine (a vinca alkaloid) is a single agent chemotherapy licensed for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen, and is the only medicine specifically approved in the EU in this disease setting. In the EU, vinflunine was approved on the basis of a single randomized Phase III study which compared vinflunine and BSC with BSC alone, in 370 patients with advanced UC, progressing after platinum-containing therapy (Bellmunt et al., 2009). In this trial, patients were only permitted one prior therapy for metastatic disease (2L patients only). The intent-to-treat (ITT) analysis showed an improvement in response rate (8.6% vs. 0%) but did not show a statistically significant OS benefit for vinflunine with BSC compared with BSC alone (6.9 vs. 4.6 months; HR = 0.88; 95% CI: 0.69, 1.12; p = 0.287). Key toxicities included Grade 3 or 4 neutropenia (50%), anaemia (19%), fatigue (19%) constipation (16%), nausea (2%), and vomiting (3%). It is not recommended by NICE (National Institute for Health and Care Excellence, 2013) as clinical effectiveness was not deemed to have been conclusively demonstrated and there were concerns over tolerability in this setting. Vinflunine is therefore not routinely used in clinical practice in the UK.

Since the vinflunine appraisal, NICE has published guidance on the diagnosis and management of bladder cancer (National Institute for Health and Care Excellence, 2015b). In its recommendations, the National Collaborating Centre for Cancer (NCCC) stated that management options for people who progress on or relapse after

first line treatment are controversial, and their prognosis is poor with median survival measured in a few months. Similar variability in second line practices were also noted by the ESMO Guidance Working Group (Bellmunt et al., 2014), and there is a wide variety of practice in whether to offer second line therapy to such people. Current opinion is that second line response rates are between 10-12%, regardless of the therapeutic agent used, and are often short lived (Pimlack, 2016). Additional consideration should be given to the toxicity of current treatments, so the overall clinical benefits of the available treatments are often questionable. The only evidence of second line practice in the UK comes from a survey, which represented 28 of the 42 main UK cancer centres treating UC. It shows a number of monotherapy agents being used in the second line, including docetaxel, and paclitaxel (Lamb et al., 2014) which our clinical advisors suggest are the most widely used agents in the UK, albeit based on a very limited evidence base.

3.5.2 Conclusion

Although multiple treatment options are available for earlier stages of bladder cancer which lead to positive treatment outcomes in many cases, advanced metastatic disease remains an area of extremely high unmet need. The characteristics of the population diagnosed with UC are such that there are a significant proportion of patients who are ineligible for the most effective first-line chemotherapy option of gemcitabine plus cisplatin, and for whom alternative treatment options are needed. In the second-line setting no treatment has been shown to improve survival. The only licensed agent, vinflunine, produces a median OS of 6.9 months, even in a selected population of patients. The limited evidence available for taxane monotherapy used in clinical practice suggests this approach is also of limited benefit. Internationally, the current opinion is that response rates to second line chemotherapies is between 10-12% (Pimlack, 2016). Overall, as suggested by the NCCC, there is an urgent need for novel therapies that deliver an improved therapeutic outcome for these patient groups.

3.5.3 Life expectancy, prevalence and incidence of the disease

In 2014, there were 10,063 new cases of bladder cancer in the UK, and 5,369 deaths were attributable to bladder cancer (CRUK, 2017a) (CRUK, 2017b).

Metastatic bladder cancer remains incurable with currently available therapies. The average life expectancy for mUC is 14 -15 months in the fittest patients who receive systemic cisplatin-based treatment and 8 months without treatment (Guancial et al., 2015, Sonpavde et al., 2010).

Survival is highly dependent on the stage of disease at diagnosis, as shown in Table 7. Prognostic factors for poor survival in patients with mUC include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status < 80%, and visceral metastasis (i.e., lung, liver, or bone) (Bajorin et al., 1999). The presence of any of these unfavourable features was associated with a median survival of 4 months, compared with 18 months in patients without these features (Loehrer et al., 1992). For the 4% of patients diagnosed with metastatic disease at initial diagnosis, global data suggests the 5-year survival rate is 6% (Howlader et al., 2011). Survival from the point of developing metastatic disease is similar for patients progressing from earlier disease stages and most individuals dying from bladder cancer do so from metastatic disease.

Table 7: Incidence and 5-year Survival Rates in Bladder Cancer (Howlader et al., 2011, Kaufman et al., 2009) (National Collaborating Centre for Cancer, 2015, Sharma et al., 2009, de Vos and de Wit, 2010, American Cancer Society, 2015)

<table>
<tr><th>Classification</th><th>Stage at diagnosis</th><th colspan="2">Proportion at diagnosis</th><th>5-year relative survival rate</th><th>Probability of recurrence within 5 years</th></tr>
<tr><td>Non-muscle-invasive disease</td><td>Non-invasive (Tis, Ta and T1)</td><td colspan="2">51–75%</td><td>96%</td><td>50–90%</td></tr>
<tr><td rowspan="2">Muscle-invasive disease</td><td>Localised (T2–4, N0)</td><td>35%</td><td rowspan="2">30%</td><td>69%</td><td rowspan="2">≈50%</td></tr>
<tr><td>Regional (Tx, N1)</td><td>7%</td><td>34%</td></tr>
<tr><td>Metastatic disease</td><td>Distant/metastatic (Tx, Nx, M1)</td><td colspan="2">4%</td><td>6%</td><td>NA</td></tr>
</table>

3.6 Clinical guidance and guidelines

NICE guidance:

- NICE guidelines
  - Bladder Cancer: Diagnosis and Management (NG2) (National Institute for Health and Care Excellence, 2015b)
  - Suspected Cancer: Recognition and Referral (NG12) (National Institute for Health and Care Excellence, 2016b)
- NICE Guidance on Cancer Services
  - Improving outcomes in urological cancers (CSG2) (National Institute for Clinical Excellence, 2002)
- NICE Interventional Procedures Guidance
  - Electrically-stimulated intravesical chemotherapy for superficial bladder cancer (IPG277) (National Institute for Health and Care Excellence, 2008)
  - Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer (IPG235) (National Institute for Health and Care Excellence, 2007)
  - Laparoscopic cystectomy (IPG287) (National Institute for Health and Care Excellence, 2009)
- NICE Quality Standards
  - Bladder Cancer (QS106) (National Institute for Health and Care Excellence, 2015a)
  - Suspected Cancer (QS124) (National Institute for Health and Care Excellence, 2016b)
- NICE Technology Appraisal Guidance
  - Vinflunine for the treatment of advanced or metastatic tranitional cell carcinoma of the urothelial tract (TA272) (National Institute for Health and Care Excellence, 2013)

Clinical guidelines:

There are also a number of clinical guidelines relating to bladder cancer management. Our UK clinical advisors suggested ESMO guidelines (Bellmunt et al., 2014) are not reflective of UK practice. The most applicable of these to UK practice are the European Association of Urology (EAU) guidelines (Stenzl et al., 2011).

3.7 Issues relating to current clinical practice

Table 8: Issues relating to current clinical practice

Treatment	Summary of key issues	Key references
Cisplatin-gemcitabine	• Toxicity associated with cisplatin treatment including neuropathy hearing loss, nausea and vomiting • Up to 50% of patients are not eligible for cisplatin based treatment	(Abida W, 2015, von der Maase et al., 2005, De Santis et al., 2009)
Carboplatin-gemcitabine	• Treatment toxicity including neuropathy, infection, low platelet counts, nausea and vomiting	(De Santis et al., 2009, De Santis et al., 2012)
Docetaxel	• No EU licence for this indication • No survival benefit	(electronic Medicines Compendium (eMC), 2016a, Lamb et al., 2014)
Paclitaxel	• No EU licence for this indication • No survival benefit	(electronic Medicines Compendium (eMC), 2016b, Lamb et al., 2014)
Vinflunine	• EU licence but not recommended by NICE • No survival benefit	(National Institute for Health and Care Excellence, 2013, Bellmunt et al., 2009, Bellmunt et al., 2013, Lamb et al., 2014)

NICE, National Institute for Care and Excellence

3.8 Assessment of equality issues

No equality issues related to the use of atezolizumab have been identified.

4 Clinical effectiveness

Summary of Clinical Effectiveness

- The clinical effectiveness of atezolizumab in advanced or metastatic UC has been studied in an open-label Phase II study and a supportive open-label Phase Ia study: IMvigor 210 and PCD4989g. Evidence from Phase III trials is expected in 2017 in the 2L setting, and in 2020 in 1L cisplatin-ineligble patients
- IMvigor 210 investigated the use of atezolizumab in two cohorts relevant to the scope of this appraisal:
  - Cohort 1: first-line patients unfit for cisplatin-based chemotherapy (n=119)
  - Cohort 2: patients whose disease has progressed during or following one or more lines of therapy, including at least one prior platinum-based chemotherapy regimen (n=310).
- The primary endpoint in both populations (ORR) identified a clinically meaningful improvement with atezolizumab, when considered vs. a historical ORR of 10% with existing treatment options:
  - Cohort 1: Patients treated with atezolizumab had an ORR per IRF (independent review facility) of 19.3% (95% CI: 12.66, 27.58) at the pre-planned primary analysis. At 17.2 months median follow-up duration, the ORR per IRF rose to 22.7% (95% CI: 15.52, 31.27).
  - Cohort 2: Patients treated with atezolizumab had an ORR per IRF of 15.1% (95% CI: 11.3, 19.6) at the pre-planned primary analysis. At 20-months follow-up, the ORR per IRF was 15.8% (95% CI: 11.9, 20.4).
- Earlier NICE appraisals have recognised the limitations of using ORR and PFS in the assessment of immunotherapies: OS and DOR are generally regarded as having greater value
  - DOR: median values not reached in either population (July 2016 datacut)
  - Median OS: cohort 1 = 15.9 months (95% CI, 10.4 to NE); cohort 2 = 7.9 months (95% CI, 6.7–9.3)
- Only single arm studies are currently available for atezolizumab and many of the comparators of interest.
- Derivation of comparative efficacy required the development of a prediction model using prognostic factors from IMvigor 210, effectively building an atezolizumab ‘arm’ into the comparator trials, allowing a NMA to be constructed for OS

4.1 Identification and selection of relevant studies

4.1.1 Search strategy overview]

A systematic literature review (SLR) was conducted between June and August 2016 to identify all relevant published and unpublished randomised controlled trial (RCT) and non-randomised controlled clinical trial (CCT) evidence relating to pharmacological treatments used in the indications for atezolizumab, i.e. locally advanced or mUC after prior chemotherapy (i.e. second-line, third-line, and subsequent lines), as well as first-line use in those patients who are considered cisplatin-ineligible.

The aim of this SLR was to identify studies eligible for an indirect comparison with atezolizumab in either of the two indications mentioned above. The atezolizumab registration study – NCT02108652 (IMvigor 210) – is a single-arm Phase II study, therefore RCTs, CCTs, and single-arm trials were considered. The SLR was not restricted to comparators only relevant for the UK (i.e. gemcitabine plus carboplatin in 1L cisplatin-ineligible patients and BSC, docetaxel and paclitaxel in 2L and subsequent lines), but comprised therapeutic classes and a broad range of potential comparators. The goal was to capture current and upcoming treatments for all markets in the relevant indications for atezolizumab.

4.1.2 Search strategy details

Table 9 contains details of the sources that were searched.

Table 9: List of sources used in the search strategy

Type of database	Database	Database provider	Date of search
Bibliographic	Medline (includes Medline in Process and other non-indexed citations (with status: publisher, in-data review or Pubmed-not-Medline)	DIMDI (Deutsches Institut für Medizinische Dokumentation und Information)	June 20, 2016
	Embase	Embase.com	June 20, 2016
	Cochrane Library (includes Cochrane Reviews, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials, Health Technology Assessment (HTA) Database, NHS Economic	Wiley – Cochrane Library	June 20, 2016

	Evaluation Database (NHSEED))		
Study registries	International Clinical Trials Registry Platform (ICTRP)	-	July 13, 2016
	EU Clinical Trial Register (https://www.clinicaltrialsregister.eu/)	-	July 6, 2016
	US National Institute of Health's (NIH) clinical trial registry (clinicaltrials.gov)	-	July 5, 2016
Conference abstracts (Event dates from 2015–2016)*	American Society of Clinical Oncology (ASCO)	-	July 25, 2016
	ASCO Genitourinary Cancers Symposium (ASCO-GU)	-	July 25, 2016
	Cancer Survivorship Symposium	-	July 25, 2016
	ASCO Annual Meeting	-	July 25, 2016
	European Society of Medical Oncology (ESMO) / European Cancer Congress (ECCO)	-	July 26 + July 29, 2016
	ESMO Symposium on Immuno-Oncology	-	July 29, 2016
	European Association of Urology (EAU)	-	July 28, 2016
	European Meeting on Urologic Cancers (EMUC)	-	July 25, 2016
	American Urological Association (AUA)	-	July 28, 2016
HTA-Agencies and Drug Regulatory Agencies	Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Reviews (CDR) Reports	-	30 Aug, 2016
	CADTH pan-Canadian Oncology Drug Review	-	30 Aug, 2016
	Pharmaceutical Benefits Advisory Committee (PBAC)	-	31 Aug, 2016
	National Institute for Health and Care Excellence (NICE)	-	31 Aug, 2016
	National Institute for Health Research (NIHR)	-	30 Aug, 2016
	U.S. Food and Drug administration (FDA)	-	31 Aug, 2016
	European Medicines Agency (EMA)	-	31 Aug, 2016

*Only conferences searched which had at least one hit are included here.

4.1.3 Study selection

4.1.3.1 Inclusion/exclusion selection criteria

The eligibility criteria (based on the PICO framework) used for the SLR are presented in Table 10.

Table 10: Eligibility criteria for systematic literature review of RCT evidence

Domain	Inclusion criteria	Exclusion criteria
Population	Patients with locally advanced/metastatic urothelial carcinoma (excluding adjuvant and neoadjuvant stages of the treatment pathway) Subgroups include: • 1st line therapy cisplatin-ineligible • 2nd line therapy • 3rd line therapy or more Subpopulations PD-L1 expression (PD-L1 expression 2/3) to be considered	Patients <18 years of age Healthy patients Animal studies Disease stages II and lower
Intervention	Any other pharmacological intervention used for patients in the first- or later lines of therapy for advanced/metastatic urothelial carcinoma (investigational (phase II/III/IV) and licensed), such as: • Atezolizumab • Nivolumab • Pembrolizumab • Vinflunine • Vinblastine • Gemcitabine • Pemetrexed • Docetaxel • Paclitaxel • Nab-paclitaxel • Ifosfamide • Fluorouracil • Methotrexate • Carboplatin • Cisplatin • MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) • Doxorubicin • Granulocyte colony stimulating factor • Vandetanib • Afatinib • Pazopanib	Not including intervention of interest

	• Avelumab • Ramucirumab • Palbociclib • Everolimus • Gefitinib • Erlotinib • Cetuximab • Panitumumab • Trastuzumab • Lapatinib • Dovitinib • Bevacizumab • Aflibercept • Sunitinib • Cabozantinib • Cabazitaxel • Eribulin • Ipilimumab And any other applicable chemotherapies, immunotherapies, antineoplastic agents, antineoplastic protocols, molecular-targeted therapies, cancer vaccines, protein kinase inhibitors, angiogenesis inhibitors, taxanes, taxoids, etc.	
Comparators	• Any pharmacological intervention used • Placebo • Best supportive care	Radiotherapy, surgery, and other non-pharmaceutical treatments
Outcomes	Studies to be included must evaluate at least one of the following endpoints: • Overall survival (OS) • Progression free survival (PFS) • Time to progression (TTP) • Objective response rate (ORR) • Complete response (CR) • Partial response (PR) • Stable disease (SD) • Progressive disease (PD) • Disease control rate (DCR) • Duration of response (DoR) • Health-related quality of life (HRQoL) (EORTC-QLQ-C30) • Safety outcomes (not used for study selection)	Not including outcome of interest
Study design	• Randomised controlled trials (RCT) • Non-randomised controlled trials (CCT)	Phase I studies, reviews (systematic and non-systematic), meta-analyses, HTA, guidelines, cross-sectional and claims data

	• Single-arm trials	analysis, retrospective chart reviews and analysis of hospital databases and registry, prospective consecutive patients, observational studies, patient programs, case reports

HTA, Health Technology Assessment

There were no restrictions to the timeframe of the bibliographic search and search of the study registries, however, the search for conference abstracts was restricted to 2015–2016 (Table 11).

Table 11: Further parameters and restrictions for the systematic literature search

Language	Publications with abstract in English included but full text in a language other than English, French, German, Italian, Spanish will not be included (it will only be listed for information)
Country	No restriction
Timeframe	No restriction in bibliographic search and search of study registries Restriction to conferences from 2015–2016 with respect to separate search for conference abstracts
Publication type	• Full-texts, congress abstracts erratum to a study included • Congress proceedings, oral presentation, letters, comments not included

4.1.3.2 Review strategy

Literature identified was initially assessed based on the title and abstract according to the predefined inclusion / exclusion PICO criteria (Section 4.1.3.1, Table 10). Papers not meeting the inclusion criteria were excluded and allocated a “reason code” to document the rationale for exclusion. Papers included after this stage were assessed based on the full text, yielding the final data set for inclusion. The full texts of these studies were screened and those potentially suitable for NMA were selected (See Section 4.10 for indirect and mixed treatment comparisons).

The selected sources were reviewed in detail and all study- and patient-related information, clinical outcomes and QoL data of interest extracted into data spreadsheets. A second reviewer independently reappraised the extracted data. In case of any discrepancies, a consensus was sought by discussion or by consultation with a third reviewer.

4.1.4 Search results

The systematic literature search for RCTs, CCTs and single-arm trials on atezolizumab and its comparators retrieved 18,858 citations (Table 12).

Table 12: Systematic review literature database search results

Database	RCT	CCT	Combined (including duplicates)
Medline	7,193	3,104	7,826
Embase	4,195	9,851	10,105
Cochrane Library	-	-	927
Total (including duplicates)			**18,858**
Total (after removing 3567 duplicates)			**15,291**

CCT, Non-randomised controlled trial; RCT, randomised controlled trial

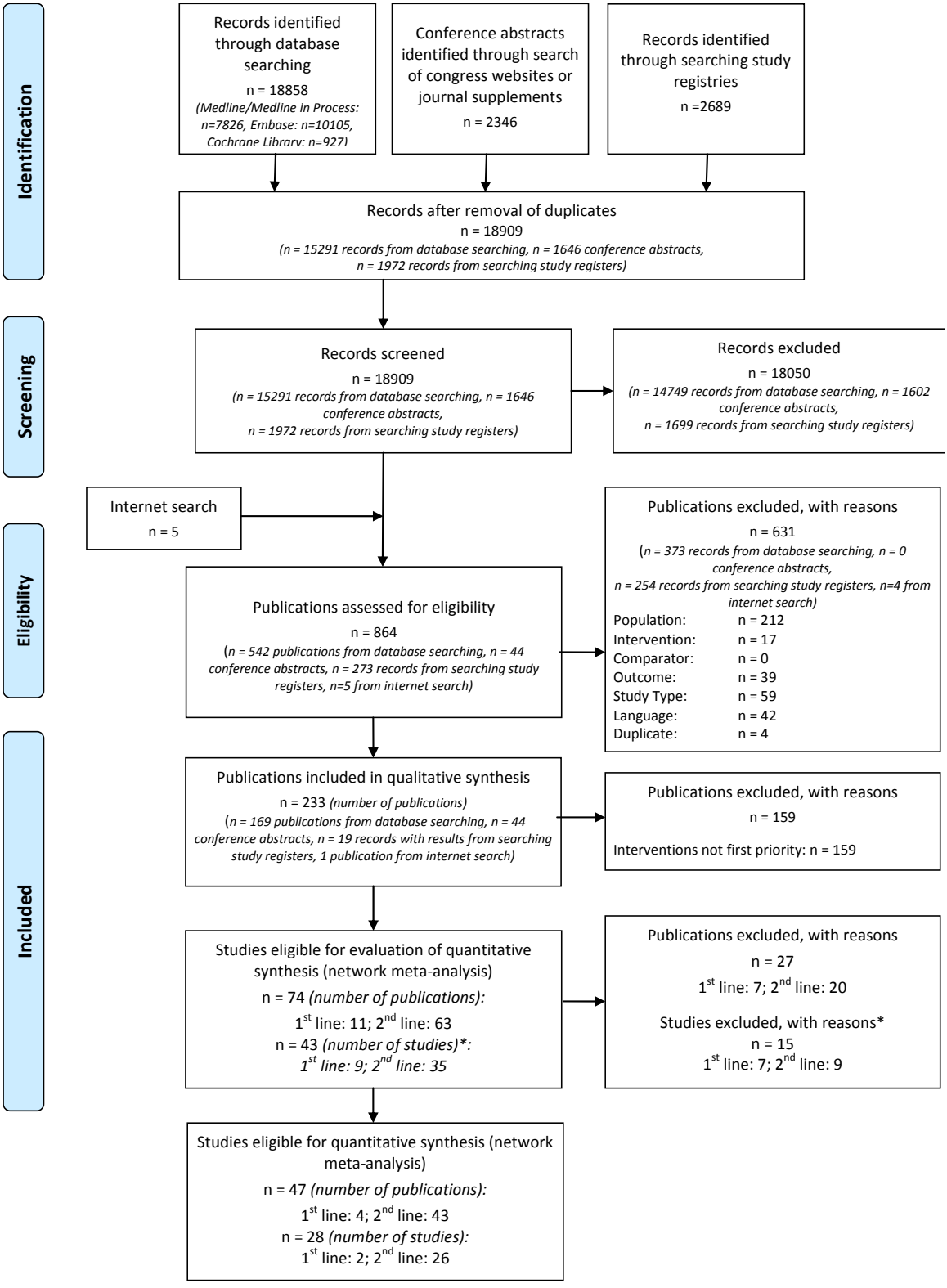
Additionally, hand searches on study registries and conference websites were performed to complement the literature search. To complete information retrieval, websites of HTA and Drug Regulatory Agencies (Canadian Agency for Drugs and Technologies in Health [CADTH], CADTH Common Drug Review [CDR] Reports, CADTH pan-Canadian Oncology Drug Review, Pharmaceutical Benefits Advisory Committee, NICE, National Institute for Health Research, U.S FDA, European Medicines Agency [EMA]) were searched for additional information on comparators eligible for the network-meta analysis. A total of 18,909 records were retrieved for selection.

The original literature search conducted in June and July 2016 revealed a total of 23,893 citations. After excluding duplicates (n=4,984) and screening against inclusion / exclusion criteria, 18,050 titles / abstracts were excluded (Figure 3). In total, 864 citations were found to be eligible for the screening at full-text level: 542 records from the search, supplemented by 44 conference abstracts, 273 records from study registers and 5 records from an internet search.

After full-text screening, 233 publications were selected for inclusion in the review, 169 full texts from database searching, 44 records identified through conference

websites, 19 records from study registries, and 1 publication from an internet search. Due to the large number of studies included in the review, the studies were divided into categories in order to prioritise them in terms of the importance of the comparators in the trials. Priority 1 studies included only those with one of the following interventions identified as relevant comparators based on clinical guidelines and standards of care in the UK, France, Australia, Canada and Sweden: BSC, carboplatin plus paclitaxel, docetaxel, paclitaxel, nab-paclitaxel, vinflunine, gemcitabine, gemcitabine plus paclitaxel, MVAC, carboplatin, cisplatin, oxaliplatin (platinum-based re-challenge if >12 months since last dose), pembrolizumab, nivolumab, and gemcitabine plus cisplatin for 2nd line as well as gemcitabine plus carboplatin, gemcitabine plus paclitaxel and BSC for the first-line cisplatin-ineligible population. In total, 74 publications (43 studies) were categorised as priority 1. Papers not categorised as priority 1 did not include the comparators of interest, as such these papers were not relevant to the decision problem. These publications stood for potential inclusion into the NMA. After screening these 74 full-text publications to identify those eligible for quantitative synthesis (NMA), 47 publications were identified as eligible. The PRISMA flow diagram for the study selection process for the clinical effectiveness evidence is shown in Figure 3.

Figure 3: PRISMA flow diagram of the study selection process



* The eligible studies include the atezolizumab study consisting of 2 parts: Cohort 1 (1st line) and Cohort 2 (2nd line).

4.1.5 Additional hand search to identify Atezolizumab studies

The 47 publications identified in Figure 3 were hand searched by two reviewers to identify any trials directly comparing atezolizumab versus any comparator. No studies were identified; therefore, there are no published randomised-controlled studies which include atezolizumab.

4.2 List of relevant randomised controlled trials

No RCT evidence was identified. Please see Section 4.1 for further details.

4.3 Summary of methodology of the relevant randomised controlled trials

No RCT evidence was identified. Please see Section 4.1 for further details.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

No RCT evidence was identified. Please see Section 4.1 for further details.

4.5 Participant flow in the relevant randomised controlled trials

No RCT evidence was identified. Please see Section 4.1 for further details.

4.6 Quality assessment of the relevant randomised controlled trials

No RCT evidence was identified. Please see Section 4.1 for further details.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

No RCT evidence was identified. Please see Section 4.1 for further details.

4.8 Subgroup analysis

No RCT evidence was identified. Please see Section 4.1 for further details.

4.9 Meta-analysis

One phase II study was identified for atezolizumab, as such a meta-analysis was not required or feasible.

4.10 Indirect and mixed treatment comparisons

Summary of Indirect treatment comparison

Only single arm studies are currently available for atezolizumab and many of the comparators of interest. As such derivation of comparative efficacy required several steps:

1 A set of key prognostic factors for mUC were identified

2 Studies for comparators were identified through the SLR. In order to allow construction of the prediction model, included studies were required to report at least 1 of the identified key prognostic factors, and present KM curves for OS and/or PFS

3 This resulted in a total of 7 included comparators studies: 2 for gemcitabine + carboplatin, 1 for paclitaxel, 2 for docetaxel and 2 for BSC.

4 A prediction model was built based on the prognostic factors in the individual patient data (IPD) set for atezolizumab from the IMvigor 210 trial. This model predicted atezolizumab outcomes for the comparator trials – effectively building an atezolizumab 'arm' into the comparator trials

5 With each single arm comparator trial having a predicted atezolizumab control group, the analysis proceeded in line with traditional NMA. The constructed 'control' arms allowed inference about relative treatment effects under trial settings for the competing interventions via traditional NMA.

6 The NMA included fractional polynomial models for OS, as these models do not rely on the proportional hazards assumption.

Detail and rationale of all stages are further described below.

4.10.1 Literature search

One SLR was conducted to identify all available evidence for treatments in mUC. Details of the search strategy are available in section 4.1 above. As detailed above, the literature search did not identify any comparative studies for atezolizumab in mUC.

The relevant comparators for the appraisal are: gemcitabine + carboplatin for 1L cisplatin-ineligible patients, and docetaxel, paclitaxel and BSC for 2L patients. As no comparative data are available for atezolizumab, an indirect treatment comparison is necessary to conduct incremental cost-effectiveness analysis. Comparative data will be available in 2017, with a pIII study for 2L atezolizumab (IMvigor 211) and in 2020 with a pIII study for 1L atezolizumab (IMvigor 130). IMvigor 211 includes 2 of the 3 comparators of interest for 2L treatment (docetaxel and paclitaxel), and IMvigor 130 includes the comparator of interest for 1L treatment (gemcitabine + carboplatin).

4.10.2 Search strategy

The search described in section 4.1 did not limit by intervention. This ensured inclusion of all relevant evidence for the population. The search identified 43 individual studies which met the inclusion criteria defined in Table 10.

4.10.3 Comparators of interest

The comparators of interest from the appraisal scope are gemcitabine+ carboplatin for 1L treatment; and paclitaxel, docetaxel or BSC for 2L treatment. Rationale for the exclusion of certain comparators can be found in section 1.1.

4.10.4 Identification of prognostic factors for prediction model

As the registration study for atezolizumab in mUC is single arm, it was anticipated a connected network would not be available. Given the availability of IPD for atezolizumab, a simulated treatment comparison (STC) was planned, and is described as ‘prediction model’ hereinafter.

The prediction model requires identification of prognostic factors for advanced or mUC. As described in section 3.5.3, the literature identified performance status and presence of liver metastases as prognostic factors for poor outcomes in patients with

mUC. This was taken as a starting point for consideration of prognostic factors in the prediction model, which was extended to include additional variables for age and gender. Given the limitations of research in mUC it is difficult to perform a robust analysis to identify all prognostic factors, particularly when all these factors must also be reported in published evidence for comparators. The extension of those factors identified by (Bellmunt et al., 2010) to additional variables was seen as a reasonable and parsimonious approach to development of the prediction model in this unresearched area.

The variables used to characterise the study population and to best predict the clinical outcomes are: age (≥ 65 years); gender; performance status [ECOG≥1 or Karnofsky Performance Status scale ≤90%], and; presence of liver metastasis at baseline (Bellmunt et al., 2010, Agarwal et al., 2014, Pond et al., 2014, Witjes et al., 2014). Preferably, the prediction model would include only evidence from studies reporting all prognostic factors, however due to the limited amount of data available in mUC, studies were included when at least 1 out of the 4 predictors were reported – although included studies for the comparators of interest all reported minimum 3 of the 4 factors (Table 17 below).

4.10.5 Study selection for comparative evidence

The SLR confirmed the available evidence network could not be connected to atezolizumab. Considering this, an additional objective of the SLR was to identify potential bridging studies which might enable indirect linking between relevant comparators. These studies may include comparators which are not of interest for this appraisal. All studies were evaluated regarding their feasibility for the NMA and excluded if they did not provide enough information. The NMA was planned to address 4 efficacy endpoints: OS, 12-month OS, PFS and ORR.

Study selection was conducted in two stages.

Stage one: Exclusion of any studies not reporting at least one of the four outcomes of interest: OS, 12- month OS, PFS and ORR. Following this exclusion a total of 43 studies from 74 publications remained.

Stage two: Studies were appraised for indirect comparison and NMA feasibility for each of the 4 priority outcomes and for each of the 2 treatment lines considered, along the following considerations:

- Building of the study networks and their connectivity
- Assessing the availability of baseline factors associated with the clinical outcomes of interest
- For OS and PFS outcomes, assessing the presence of Kaplan Meier (KM) curves in the corresponding publications, to be digitised and used for fractional polynomial NMA

A list of studies with rationale for exclusion at stage two are included in appendix 8.2. The primary reason for study exclusion from the NMA was limited data availability (predictors and KM curves). Following this exclusion a total of 28 studies from 47 publications remained (Table 13 for 1L, Table 14 for 2L).

Table 13: Trials identified as the evidence base for potential NMA with atezolizumab in the 1st line setting (Feasibility Assessment)

Trial name / Author	Design	Interventions	OS	12 mth OS	PFS	ORR
(Bamias et al., 2007)	Single arm Phase II	GEMCITABINE/CARBOPLATIN	✓	NR	✓	✓
NCT00014274 (EORTC Study 30986) (De Santis et al., 2009) (De Santis, 2010) (De Santis et al., 2012)	RCT	GEMCITABINE+CARBOPLATIN VS. M-CAVI	✓	NR	NR	✓

Table 14: Trials identified as the evidence base for potential NMA with atezolizumab in the 2nd line setting (Feasibility Assessment)

Trial name / Author	Design	Interventions	OS	12 mth OS	PFS	ORR
(Akaza et al., 2007)	Single arm Open label Phase II	GEMCITABINE	✓	✓	✓	✓
(Albers et al., 2002a)	Single arm Open label Phase II	GEMCITABINE	✓	NR	TTP: ✓	✓
AUO trial AB 20/99 (Phase 3) (Albers, 2008) (Albers et al., 2011)	RCT Phase III Open-Label	GEMCITABINE + PACLITAXEL (LONG TERM) VS. GEMCITABINE + PACLITAXEL (SHORT TERM)	✓	NR	✓	✓
NCT00315237 (Bellmunt et al., 2009) (Bellmunt et al., 2009) (Bellmunt et al., 2013) (Culine, 2010) (Fougeray, 2012) (Von der Maase, 2008)	RCT Phase III Open label	VINFLUNINE + BSC VS BSC	✓	✓	✓	✓

Trial name / Author	Design	Interventions	OS	12 mth OS	PFS	ORR
NCT00880334 (Choueiri et al., 2012) (Choueiri et al., 2012) (Dana-Farber Cancer Institute, 2016)	RCT Phase II Double-blind	DOCETAXEL + VANDETANIB VS DOCETAXEL + VANDETANIB-PLACEBO	✓	NR	✓	✓
2011-002424-41 (OncoGenex Technologies, 2011) ENREF 17	RCT Double-blind Phase II	CISPLATIN+GEMCITABINE+OGX-427 VS. CISPLATIN+GEMCITABINE+PLACEBO	✓	NR	✓	✓
(Culine et al., 2006)	Single arm Phase II	VINFLUNINE	✓	NR	✓	✓
(Han et al., 2008)	Single arm	MVAC	✓	✓	✓	✓
(Ikeda et al., 2011)	Single arm	GEMCITABINE + PACLITAXEL	✓	✓	✓	✓
(Joly et al., 2009)	Single arm	PACLITAXEL	✓	✓	NR	✓
NCT01711112 (Kim, 2013) (Kim et al., 2016)	Single arm	DOCETAXEL	✓	NR	✓	✓
NCT00683059 (Ko Y, 2010) (Ko et al., 2013) (Sridhar SS, 2009, Sridhar SS, 2010, Sridhar SS, 2011)	Single arm	NAB-PACLITAXEL	✓	✓(6-months)	✓	✓
(Kouno et al., 2007)	Single arm	PACLITAXEL + CARBOPLATIN	✓	NR	✓	✓

Trial name / Author	Design	Interventions	OS	12 mth OS	PFS	ORR
NCT01426126 (Lee J, 2011) (Lee et al., 2012)	Single arm	PACLITAXEL (POLYETHOXYLATED CASTOR OIL-FREE, POLYMERIC MICELLE FORMULATION)	✓	NR	✓	✓
(Matsumoto et al., 2007)	Single arm	GEMCITABINE + PACLITAXEL	✓	✓	✓	✓
(McCaffrey et al., 1997)	Single arm	DOCETAXEL	✓	NR	NR	✓
UMIN000003157 (Noguchi M, 2014) (Noguchi et al., 2016)	RCT	PERSONALIZED PEPTIDE VACCINATION (PPV) + BSC	✓	NR	✓	NR
NCT01282463 (Petrylak DP, 2015) (Petrylak DP, 2015)	RCT Phase II Open label	DOCETAXEL VS. DOCETAXEL + RAMUCIRUMAB VS. DOCETAXEL + ICRUCUMAB	✓	NR	✓	✓
(Srinivas and Guardino, 2005)	Single arm	GEMCITABINE + PACLITAXEL	✓	NR	NR	✓
(Suyama et al., 2009)	Single arm	GEMCITABINE + PACLITAXEL	✓	NR	NR	✓
NCT01928394 (Sharma P, 2016)	Single arm	NIVOLUMAB	✓	✓	✓	✓
(Sternberg et al., 2001)	Single arm	GEMCITABINE+PACLITAXEL	✓	NR	NR	✓
(Takahashi et al., 2006)	Single arm	PACLITAXEL + GEMCITABINE	✓	NR	NR	✓

Trial name / Author	Design	Interventions	OS	12 mth OS	PFS	ORR
(Vaishampayan et al., 2005)	Single arm	PACLITAXEL + CARBOPLATIN	✓	✓	✓	✓
(Vaughn et al., 2002)	Single arm	PACLITAXEL	✓	NR	NR	✓
(Vaughn et al., 2009)	Single arm	VINFLUNINE	✓	NR	✓	✓

For inclusion in the time-to-event analyses, KM curves for PFS and/or OS were required. The studies for comparators of interest which were included in the OS and PFS NMA are listed in Table 15 and Table 16 below, for 1L and 2L respectively. Any studies from Table 13 and Table 14 which were not included in the PFS and OS NMA were excluded due to unavailability of KM curves.

As inclusion of therapies additional to this appraisal scope does not facilitate construction of a connected network, studies assessing comparators not of relevance for this appraisal are not further described.

Table 15: Studies included for OS and PFS NMA (1L)

Study name/author	Study type	Interventions	KM data available
(Bamias et al., 2007)	Single arm Phase II	Gemcitabine + carboplatin	OS and PFS
NCT00014274 (EORTC Study 30986) (De Santis et al., 2009) (De Santis, 2010) (De Santis et al., 2012)	RCT	Gemcitabine + carboplatin vs. M-CAVI*	OS
IMvigor 210, cohort 1	Single arm Phase II	Atezolizumab	OS and PFS

* study arm not relevant to decision problem, so not included in analysis

Table 16: Studies included for OS and PFS NMA (2L+)

Study name/author	Study type	Interventions	KM data available
(Bellmunt et al., 2009)	RCT Phase II Open label	Vinflunine + BSC vs BSC	OS and PFS
NCT00880334 (Choueiri et al., 2012)	RCT Phase II Double-blind	Docetaxel + vandetanib* vs. docetaxel + placebo	OS and PFS
NCT01711112 (Kim, 2013)	Single arm	docetaxel	OS and PFS
NCT01426126 (Lee J, 2011) (Lee et al., 2012)	Single arm	Paclitaxel (polyethoxylated caster oil-free, polymeric micelle formulation)	OS and PFS
(Noguchi M, 2014) (Noguchi et al., 2016)	RCT	Personalized peptide vaccinations* + BSC vs BSC	OS and PFS
IMvigor 210 cohort 2	Single arm Phase II	Atezolizumab	OS and PFS

* study arm not relevant to decision problem, so not included in analysis

The reported values of prognostic factors of the studies included in the NMA are presented in Table 17.

Table 17: Selected prognostic factors for studies included within NMA

Author (year)	Treatment	Age (>65 years)	Gender	Liver Mets	ECOG PS ≥ 1
1L					
(Bamias et al., 2007)	Gemcitabine + carboplatin	0.94	0.82	NA	0.68
NCT00014274 (EORTC Study 30986) (De Santis et al., 2009) (De Santis, 2010) (De Santis et al., 2012)	Gemcitabine + carboplatin vs. M-CAVI	0.65	0.76	0.17	0.83
IMVigor 210, cohort 1	Atezolizumab	0.83	0.81	0.21	0.62
2L					
(Bellmunt et al., 2009)	Arm 1: best supportive care; Arm 2: vinflunine	0.44	0.78	NA	0.69
NCT00880334 (Choueiri et al., 2012)	Docetaxel + vandetanib vs. docetaxel + placebo	0.46	0.68	0.38	0.53
NCT01711112 (Kim, 2013)	docetaxel	0.46	0.77	0.32	1.00
NCT01426126 (Lee J, 2011) (Lee et al., 2012)	Paclitaxel (polyethoxylated caster oil-free, polymeric micelle formulation)	0.17	0.78	NA	0.62
(Noguchi M, 2014) (Noguchi et al., 2016)	best supportive care	0.50	0.80	NA	0.20
IMvigor 210 cohort 2	Atezolizumab	0.59	0.78	0.31	0.62

Additional methodological details and key patient characteristics are provided in appendix 8.3, along with a quality assessment of included studies. It is important to note that while studies were considered comparable to a basic level required for NMA, there are a number of differences between included trials that require some caution when interpreting the results, such as: differences in patient populations including baseline risk, treatment history, differences in trial designs, particularly in regard to primary efficacy outcome(s) measurements.

4.10.6 Heterogeneity and risk of bias

The assessment for risk of bias was based on 1) a critical quality appraisal of each individual study included in the feasibility assessment of the NMA and 2) a qualitative assessment of the heterogeneity across studies investigating the same drug.

Critical appraisals were based on the NICE (National institute for Clinical Excellence, 2012)and Cochrane (Cochrane, 2011)checklists for randomised clinical studies and on an adapted assessment checklist developed by NIH (National Institutes of Health, 2014) for single arm studies.

Criteria for quality assessment considered: adequacy of randomisation method, allocation concealment, homogeneity of baseline characteristics between treatment groups and blinding in RCTs. Quality assessment for single arm studies was based on adequate description and comparability of included study population, and adequate description of the underlying methods and outcomes. The study quality assessment was conducted by two independent assessors. The complete summary of the quality assessment of each study included in the NMA is listed in appendix 8.3.

The study quality was assigned to one of following categories: high, moderate to high, moderate, low to moderate, or low.

Next, a qualitative assessment of the heterogeneity across studies investigating the same drug (i.e. study population, dosage, frequency of administration) was conducted. The degree of heterogeneity between studies investigating the same drug was assigned to one of following categories: low, low to moderate, moderate, moderate to high, or high. The distributions of baseline patient characteristics in included studies are presented in appendix 8.3.

Figure 4 s**Error! Reference source not found.**ummarises the critical appraisal, the within-study heterogeneity and assessment of risk of bias.

The main differences between the included trials used for the NMA, as shown in the detailed description below, were:

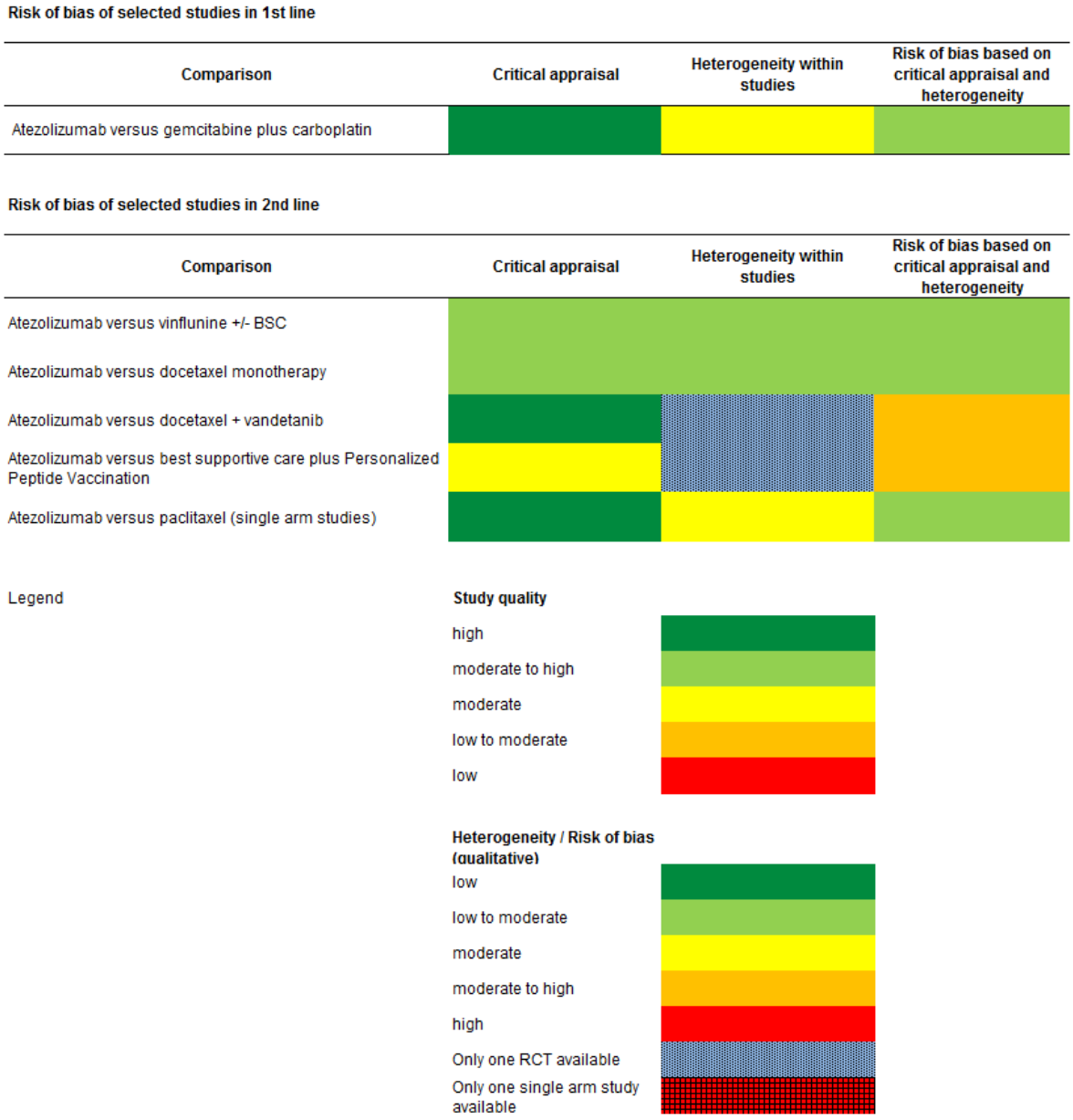
- different dosage or frequency of administration of identical drugs derived from various studies, which were combined in the network
- missing information regarding baseline characteristics
- availability of only one single abstract with limited information and/or quality

A potential source for bias is differing definitions of the same outcomes: for most of the studies, no specific definition was stated. Studies in 1L treatment have shown a low to moderate risk of bias. Compared to the atezolizumab study, the two studies with carboplatin plus gemcitabine were similar regarding median age. Differences were observed regarding proportion of metastasis and ECOG PS.

The risk of bias of studies intended for the NMA focusing on 2L treatment ranged from low to high.

The median age of patients enrolled in the atezolizumab study was comparable to age of patients in the studies selected for the NMA. Regarding other baseline characteristics (e.g. proportion of male, all site and liver metastases, ECOG PS) differences were observed.

Figure 4: Summary of Critical Appraisal, within study heterogeneity and assessment of bias for NMA included studies



4.10.7 Construction of connected network

With one single arm study available for atezolizumab in mUC, and the majority of evidence for comparators also being single arm, traditional indirect treatment comparisons were not possible.

Comparative data will be available in 2017, with a phase III study for 2L atezolizumab (IMvigor 211) and in 2020 with a phase III study for 1L atezolizumab

(IMvigor 130). IMvigor 211 includes 2 of the 3 comparators of interest for 2L treatment (docetaxel and paclitaxel), and IMvigor 130 includes the comparator of interest for 1L treatment (gemcitabine + carboplatin).

Until such time, alternative methods must be explored to estimate the comparative efficacy of atezolizumab to comparators listed in the scope. It is recognised there is inherent weakness in the comparison of single arm studies to determine a relative treatment effect. However limitations of the data availability make this unavoidable.

Possible methods of comparison of single arm studies include:

- Naïve comparison
- Simulated treatment comparison (STC)
- Matching-adjusted indirect comparison (MAIC)

Naïve comparison presents significant risk of confounding bias due to cross-trial differences. With single arm trials it is unclear which part of the result is attributable to the treatment (i.e. the treatment effect) and which part is attributable to prognostic factors or the natural course of disease (the study effect). This method is weak and alternative methods were explored to avoid naïve comparison and account for the differing trial populations.

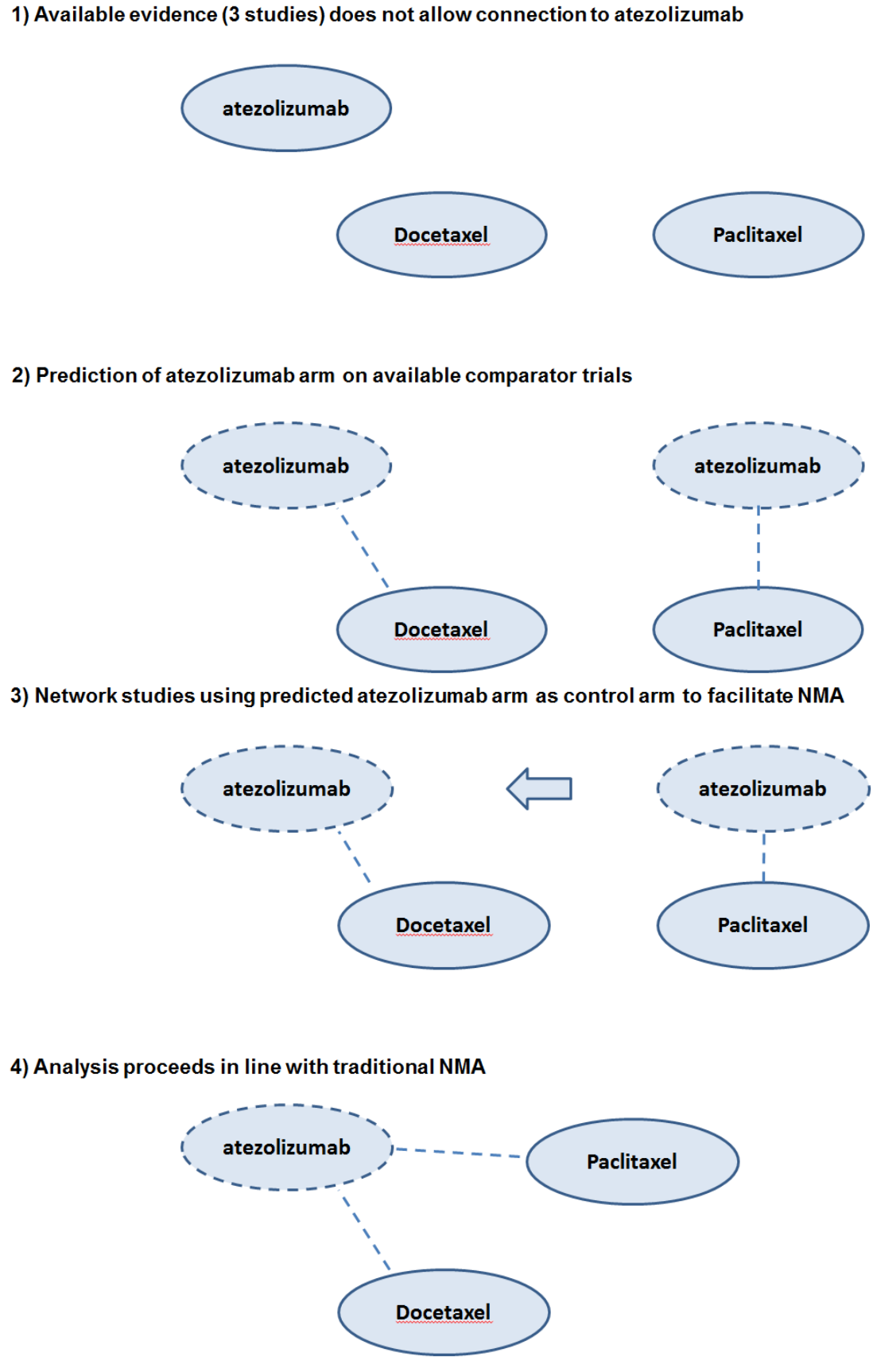
STC and MAIC both allow adjustment for cross-trial differences, which is a significant benefit over naïve comparison. A MAIC would adjust the population receiving atezolizumab to match the average baseline characteristics with a reference population. Adjustment should address all baseline characteristic available from trials included in the network, and matching is based on propensity score weighting. Adjustment is made for each comparator and applied to relevant outcomes, which introduces a level of complexity. Whilst this approach can, in theory, achieve better matching; large populations are required with robust patient level data on baseline characteristics. As propensity score weighting seeks adjustment for all reported patient characteristics, it is important to have access to relatively full datasets to ensure relevant covariates are assessed and properly incorporated into the analyses. Access to such data was not available across all trials included in the assessment.

Due to the nature of the available data for atezolizumab and comparators, a STC (referred to as a 'prediction model') was determined to be the most appropriate method for the ITC. This method also allows more transparency for assessment of results and their reliability, with a reduced need to access complete dataset.

4.10.8 Prediction model

As IPD are available for atezolizumab, a prediction model was developed for the outcomes with atezolizumab as a function of relevant patient-related factors (or prognostic factors). This model can then predict outcomes with atezolizumab for a population as observed in the single arm trials for the relevant comparators, effectively creating an atezolizumab 'arm' within these comparator studies. These "predicted controlled trials" are incorporated in an evidence network using atezolizumab as the common link, in the same way as with a standard NMA. Figure 5 below illustrates the methodology using 1L as an example.

Figure 5: Illustrative diagram of prediction model methodology (dashed line represents prediction comparison)



As described above (and displayed in Table 17), included prognostic factors for poor outcomes in patients with mUC were identified as: 1) age (≥65 years); 2) gender (males); 3) performance status using ECOG/WHO/Zubrod performance status score (collectively, "ECOG"; >0) or Karnofsky Performance Status scale (≤90%); and 4) liver metastases.

As the IMvigor 210 trial included second or later line patients in Cohort 2, the comparison of interventions for 2L mUC patients also subsequently included number of prior chemotherapies (proportion of patients receiving 2 or more prior therapies).

Cox regression models were used for time-to-event outcomes while binomial-logistic regressions were used for binary outcomes. As binary outcomes do not generate parameter inputs for the economic model, the methodology for deriving these can be found in appendix 8.4

A number of competing models were considered for each outcome, defined based on inclusion of each covariate and interaction terms (Table 18 below). One null model (m0) was defined with no covariate included and used as benchmark to compare predictive performance of other models.

Table 18: Prediction models

	Model version								
	m0	**m0a**	**m0b**	**m1**	**m2**	**m3**	**m4**	**m5**	**m6**
Age		×		×	×	×	×	×	×
Gender		×		×	×	×	×	×	×
Performance status			×	×	×	×	×	×	×
Liver Metastasis			×	×	×	×	×	×	×
Number of prior therapies*					×	×	×	×	×
Interaction Liver Metastasis × age						×			
Interaction Liver Metastasis × gender							×		
Interaction Performance status × age								×	
Interaction Performance status × gender									×

*2L+ cohort only

1000 bootstrap samples were generated from the IPD for atezolizumab in study IMvigor 210. On average, 1/3 of patients (labelled out-of bag [OOB]) were not included in each sample, with patients being sampled at random, with replacement. Parameters were estimated for each bootstrap sample, for each competing model.

For time-to-event outcomes, Cox models were fit to each of the bootstrap samples, concordance was calculated (probability that a patient with longer survival time will have a lower risk score), and the c-index values were summarised over the bootstrap samples. Model selection was based on best predictive performance.

Using the model with the best average predictive performance in combination with the distribution of patient characteristics (age, gender, liver metastasis, and performance status ≥ 1), outcomes of interest with atezolizumab for each single arm trial of interest were predicted.

From the bootstrap estimates generated, there were 1,000 predicted outcomes for each trial. An average of these was used to obtain the predicted outcomes along with a variance and 95%CI for each trial to be used in the NMA. For time-to-event endpoints, predicted log-hazards and associated standard errors over time were derived, and used as predicted atezolizumab data points in the NMA.

4.10.9 Network meta-analysis (NMA) methodology

Proportional hazard assumption

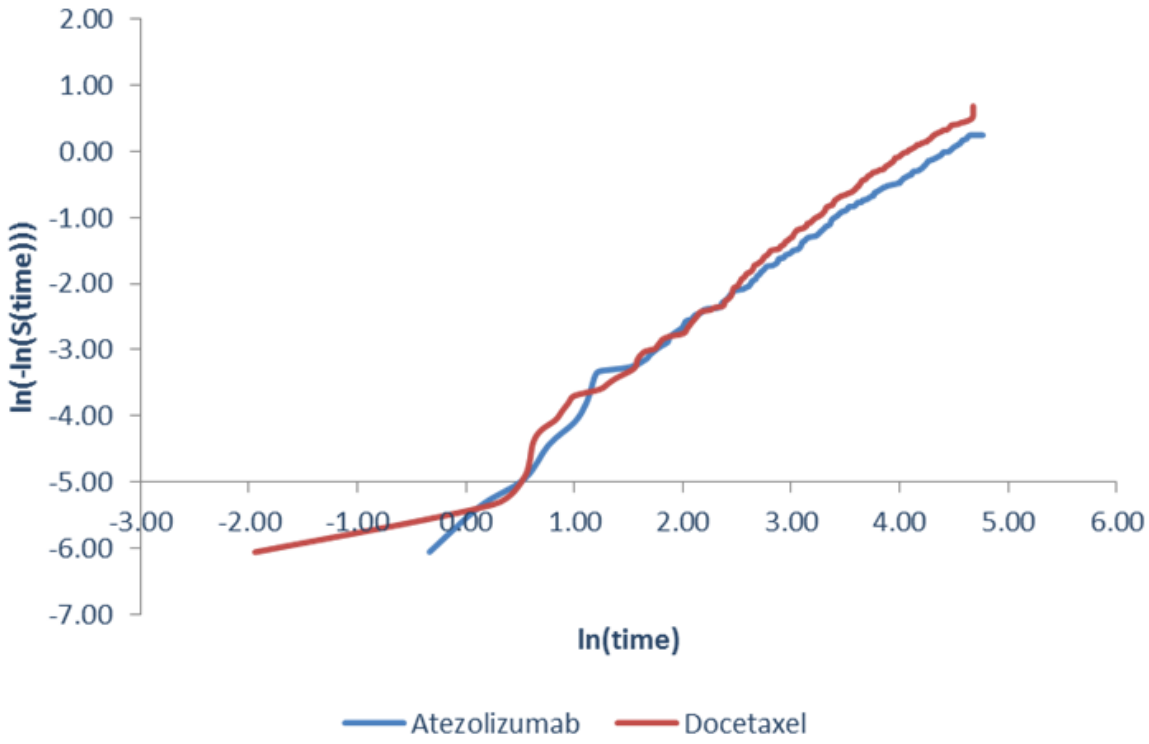
Selection of the most appropriate model to conduct the NMA was based on experience to date with immunotherapies. As there are not yet any comparative data available for atezolizumab in mUC, it was not possible to evaluate whether the proportional hazard assumption holds when comparing atezolizumab to chemotherapies, in the treatment of mUC. As such, prior immunotherapy appraisals in metastatic oncology, atezolizumab evidence in other indications, and results of the prediction model were all assessed to determine if the proportional hazard assumption is likely to hold.

Prior immunotherapy appraisals in melanoma (national institute for Clinical Excellence, 2015, national institute for Clinical Excellence, 2016) and NSCLC

(National Institute for Health and Care Excellence, 2017a, National Institute for Health and Care Excellence, 2017c)for pembrolizumab and nivolumab have determined the proportional hazards assumption is unlikely to hold when comparing these therapies to traditional chemotherapies for time-to-event outcomes (National Institute for Health and Care Excellence, 2017c, National Institute for Health and Care Excellence, 2017a, National Institute for Health and Care Excellence, 2017b).

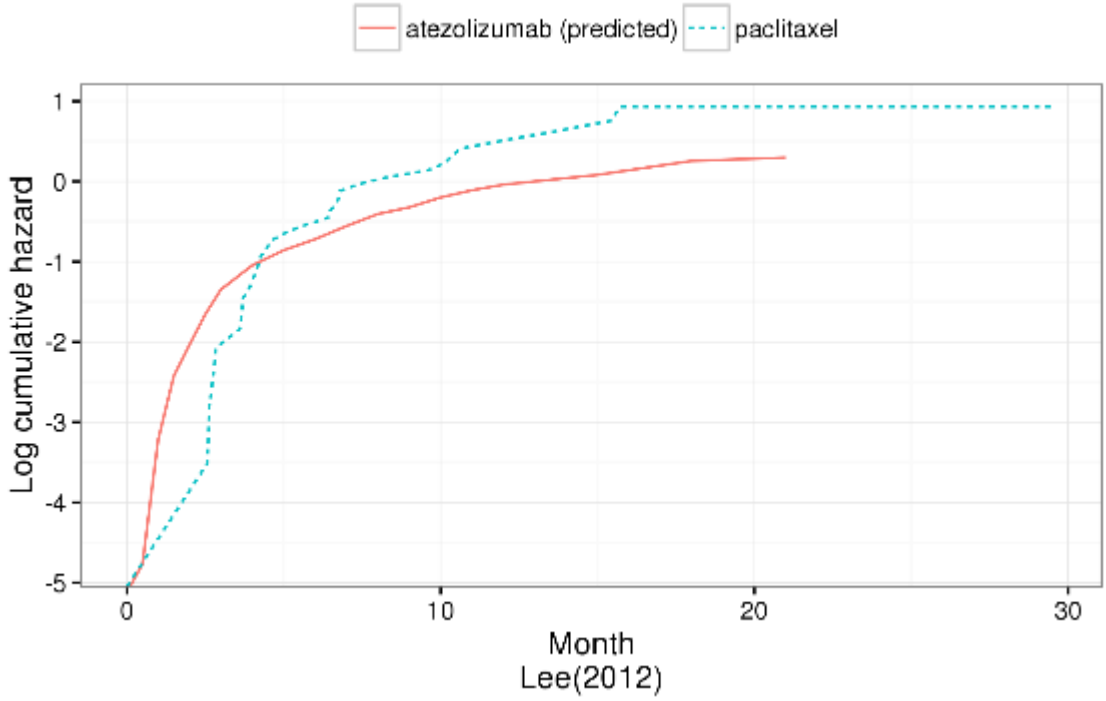
Comparative data are available for atezolizumab vs. docetaxel in NSCLC from the recently-published OAK study (Rittmeyer et al., 2016). As seen in Figure 6, the log cumulative hazard plots demonstrate the proportional hazard assumption is violated, due to curves crossing.

Figure 6: Log-log plot for OS in NSCLC patients in OAK study



Finally, evaluation of the log cumulative hazard plots from the prediction model for comparators vs atezolizumab in mUC also suggest the assumption does not hold. Figure 7 provide the paclitaxel comparison as an example.

Figure 7: Log-log plot for prediction model derived OS HR for paclitaxel vs. atezolizumab (Lee J, 2011)



NMA Methodology

The NMA was conducted under a Bayesian framework.

For binary outcomes (ORR and 12 month OS), both random effects (RE) and fixed effects (FE) models were explored. As binary outcomes do not generate parameter inputs for the economic model, methodology and results for these outcomes are not further described below, but can be found in appendix 8.4.

Based on the likely violation of the proportional hazards assumption for atezolizumab vs. chemotherapy comparators in mUC, fractional polynomial models were developed for time-to-event outcomes (PFS and OS). In order to test the impact of this assumed violation, proportional hazards models were also considered.

FE models were first fit, with RE models subsequently fit if the data allowed. Six models were considered in the FE framework:

- "Zero order model", i.e. first order fractional polynomial, without the time-dependent term (coefficient β1jk = 0). This corresponds to the Exponential model

and assumes proportional hazards. This model was included to allow assessment of the proportional hazards assumption (e.g. through the deviance information criterion (DIC), which was possible as this model was fitted to the same data as the more complex models).

- First order fractional polynomials with exponent P1 = 0 (equivalent to Weibull model), and P1 = 1 (equivalent to Gompertz model).
- Second order fractional polynomials with exponents P1, P2 in (0, 1), i.e. P1=P2=0; P1=0, P2=1; and P1=P2=1.

The fractional polynomial models covered a broad range of shapes of the hazard function, including constant, monotonically increasing, monotonically decreasing, U-shaped, and inverted-U-shaped hazard ratio curves. This was considered broad enough for the present data and did not, therefore, include higher order polynomials or additional exponents (P1, P2). Additionally, the limited available evidence base was anticipated to present challenge for the fitting of these latter models.

Digitalised KM curves were divided into monthly time intervals, with extracted survival proportions from each time interval used to calculate patients at risk at the beginning of the time interval, and incident number of deaths. Binomial likelihood distribution derived event probability from the underlying hazard function given by a fractional polynomial, for each time interval (Jansen, 2011). The predicted log-hazard with atezolizumab for each trial at multiple time points was captured with a normal distribution.

For the base-case analysis, informative priors for the FE model parameters were taken from (Turner et al., 2012, Turner et al., 2015). This was due to the limited evidence base with which to estimate between-trial standard deviation. Sensitivity analyses were conducted with weakly informative priors, and vague priors as described in Table 19 below.

Table 19: Priors for between study heterogeneity

Endpoint	Base case: Informative prior derived from Turner (2015)	Weakly informative prior	Vague prior
ORR	τ2 ~ Log-normal (-2.94, 1.792) Source in Turner (2015) Table IV: Internal/external structure related outcomes, pharmacological vs pharmacological	τ2 ~ Log-normal (-2.94, 2.22) Log-normal with same median as base case but 2x larger upper 95% quantile.	τ ~uniform (0,2)
OS: 12-months milestone survival	τ2 ~ Log-normal (-4.18, 1.412) Source in Turner (2015) Table IV: All-cause mortality, pharmacological vs pharmacological	τ2 ~ Log-normal (-4.18, 1.82) Log-normal with same median as base case but 2x larger upper 95% quantile	τ ~uniform (0,2)
OS: digitized KM curves	τ2 ~ Log-normal (-4.18, 1.412) Source in Turner (2015) Table IV: All-cause mortality, pharmacological vs pharmacological	τ2 ~ Log-normal (-4.18, 1.82) Log-normal with same median as base case but 2x larger upper 95% quantile.	τ ~uniform (0,2)
PFS: digitised KM curves	τ2 ~ Log-normal (-2.94, 1.792)Source in Turner (2015) Table IV: Internal/external structure related outcomes, pharmacological vs pharmacological	τ2 ~ Log-normal (-2.94, 2.22) Log-normal with same median as base case but 2x larger upper 95% quantile.	τ ~uniform (0,2)

KM, Kaplan Meier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival
τ2 the random effects variance, τ the random effects standard deviation

4.10.10 Model selection

The DIC compared the goodness-of-fit of competing fixed and RE models, and competing survival and fractional polynomial models. Differences in DIC of less than 5 points were not considered meaningful (Sutton, 2012)

Due to the complexity of the fractional polynomial models, a staggered approach to model selection was taken. This is in contrast to the general preference given to RE models.

FE versions of the models were initially fit. Model fit was assessed, with the RE version of the best performing FE model fit, as per the priors in Table 19. The models were then compared again in terms of DIC and the best performing model was reported as base case.

Model fit was compared using DIC, and additional criteria due to the complexity of the fractional polynomial models. To avoid over-fitting, posterior correlation between parameters were explored – models with excessive posterior correlation indicates over-fitting. The ability of the models to be used for extrapolations and comparisons of estimates against observed KM curves was also considered.

4.10.11 Base-case analysis

When subsequently applied in the economic models for 1L and 2L, the PFS results of the fractional polynomial NMA were unreliable and clinically implausible. As such, an alternative method to derive PFS curves for comparators was utilised. Full details are discussed in section 5.3.4.

As the ORR, 12 month OS, and PFS results of the NMA are not incorporated into the economic model, the results are not discussed in this section. The PFS results are available in appendix 8.5, and ORR and 12 month OS results are available on request.

4.10.11.1 Overall survival: Base-case results (1L)

Including interaction terms did not improve the predictive performance. Therefore, model m1 which contained the four main prognostic factors (proportion above 65, male, proportion with ECOG>=1, liver metastasis) was selected (see Table 20 below). Overall, the predictive performance was limited.

Table 20: Parameter estimates and performance of competing models

Model	m0a	m0b	m1	m2	m3	m4	m5
Parameter							
p65	0.34 (-0.4, 1.2)		0.22 (-0.46, 1.06)	0.85 (-0.14, 2.1)	0.28 (-0.41, 1.11)	-0.16 (-1.15, 1.09)	0.23 (-0.46, 1.03)
male	-0.13 (-0.74, 0.61)		-0.14 (-0.83, 0.63)	-0.04 (-0.72, 0.7)	0.01 (-0.79, 0.88)	-0.12 (-0.8, 0.66)	-1.09 (-2.21, 0.07)
ecog1		0.73 (0.17, 1.33)	0.72 (0.13, 1.32)	0.74 (0.17, 1.33)	0.72 (0.13, 1.32)	0.17 (-1.38, 1.53)	-0.31 (-1.62, 0.99)
liverMet		0.79 (0.15, 1.41)	0.79 (0.13, 1.42)	2.53 (1.27, 4.06)	1.52 (0.25, 3.26)	0.78 (0.12, 1.43)	0.8 (0.13, 1.44)
liverMet.p65				-2.01 (-3.71, -0.59)			
liverMet.male					-0.83 (-2.64, 0.67)		
ecog1.p65						0.66 (-0.82, 2.26)	
ecog1.male							1.31 (-0.16, 2.83)
errorsum[1]	2.89 (1.01, 6.51)	2.85 (1.07, 6.56)	2.88 (1.03, 6.74)	2.86 (1.06, 6.37)	2.88 (1.06, 6.63)	2.87 (1.07, 6.67)	2.86 (1.03, 6.67)
RSS[2]	0.34 (0.04, 1.35)	0.34 (0.04, 1.28)	0.34 (0.04, 1.31)	0.34 (0.04, 1.24)	0.34 (0.04, 1.31)	0.34 (0.04, 1.26)	0.34 (0.04, 1.33)
c.index[3]	0.55 (0.5, 0.6)	0.64 (0.58, 0.7)	0.66 (0.59, 0.72)	0.67 (0.61, 0.73)	0.66 (0.6, 0.72)	0.66 (0.6, 0.72)	0.67 (0.6, 0.73)

[1]Sum of absolute differences between observed and predicted.
[2]Sum of squared differences between observed and predicted.
[3]Concordance index.

Using this model, atezolizumab OS KMs were predicted for each comparator study. Figure 8 and Figure 9 below show these curves, with observed atezolizumab curve taken from cohort 1 of the IMvigor 210 included for comparison. The adjusted atezolizumab curves were almost identical to the original OS KM curves from IMvigor210.

Figure 8: Observed gemcitabine + carboplatin (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from DeSantis(2012)

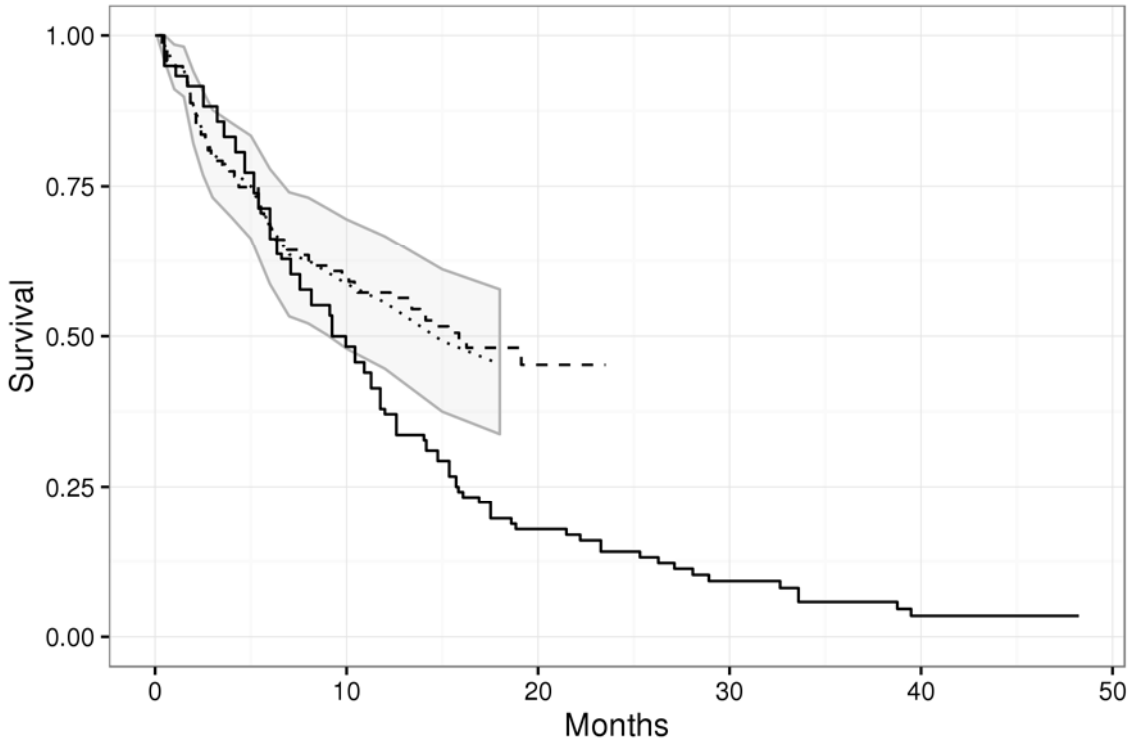
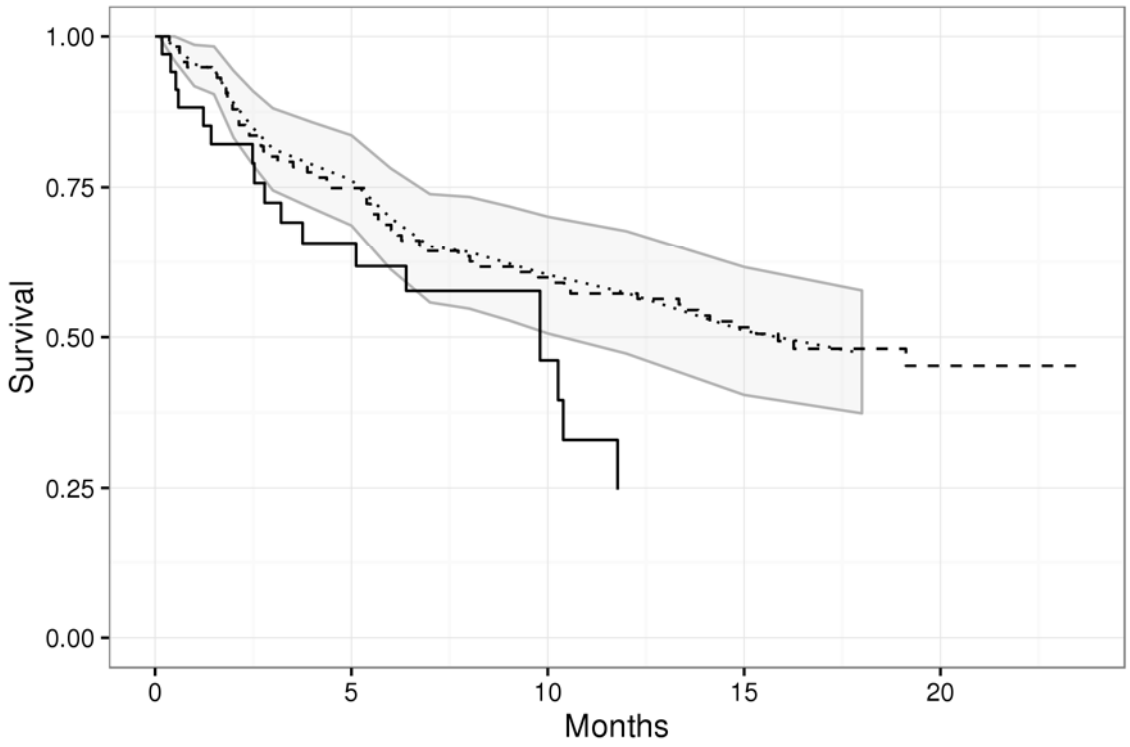


Figure 9 : Observed gemcitabine + carboplatin (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Bamias(2007)



Given the limited evidence base, the zero-order and the two first order fractional polynomial models were fit, but the second order fractional polynomial models were not utilised.

Table 21: Overview and model comparison for the FE fractional polynomial model for OS (1L)

Model	P parameter	Comment	DIC	pD	meanDev
Zero order fractional polynomial	NULL	Exponential model, proportional hazards	236.2	3	233.2
First order fractional polynomial	P1=0	Weibull model	240	6	234
First order fractional polynomial	P1=1	Gompertz model	236.9	6	230.9

The zero-order model had the lowest DIC, though DIC differences were not large enough to differentiate between models (differences of less than 5 points; Table 21). The more complex first order fractional polynomials did not perform better than the proportional hazards model with exponential distribution. Therefore, the zero-order model was selected as base case.

For the zero-order model, the estimated hazard ratio for atezolizumab vs gemcitabine+carboplatin was 0.6 with 95% credible interval (0.47, 0.82).

4.10.11.2 Overall survival: Base-case results (2L+)

Including interaction terms or the number of prior chemotherapies did not improve the predictive performance, as seen in Table 22 below. Therefore, model m1 which contained the four main prognostic factors (proportion above 65, male, proportion with ECOG ≥1, liver metastasis) was selected.

Table 22: Parameter estimates and performance of competing models– OS 2L+

Model	m0a	m0b	m1	m2	m3	m4	m5	m6
Parameter								
p65	0.05 (-0.23, 0.32)		0.05 (-0.25, 0.34)	0.07 (-0.23, 0.38)	-0.02 (-0.39, 0.36)	0.03 (-0.27, 0.36)	-0.07 (-0.54, 0.41)	0.07 (-0.24, 0.38)
male	-0.11 (-0.41, 0.2)		-0.13 (-0.42, 0.17)	-0.12 (-0.42, 0.19)	-0.11 (-0.42, 0.22)	0.08 (-0.32, 0.49)	-0.13 (-0.43, 0.19)	-0.27 (-0.81, 0.32)
ecog1		0.72 (0.43, 1.02)	0.72 (0.43, 1.02)	0.73 (0.43, 1.02)	0.74 (0.44, 1.04)	0.76 (0.47, 1.05)	0.62 (0.19, 1.05)	0.57 (-0.01, 1.16)
liverMet		0.5 (0.23, 0.79)	0.51 (0.22, 0.82)	0.52 (0.24, 0.82)	0.38 (-0.05, 0.85)	0.98 (0.39, 1.56)	0.53 (0.24, 0.83)	0.51 (0.22, 0.82)
priorChem2				-0.13 (-0.41, 0.17)	-0.13 (-0.41, 0.17)	-0.1 (-0.39, 0.2)	-0.12 (-0.41, 0.18)	-0.13 (-0.43, 0.16)
liverMet.p65					0.24 (-0.35, 0.82)			
liverMet.male						-0.59 (-1.28, 0.11)		
ecog1.p65							0.2 (-0.38, 0.79)	
ecog1.male								0.21 (-0.5, 0.86)
errorsum[1]	4.25 (1.83, 9.22)	4.03 (1.81, 8.57)	4.05 (1.81, 8.69)	4.06 (1.83, 8.62)	4.06 (1.78, 8.8)	4.07 (1.79, 8.6)	4.06 (1.83, 8.6)	4.08 (1.84, 8.64)
RSS[2]	0.29 (0.05, 1)	0.26 (0.05, 0.91)	0.26 (0.05, 0.92)	0.26 (0.05, 0.91)	0.26 (0.05, 0.92)	0.26 (0.05, 0.93)	0.26 (0.05, 0.91)	0.27 (0.05, 0.91)
c.index[3]	0.52 (0.5, 0.55)	0.63 (0.59, 0.66)	0.63 (0.6, 0.67)	0.64 (0.6, 0.67)	0.64 (0.61, 0.68)	0.64 (0.61, 0.68)	0.64 (0.6, 0.68)	0.64 (0.6, 0.68)

[1]Sum of absolute differences between observed and predicted.
[2]Sum of squared differences between observed and predicted.
[3]Concordance index.

Using this model, atezolizumab OS KMs were predicted for each comparator study. Figure 10,

Figure **11**, Figure 12 and Figure 13 below show these curves. The observed atezolizumab curve, taken from cohort 2 of IMvigor 210, is included for comparison.

As the predicted atezolizumab arm (represented as 'dotted' in figures) is adjusted for the population of the comparator trial, it is not anticipated the curves will necessarily align with the atezolizumab observed curves from IMvigor 210 (dashed lines). This effect is seen in Figure 10.

Figure 10: Observed BSC (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Noguchi (2016)

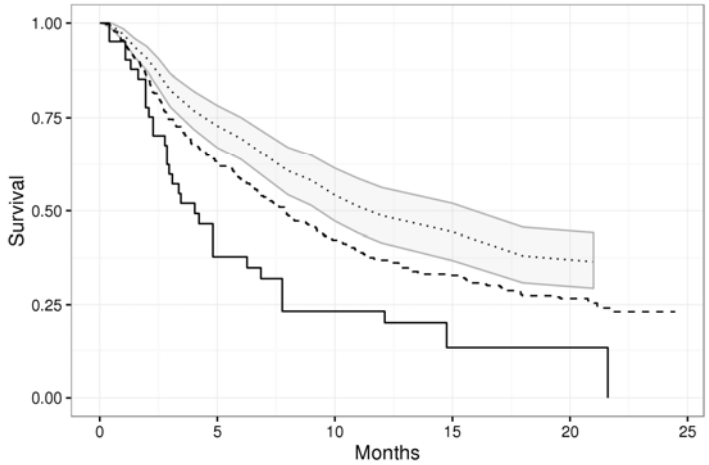


Figure 11: Observed BSC (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Bellmunt(2013/2009)

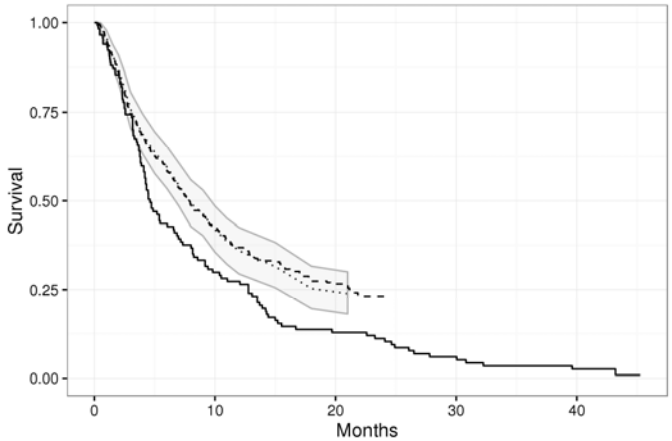


Figure 12: Observed docetaxel (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Choueiri(2012)

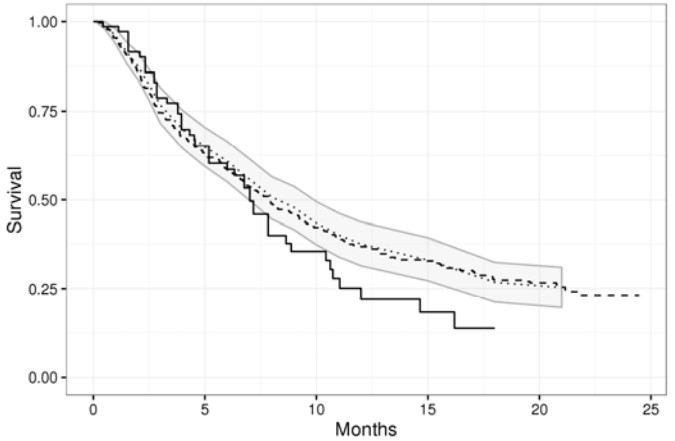


Figure 13: Observed paclitaxel (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Lee(2012)

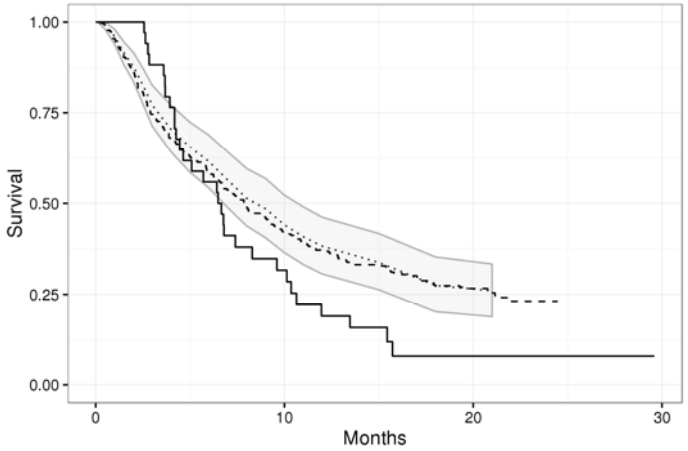
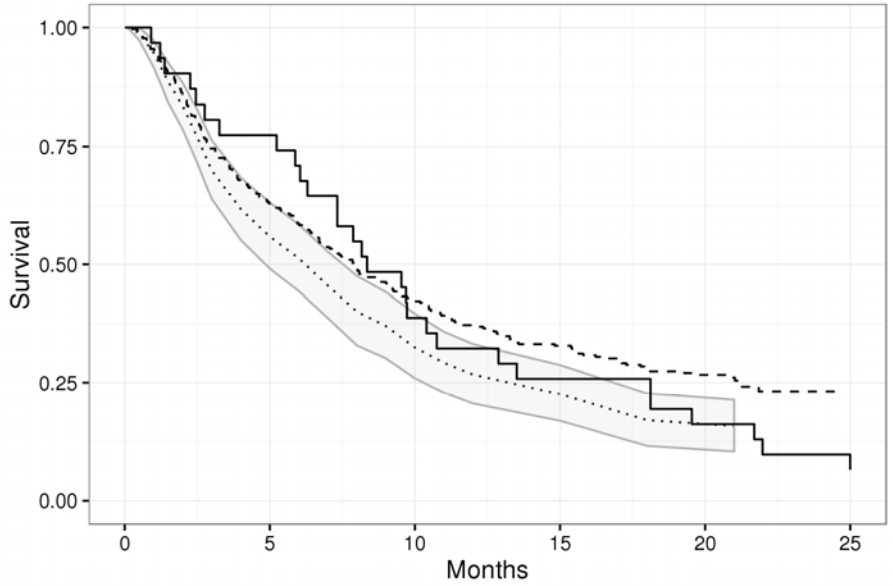


Figure 14: Observed docetaxel (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Kim(2016)



For incorporation of these results into the NMA, the FE model was first fit for the fractional polynomial (as described above). A random effects model was explored in sensitivity analysis.

Table 23: Overview and model comparison under FE fractional polynomial model for OS (2L+)

						Absolute posterior correlations between effect estimates in the FP	
Model	**P parameters**	**Comment**	**DIC**	**pD**	**mean Dev**	**Min.**	**Max.**
Zero order fractional polynomial	NULL	Exponential model, proportional hazards	1742.3	25	1717.3	--	--
First order fractional polynomial	P1=0	Weibull model	1746.6	49.9	1696.7	0.81	0.94
First order fractional polynomial	P1=1	Gompertz model	1654.7	49.9	1604.9	0.73	0.82
Second order fractional polynomial	P1=0, P2=0	NULL	1492.3	74.9	1417.5	0.45	0.98
Second order fractional polynomial	P1=0, P2=1	NULL	1519.9	74.9	1445	0.14	0.93
Second order fractional polynomial	P1=1, P2=1	NULL	1588.2	75.2	1513	0.82	0.99

DIC, Deviance information criterion, pD, model complexity

Taking into account the posterior correlation estimation and DIC values (Table 23 above), the Gompertz model was chosen for the primary OS analysis, based on the following reasoning:

- Among the zero- and first-order models, the Gompertz model had the lowest DIC and acceptable posterior correlations between contrasts estimates (though large even for the Gompertz model);

- Although the second order fractional polynomial models provided a lower DIC, they showed an extremely large posterior correlation among most contrast estimates (>0.9), which suggested over-fitting leading to unstable estimates.

Figure 15, Figure 16 and Figure 17 show the HR estimates for the comparators of interest

Figure 15: H estimates for atezolizumab vs BSC for OS under FE fractional polynomial model

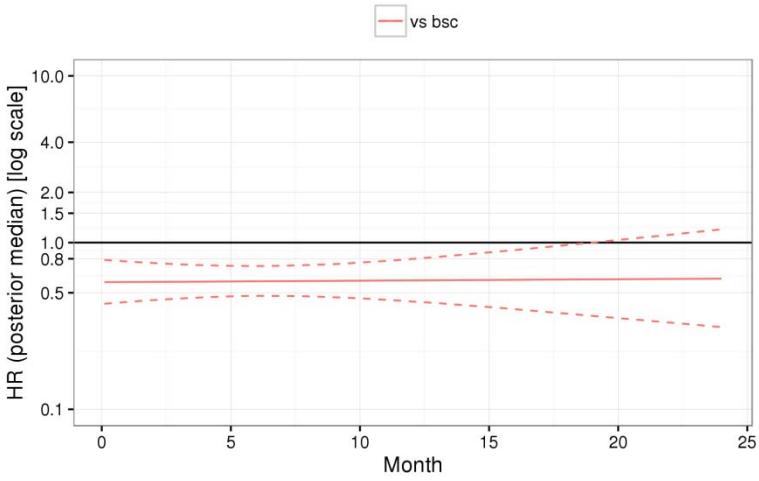


Figure 16: HR estimates for atezolizumab vs paclitaxel for OS under FE fractional polynomial model.

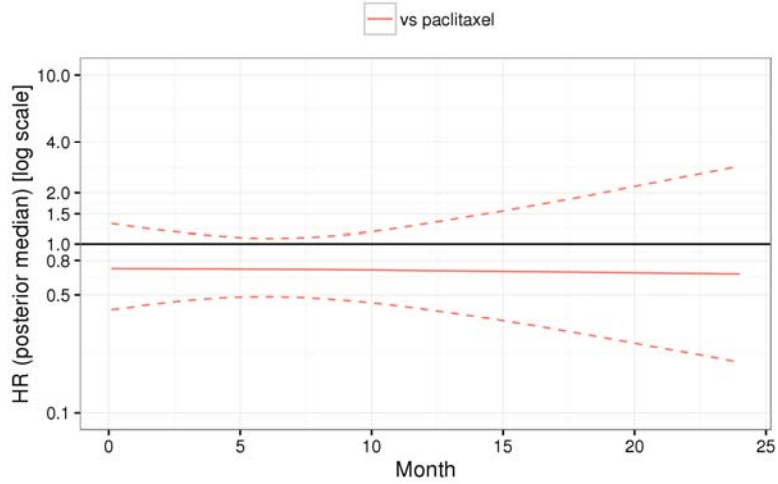


Figure 17: HR estimates for atezolizumab vs docetaxel for OS under FE fractional polynomial model.

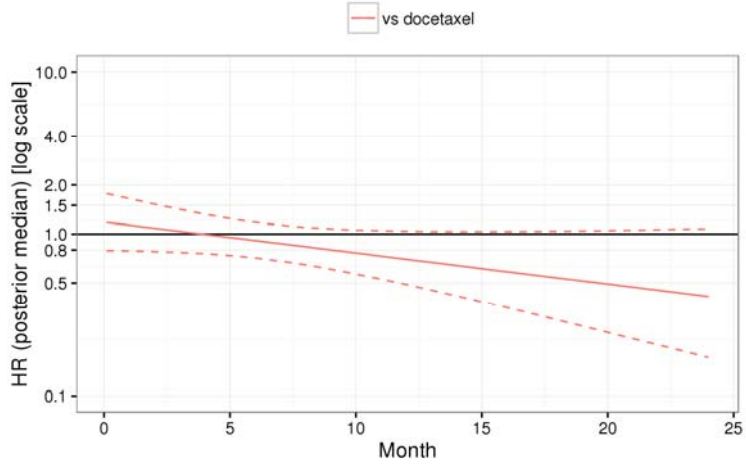


Table 24 provides contrast estimates of the intercept and slope parameters of the logHR function, with respect to comparators of interest vs atezolizumab (the network reference), as well as the posterior correlation between the intercept and slope parameters.

Table 24: Contrast estimates and posterior correlations for OS under FE fractional polynomial model for comparators of interest (2L+)

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation between intercept and slope
BSC	0.547	0.238	0.848	-0.002	-0.038	0.034	-0.736
paclitaxel	0.333	-0.280	0.901	0.003	-0.073	0.070	-0.738
docetaxel	-0.168	-0.581	0.234	0.044	-0.008	0.092	-0.787

BSC, best supportive care

4.10.12 Programming language

For programming language please see appendix 8.6

4.10.13 Appraisal of ITC methodology

The validity of the ITC is largely dependent upon how well the prediction model describes the outcome of interest. This method cannot be considered as strong as an NMA of RCTs because there will always be uncertainty regarding any unknown or unmeasured prognostic factors which may influence the outcome of interest but are not captured in the prediction model. However, in the absence of RCT data, this is unavoidable.

There is risk of ecological bias due to the use of average covariate values from the trials with competing interventions to predict the atezolizumab arms. However, this limitation cannot be overcome in the absence of IPD from other trials.

Not all trials reported baseline values for the covariates of interest (see Table 17). The missing covariate values of such trials were imputed by generating, at every bootstrap iteration, a random value from a uniform distribution, with boundaries

defined by the range of reported values across the studies included in the analysis. This does not account for the correlation structure between covariates. However, given the limited number of studies in the analysis, the approach was considered most practical, and is expected to be conservative as it overestimates the uncertainty of the predicted outcomes.

4.11 Non-randomised and non-controlled evidence

Summary of Clinical Evidence

- The clinical effectiveness of atezolizumab in advanced or metastatic UC has been studied in an open-label Phase II study and an open-label Phase Ia study: IMvigor 210 and PCD4989g (NCT02108652 and NCT01375842, respectively)
- IMvigor 210 includes two population cohorts:
  - Cohort 1: first-line patients unfit for cisplatin-based chemotherapy (n=119)
  - Cohort 2: patients whose disease has progressed during or following one or more lines of therapy, including at least one prior platinum-based chemotherapy regimen (n=310).
- PCD4989g comprises patients with locally advanced or metastatic solid malignancies or haematologic malignancies. The safety-evaluable population included 95 patients with locally advanced or metastatic UC
- Objective response rate (ORR):
  - Cohort 1: Patients treated with atezolizumab had an ORR per IRF (independent review facility) of 19.3% (95% CI: 12.66, 27.58) at the pre-planned primary analysis. At 17.2 months median follow-up duration, the ORR per IRF rose to 22.7% (95% CI: 15.52, 31.27).
  - Cohort 2: Patients treated with atezolizumab had an ORR per IRF of 15.1% (95% CI: 11.3, 19.6) at the pre-planned primary analysis. At 20-months follow-up, the ORR per IRF was 15.8% (95% CI: 11.9, 20.4).
  - PCD4989g: Patients treated with atezolizumab had an ORR per INV (investigator) of 26.6% (95% CI: 18.01, 36.71)
- Duration of response (DOR)
  - Median duration of response had not been reached at the time of the latest available data cut.
  - Cohort 2: Median duration of response had not been reached at the time of the latest available data cut.
  - PCD4989g: median DOR per INV of 22.1 months (95% CI: 12.12, NE)

- Progression-free survival (PFS)
  - Cohort 1: Median PFS was 2.7 months (95% CI: 2·1–4·2)
  - Cohort 2: Median PFS was 2.1 months (95% CI: 2·1–2.1)
  - PCD4989g median PFS per INV RECIST v1.1 was 2.7 months
- Overall survival (OS)
  - Cohort 1: The median OS was 15.9 months (95% CI, 10.4 to NE)
  - Cohort 2: The median OS was 7.9 months (95% CI, 6.7–9.3)
  - PCD4989g median OS was 10.1 months (95% CI: (7.29, 16.99)
- Safety
  - Overall, atezolizumab in IMvigor 210 and PCD4989g was well tolerated, with a low rate of AEs leading to withdrawal from treatment (7.6% in Cohort 1, and 3.9% in Cohort 2, 4.2% in PCD4989g)
  - The safety profile of atezolizumab in IMvigor 210 remains consistent with previous analyses and no new safety concerns were identified with longer follow-up.

4.11.1 Non-randomised evidence for atezolizumab in mUC

As described in Section 4.1, the SLR did not identify any RCT studies with atezolizumab. Table 25 provides a list of non-randomised evidence for atezolizumab in mUC.

Table 25: Non-randomised and non-controlled evidence for atezolizumab in mUC

Study number (acronym)	Objective	Population	Intervention	Justification for inclusion
GO29293 IMvigor 210 Single arm Phase II (F. Hoffmann-La Roche Ltd, 2014, Rosenberg et al., 2016a)	Assess the efficacy and safety of atezolizumab in 2 cohorts: Cohort 1 – First-line patients unfit for cisplatin-based chemotherapy Cohort 2 – patients whose disease has progressed during or following one or more lines of therapy, including at least one prior platinum-based chemotherapy regimen (either containing cisplatin or carboplatin)	Histologically or cytologically documented locally advanced (on the TNM staging system, T4b and any N; or any T and N2-3) or metastatic (M1, stage IV) urothelial carcinoma (including of the renal pelvis, ureter, urinary bladder, or urethra)	Atezolizumab	This study provides efficacy and safety data of atezolizumab in patients with locally advanced or metastatic urothelial carcinoma
PCD4989g Open-label Phase Ia (F. Hoffmann-La Roche Ltd, 2015a)	Evaluate the safety, tolerability, and pharmacokinetics of atezolizumab administered as single agent by IV infusion to patients	Locally advanced or metastatic solid tumours (including UC) or haematologic malignancies	Atezolizumab	This study provides the safety, tolerability, and pharmacokinetics of atezolizumab (results presented in Section 4.11.11)

IV, intravenous; UC, urothelial carcinoma

The scope of this appraisal is to describe the clinical and cost effectiveness of atezolizumab within its anticipated marketing authorisation for treating locally-advanced or metastatic UC, in patients whose disease has progressed after prior chemotherapy or for whom cisplatin-based chemotherapy is unsuitable.

IMvigor210 provides the principal evidence base in relation to the scope. IMvigor 210 is a Phase II, single-arm clinical trial to evaluate the efficacy and safety of atezolizumab in either:

- Cohort 1: patients with advanced UC who were medically ineligible to receive cisplatin chemotherapy (cisplatin-ineligible), and were either previously untreated or had disease progression at least 12 months after their last dose

of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen (n=119), or;

- Cohort 2: patients with advanced UC who had disease progression following treatment with a platinum-based chemotherapy regimen (n=310) (Rosenberg et al., 2016a).

The **primary analyses for Cohort 2** were performed when a minimum of 24 weeks follow up had elapsed after the last patient in Cohort 2 has been enrolled. At the time of the primary analysis of Cohort 2, an **interim analysis of Cohort 1** was performed. The **primary analysis of Cohort 1** was performed when a minimum of 24 weeks follow up had elapsed after the last patient in Cohort 1 had been enrolled, at which point there was also an **updated analysis of Cohort 2**.

Table 26 shows the data cut-off dates for the IMvigor 210 analyses. The primary analyses results are taken from the 5th May 2015, and 14th September 2015 data cuts for cohort 2 and cohort 1 respectively. The secondary results presented in this submission are taken from the 4th July 2016 data cut.

Table 26: IMvigor 210 data cuts

Date of data-cut	Analysis	Reference
5th May 2015	Primary analysis of Cohort 2 Interim efficacy analysis of Cohort 1	IMvigor 210 (CSR)
14th September 2015	Primary analysis of Cohort 1 Updated analysis of Cohort 2	IMvigor 210 (CSR)
5th May 2015 14th September 2015	Primary, *and* Updated analysis of Cohort 2	Rosenberg 2016 (2L)
4th July 2016	Follow up analysis Cohort 1 and 2	Supplemental results report for study IMvigor 210
4th July 2016	Follow up analysis of	Bellmunt 2016 ESMO

	Cohort 1	(1L)
4th July 2016	Follow up analysis of Cohort 2	Loriot 2016 ESMO (2L)
5th May 2015 14th September 2015 4th July 2016	Interim, *and* Primary, *and* Updated analysis of cohort 1	Balar 2016 (1L)

CSR, clinical study report; ESMO, European Society for Medical Oncology;

The results of IMvigor 210 are supported by results from the bladder cancer cohort from study PCD4989g (n=95). This includes a significant number of patients treated with the Phase II/III dose of atezolizumab in mUC and the prolonged follow up in this study helps establish the durability of responses in this patient population. A brief summary of the results from this study can be found in Section 4.11.11.

4.11.2 Rationale for exclusion of trials

No trials investigating atezolizumab in patients with mUC were excluded from this submission. Results from the IMvigor 210 trial are presented here, supported by a brief summary of the PCD4989g study results in Section 4.11.11.

4.11.3 Summary of the methodology of non-randomised trials

IMvigor 210 is a single arm trial of atezolizumab, with 438 patients with mUC enrolled into two separate cohorts (F. Hoffmann-La Roche Ltd, 2015b). A summary of the methodology of this trial is provided in Table 27.

Table 27: Summary of the methodology of the non-randomised and non-controlled atezolizumab Phase II study

Trial number (Acronym)	GO29293 (IMvigor 210)
Location	Patients were recruited from 70 centres in North America and Europe, including 3 sites in the UK (Rosenberg et al., 2016a)
Trial design	Global single-arm open-label Phase II study (F. Hoffmann-La Roche Ltd, 2015b)
Eligibility criteria for participants	Patients with locally advanced or metastatic UC were enrolled regardless of their PD-L1 expression, or number of prior therapies (from first-line cisplatin-ineligible patients to heavily-treated patients with exposure to multiple prior regimens). Patients were enrolled into one of two cohorts (F. Hoffmann-La Roche Ltd, 2014): Cohort 1: chemotherapy-naïve patients who are cisplatin-ineligible (N=119) Cohort 2: patients who have progressed during or after at least one platinum chemotherapy regimen (N=310)
PD-L1 subgroups	Baseline PD-L1 expression in tumour specimens was centrally evaluated using the VENTANA PD-L1 (SP142) immunohistochemistry assay (Ventana Medical Systems, Mountain View, California, US) (Bellmunt et al., 2016). PD-L1 expression on IC was evaluated based on three scoring levels (Bellmunt et al., 2016): • IC2/3, ≥5% PD-L1 expression in IC • IC1, ≥1% and <5% PD-L1 expression in IC • IC0, <1% PD-L1 expression in IC
Trial drugs, permitted and disallowed concomitant medication	Single-agent atezolizumab 1200 mg administered by intravenous infusion on Day 1 of each 21-day cycle until disease progression per RECIST v1.1 (Cohort 1 only) or until lack of clinical benefit (Cohort 2) (F. Hoffmann-La Roche Ltd, 2015b)
Patient monitoring	Patients had tumour assessments at baseline, every 9 weeks for 12 months, and every 12 weeks thereafter. Patients who discontinued treatment continued follow-up assessments for survival and subsequent anti-cancer therapy every ≈3 months until death, loss to follow-up, withdrawal of consent, or study termination, whichever occurred first (Bellmunt et al., 2016, Loriot et al., 2016)
Primacy outcomes	Co-primary endpoint: • IRF-assessed ORR (confirmed) per RECIST v1.1 (central independent review; Cohort 1 & 2), and; • INV-assessed ORR (per modified RECIST; immune-related response criteria [Cohort 2 only]) (F. Hoffmann-La Roche Ltd, 2014)
Secondary outcomes	DOR and PFS assessed by the IRF and investigator per RECIST v1.1, OS, and 1-year OS. DOR and PFS per modified RECIST will be additional secondary endpoints. The efficacy endpoints as assessed by modified RECIST are applicable only to Cohort 2 (F. Hoffmann-La Roche Ltd, 2014)

Exploratory objectives	• Further evaluate anti-tumour activity by IHC categories • Evaluate the relationship between tumour biomarkers (including but not limited to PD L1, PD-1, and others), as defined by IHC and efficacy • Assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumour tissue and blood and their association with disease status and/or response to study treatment • Evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumour volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumour immune infiltration) from true disease progression • Evaluate investigator-assessed TIR per RECIST v1.1 • Evaluate investigator-assessed TIR per modified RECIST • Evaluate DCR

DCR, disease control rate; DOR, duration of response; IHC, immunohistochemistry; IRF, independent Review Facility; INV, investigator; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumour; TCGA, The Cancer Genome Atlas; TIR, time in response; UC, urothelial carcinoma

4.11.4 Statistical analysis of the non-randomised and non-controlled evidence

As a single arm study, assessment of the primary endpoint did not involve formal statistical comparison between a control and intervention group.

The efficacy analyses were performed on the intention-to-treat population. For the primary endpoint of ORR, a hierarchical fixed-sequence testing procedure was used to compare the ORR between the treatment group and a historical control for three pre-specified populations in the following order (Rosenberg et al., 2016a):

- Objective response-evaluable patients with a PD-L1 immunohistochemistry score of IC2 or 3 (IC2/3)
- Objective response-evaluable patients with a score of IC1, 2, or 3 (IC1/2/3)
- All objective response-evaluable patients

Hypothesis tests were carried out on these three populations sequentially on the basis of independent review facility-assessed ORR according to Response Evaluation Criteria In Solid Tumour (RECIST) v1.1 followed by the investigator-assessed ORR according to immune-modified RECIST at a specific two-sided α level of 0·05 for each test, while controlling the overall type I error at the same α level. If no statistical significance was detected at a particular level in the hierarchy, then no further hypothesis testing was done. The study was designed to estimate the

ORR in patients receiving atezolizumab and to detect an improvement in the ORR compared with a historical 10% response rate (Rosenberg et al., 2016a).

IMvigor 210 had a variable range of statistical power at different alternative ORRs. The aim was to enrol a minimum of around 100 patients with an immunohistochemistry score of IC2/3, resulting in an overall sample size of approximately 300 patients based on an estimated 30% prevalence for the IC2/3 population. The 95% CI using the Clopper-Pearson method for an observed ORR of 40% was 30–50%, and the study would have 100% power to detect a 30% increase in ORR from 10% to 40%. Alternatively, the 95% CI using the Clopper-Pearson method for an observed ORR of 20% was 13–29%, and the study would have 85% power to detect a 10% increase in ORR from 10% to 20%. The primary analysis was triggered by a minimum of 24 weeks of follow-up from the final patient enrolled (data cut-off: 5th May 2015 for cohort 2, and 14th September 2015 for cohort 1).

4.11.5 Participant flow in the studies

Study population and baseline characteristics for Cohort 1

The Cohort 1-specific inclusion criteria included (Bellmunt et al., 2016):

- No prior treatment for mUC (12 months since perioperative chemotherapy)
- ECOG PS 0–2

Cisplatin ineligibility based on ≥1 of the following:

- Glomerular filtration rate (GFR) <60 and 30 mL/min by Cockcroft-Gault formula
- Grade ≥2 hearing loss (25 dB at 2 contiguous frequencies)[1]
- Grade ≥2 peripheral neuropathy[1]
- ECOG PS 2

1: CTCAE v 4 (National Cancer Institute Comment Terminology Criteria for Adverse Events version 4

The eligibility criteria for Cohort 1 are presented in Table 28.

The baseline characteristics and demographics for the Cohort 1 patient population were consistent with what is observed in the general UC population and in other clinical trials for 1L cisplatin-ineligible urothelial carcinoma (5 patients from the UK

were enrolled in Cohort 1 of IMvigor 210) (Bellmunt et al., 2009) (Table 29). The most common reasons for patients being cisplatin-ineligible were baseline impaired renal function (GFR >30 but <60 mL/min; 69.7%) followed by ECOG PS of 2 (20.2%); impaired renal function is a common reason for patients being cisplatin-ineligible (Balar et al., 2016b) because pre-existing renal impairment is a risk factor for cisplatin-induced nephrotoxicity (Galsky et al., 2011). Baseline characteristics were representative of patients with poor prognostic factors including: ECOG PS = 2 (20.2% of patients); visceral metastasis (65.5%); liver metastasis (21.0%); two Bajorin Risk Factors (15.1%); creatinine clearance < 60 mL/minute (70.6%) (F. Hoffmann-La Roche Ltd, 2016b).

15.1% of patients within the cisplatin-ineligible Cohort 1 have been recorded as having previous cisplatin chemotherapy. These patients are likely to have received this as a neoadjuvant treatment in an earlier disease setting and subsequently experienced progressive disease and been deemed cisplatin ineligible at the time of selection of first line treatments in the metastatic setting.

Study population and baseline characteristics for Cohort 2

The Cohort 2-specific inclusion criteria included:

- Progression during or following platinum with no restrictions on the number of prior line of therapy
- Creatinine clearance ≥ 30 mL/min
- ECOG PS 0–1

The eligibility criteria for Cohort 2 are presented in Table 28.

The demographic profile of the safety evaluable population of Cohort 2 is representative of the general UC population in clinical practice (17 patients from the UK were enrolled in Cohort 2 of IMvigor 210) and consistent with patient populations in other recent clinical trials in 2L UC (i.e., vinflunine and taxanes) (Bellmunt et al., 2009) (Table 29). The median age of the all-patient population for Cohort 2 was 66.0 years, with a range from 32 to 91 years (Table 29). The majority of patients were male (78%) and white (91%). A total of 96 patients (31%) had liver metastasis, and 193 patients (62%) had ECOG 1 performance status. In Cohort 2, approximately

40% of patients received ≥ 2 regimens in the metastatic setting, consistent with a heavily pre-treated population. There were 227 patients (73%) with a prior cisplatin−based regimen; 80 patients (26%) had a prior carboplatin and no other platinum-based regimen, which is broadly representative of UK clinical practice in mUC..

Table 28: Inclusion and exclusion criteria for Cohort 1 & 2 of IMvigor 210 (F. Hoffmann-La Roche Ltd, 2014)

Cohort	Inclusion criteria	Exclusion criteria
Cohort 1 & 2	• Signed Informed Consent Form • Ability to comply with protocol • Age ≥ 18 years • Histologically or cytologically documented locally advanced (T4b, any N; or any T, N 2–3) or metastatic (M1, Stage IV) TCC (also termed urothelial cell carcinoma) of the urothelium (including renal pelvis, ureters, urinary bladder, urethra) o Patients with mixed histologies are required to have a dominant transitional cell pattern o Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical stage T4b) or bulky nodal metastasis (N2–N3) • Representative FFPE tumour specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to have sufficient viable tumour content prior to study enrollment; tumour specimens will be evaluated for PD-L1 expression; patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor • ECOG performance status of 0 or 1 (Patients with ECOG performance status of 2 are allowed in Cohort 1) • Life expectancy ≥ 12 weeks • Measurable disease, as defined by RECIST v1.1	Cancer-specific criteria: • Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment; the following exceptions are allowed: o Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging o Hormone-replacement therapy or oral contraceptives • Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to enrolment • Active or untreated CNS metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments • Patients with treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria: o Evaluable or measurable disease outside the CNS o No metastases to midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm) o No history of intracranial or spinal cord haemorrhage o No evidence of significant vasogenic oedema o No ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dose allowed

	• Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment • For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of atezolizumab	o No stereotactic radiation, whole-brain radiation or neurosurgical resection with 4 weeks prior to Cycle 1, Day 1 o Radiographic demonstration of interim stability (i.e., no progression) between the completion of CNS-directed therapy and the screening radiographic study o Screening CNS radiographic study ≥ 4 weeks since completion of radiotherapy or surgical resection and ≥ 2 weeks since discontinuation of corticosteroids • Leptomeningeal disease • Uncontrolled tumour-related pain • Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) • Uncontrolled hypercalcemia (> 1.5 mmol/L ionised calcium or Ca >12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab General medical exclusion criteria: • Pregnant and lactating women • History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins • Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation • History of autoimmune disease • History of idiopathic pulmonary fibrosis, organising pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan • Serum albumin < 2.5 g/dL • Positive test for HIV • Patients with active HBV (chronic or acute, defined as having a positive hepatitis B surface

		antigen [HBsAg] test at screening) or HCV • Active tuberculosis • Severe infections within 4 weeks prior to Cycle 1, Day 1 • Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1 • Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1 • Received therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1 • Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina • Major surgical procedure other than for diagnosis within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study • Prior allogeneic stem cell or solid organ transplant • Administration of a live, attenuated vaccine within 28 days prior to randomisation or anticipation that such a live attenuated vaccine will be required during the study • Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications Medication-related exclusion criteria: • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies • Treatment with systemic immunostimulatory agents (including but not limited to IFNs,

		IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1 • Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF anti-TNF agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial
Cohort 1-specific	• No prior chemotherapy for inoperable locally advanced or metastatic or recurrent UC o For patients who received prior adjuvant/neoadjuvant chemotherapy or chemoradiation for UC, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting o Prior local intrarvesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment • Ineligible (“unfit”) for cisplatin-based chemotherapy as defined by any one of the following criteria: o Impaired renal function (GFR > 30 but < 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethylenediaminetetra acetate) or, if not available, by calculation from serum/plasma creatinine o A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies o Grade ≥ 2 peripheral neuropathy (i.e., sensory alteration or paresthesias including tingling) o ECOG performance score of 2	

Cohort 2-specific	• Disease progression during or following treatment with at least one platinum containing regimen (e.g., GC, MVAC, CarboGem) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence o A regimen is defined as patients receiving at least two cycles of a platinum containing regimen. Patients who have received one cycle of a platinum-containing regimen but discontinued due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity may also be eligible o Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen will be considered as second-line patients o Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port	

CNS, central nervous system; CT, computed tomography; CTLA, cytotoxic-T-lymphocyte-associated antigen; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; GC, Gemcitabin plus cisplatin; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; MVAC, methotrexate, vinblastinem doxorubicin and cisplatin; RECIST, response evaluation criteria in solid tumours; TCC, transitional cell carcinoma; TNF, tumour necrosis factor; UC, urothelial cancer; ULN, upper normal limit

Table 29: Baseline characteristics for Cohort 1 and Cohort 2 from IMvigor 210 (F. Hoffmann-La Roche Ltd, 2016b)

IMvigor 210	Cohort 1: 1L Cisplatin-ineligible population n=119[a]	Cohort 2: Platinum-treated mUC n=310
Age, median (range)	73.0 (51–92)	66.0 (32–91)
≥ 80 years	21.0%	7.7%
Male | Female	80.7% | 19.3%	77.7% | 22.3%
PD-L1 status on IC		
IC0 | IC1 | IC2/3[b] | IC1/2/3	32.8% | 40.3% | 26.9% | 67.2%	33.2% | 34.5% | 32.2% | 66.8%
Primary tumour site[c]		
Bladder/urethra	71.4%	76.8%

Renal pelvis/ureter	27.7%	22.2%
Metastatic disease	92.4%	93.9%
Visceral sites[d]	65.5%	78.4%
Liver only	21.0%	31.0%
Lymph node only	26.1%	13.9%
Prior therapy		
Radiotherapy	10.1%	31.9%
Perioperative chemotherapy[e]	20.2%	18.0%
Cisplatin-based	15.1%*	72.9%
Carboplatin-based	0.8%	26.1%
Number of prior regimens (metastatic setting)	n=0, 98.3% n=1, 1.7%	n=0, 18.1% n=1, 39.0% n=2, 21.3% n≥3, 21.6%
Renal impairment, GFR <60 and >30 mL/min	69.7%	35%
Hearing loss, 25 dB[f]	14.3%	N/A
Peripheral neuropathy, ≥Grade 2	5.9%	N/A
ECOG 0	37.8%	37.7%
ECOG 1	42.0%	62.3%
ECOG PS 2	20.2%	0.3%
Renal impairment and ECOG PS 2	6.7%	N/A
Prior cystectomy or nephroureterectomy	N/A	73.5%
Haemoglobulin ≤ 10 g/dl	N/A	22.3%

ECOG, Eastern Cooperative Oncology Groups; GFR, glomerular filtration rate; IC, immune cell; mUC, metastatic urothelial cancer

[a]Efficacy and safety-evaluable patient population. [b]PD-L1 expression on IC was evaluated (VENTANA SP142 immunohistochemistry [IHC] assay) based on 3 scoring levels: IC0 (<1%), IC1 (≥1% but <5%), IC2/3 (≥5%). [c]One patient with prostatic urethra primary site not included. [d]Visceral metastasis defined as liver, lung, bone, any non-lymph node or soft tissue metastasis. [e]Includes neoadjuvant/adjuvant chemotherapy for all but 1 patient, who received targeted therapy. [f]At 2 contiguous frequencies.

*15.1% of Cohort 1 patients recorded prior cisplatin chemotherapy. This is likely due to treatment with cisplatin in the neoadjuvant setting, and following progression patients are subsequently deemed cisplatin ineligible.

4.11.6 Quality assessment of the relevant non-randomised evidence

An independent Data Monitoring Committee (iDMC) reviewed the safety data every 6 months after first patient in (F. Hoffmann-La Roche Ltd, 2014). All summaries and analyses for the IDMC's review were prepared by an independent Data Coordinating Center (iDCC). Members of the iDCC were external to Roche (F. Hoffmann-La Roche Ltd, 2014).

CT scans or MRI scans were submitted to an independent review facility (IRF) for central review (F. Hoffmann-La Roche Ltd, 2014).

Safety analyses were performed on all treated patients, i.e., enrolled patients who received any amount of the study treatment. Efficacy analyses were primarily based on the intent-to-treat (ITT) population, i.e., enrolled patients who received any amount of the study drug. ORR analyses were an exception as it was performed on the objective response-evaluable population, i.e., ITT patients who have measureable disease per RECIST v1.1 at baseline. DOR and time in response (TIR) analyses were performed on the subset of patients who achieved an objective response. OS and PFS analyses were performed on the ITT population regardless of whether they had measurable disease per RECIST v1.1 at baseline (F. Hoffmann-La Roche Ltd, 2014).

4.11.7 Methods for assessing risk of bias

IMvigor 210 is a Phase II single arm study therefore the risk of bias was not assessed.

4.11.8 Summary of responses applied to each of the quality assessment criteria

There is only one non-randomised trial presented in this submission.

4.11.9 Complete quality assessment

No RCT evidence was identified. Please see Section 4.1 for further details.

4.11.10 Clinical effectiveness results of the relevant non-randomised evidence

4.11.10.1 IMvigor 210

The co-primary endpoints in IMvigor 210 are ORR per IRF-RECIST[1] v1.1 (Cohort 1 and Cohort 2) and per INVmodified RECIST (mRECIST[2]; Cohort 2 only), both compared to a historical control ORR of 10%. Secondary endpoints include DOR, PFS, and OS.

In the following section, results by outcome are presented first by Cohort 1, followed be the complementary set of results for Cohort 2. IC subgroups results are shown only for ORR in Cohort 1 and Cohort 2 as per the pre-planned primary analyses; unless otherwise specified, the results refer to the all-patient population.

4.11.10.2 Efficacy results for cohort 1 (1L)

Primary efficacy results for Cohort 1 have a cutoff date of 14th September 2015 (hereafter referred to as the cohort 1 primary analysis) and results from the updated analyses shown have a later cutoff date of 4th July 2016 (hereafter referred to as the cohort 1 15-month follow-up analysis) (F. Hoffmann-La Roche Ltd, 2016b). The 1L primary efficacy analysis was carried out when the last patient enrolled had a minimum of 6 months follow-up (Balar et al., 2016b).

With a median follow-up of 17.2 months, 25 (21%) patients had been treated for more than 52 weeks and 17 (14%) remained on treatment (Balar et al., 2016b). The median treatment duration was 15 weeks (range 0–102) (Balar et al., 2016b).

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[1] RECIST provides strict definitions of the number and minimum sizes of target lesions, and precise definitions of objective response and progression THERASSE, P., ARBUCK, S. G., EISENHAUER, E. A., WANDERS, J., KAPLAN, R. S., RUBINSTEIN, L., VERWEIJ, J., VAN GLABBEKE, M., VAN OOSTEROM, A. T., CHRISTIAN, M. C. & GWYTHER, S. G. 2000. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst,* 92**,** 205-16.

[2] mRECIST quantifies only the viable portions of the tumour LLOVET, J. M., DI BISCEGLIE, A. M., BRUIX, J., KRAMER, B. S., LENCIONI, R., ZHU, A. X., SHERMAN, M., SCHWARTZ, M., LOTZE, M., TALWALKAR, J., GORES, G. J. & PANEL OF EXPERTS IN, H. C. C. D. C. T. 2008. Design and endpoints of clinical trials in hepatocellular carcinoma. Ibid.100**,** 698-711, LENCIONI, R. & LLOVET, J. M. 2010. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis,* 30**,** 52-60.

ORR and DOR cohort 1 (1L)

The cohort 1 primary analysis (median follow-up duration of 8.5 months [range 0.2–14.3]) shows that, compared with a historical control of 10%, the ORR of the all-patient population was 19.3% (95% confidence interval [CI]: 12.66, 27.58) (F. Hoffmann-La Roche Ltd, 2015b) (Table 30).

Table 30: IMvigor 210 (Cohort 1) Objective response rate by IRF – RECIST v1.1 criteria by independent review, preplanned cohort 1 primary analysis, data cutoff: 14th September 2015 (F. Hoffmann-La Roche Ltd, 2015b)

	All patients (n = 119)	IC2/3 (n = 32)	IC1/2/3 (n = 80)
ORR, % (95% CI)	19.3 (12.66, 27.58)	21.9 (9.28, 39.97)	18.8 (10.89, 29.03)
CR rate, % (95% CI)	5.0 (1.87, 10.65)	3.1 (0.08, 16.22)	3.8 (0.78, 10.57)

CI, confidence interval; CR, complete response; IC, immune cell; ORR, objective response rate

At the cohort 1 15 month follow-up analysis, the ORR further increased to 22.7% (95% CI, 15.52–31.27) in the all–patient population (Table 31) (Balar et al., 2016b, F. Hoffmann-La Roche Ltd, 2016b). The updated ORR by PD-L1 subgroup rose to 28% (95% CI, 14–47) in the IC2/3 subgroup and 24% (95% CI,15–35) in the IC1/2/3 subgroup (Balar et al., 2016b). Complete responses were seen in 11 (9%) patients (Table 31) (Balar et al., 2016b).

Median response duration had not been reached and 19 (70%) of 27 responses were ongoing (Balar et al., 2016b).

Table 31: IMvigor 210 (Cohort 1) Objective response rate by IRF per RECIST v1.1, cohort 1 15-month follow-up analysis, data cutoff: 4th July 2016 (Bellmunt et al., 2016, F. Hoffmann-La Roche Ltd, 2016b)

Subgroup	All patients n=119
ORR, % (95% CI)[a]	22.7 (15.52, 31.27)
CR rate, %	9.2

CR, complete response; ORR, objective response rate

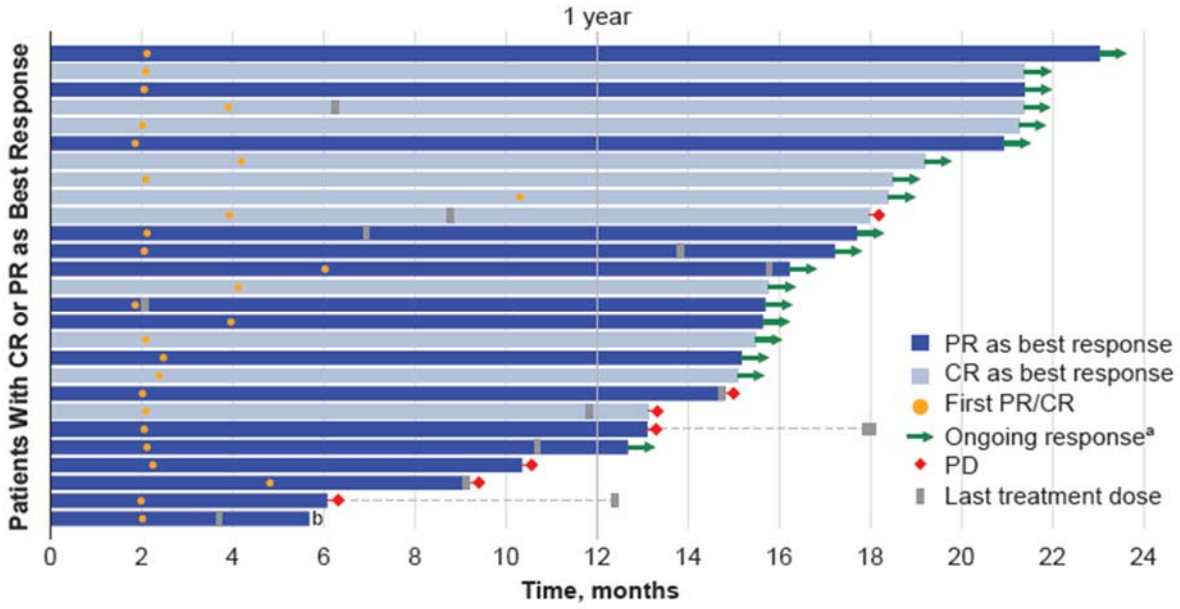
[a] Includes 20 patients with missing/unevaluable responses. All treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1.

With longer follow-up at the cohort 1 15 month follow up analysis, all-patient ORRs have remained consistent with the cohort 1 primary analysis, and additional patients with CR have been observed (Bellmunt et al., 2016).

The efficacy results from the cohort 1 15-month follow-up analysis have confirmed the finding from the cohort 1 primary analysis, that response rate across unselected patients exceeds the 10% historical control (Table 30). It also demonstrated that the majority of responses were longer than a year in duration with many still ongoing at the time of analysis (see Figure 17) (Bellmunt et al., 2016, F. Hoffmann-La Roche Ltd, 2016b)

Median time to onset of first response was 2.1 months (range 1.8–10.5), which was consistent with the timings of the first scan in the protocol, but late responses were also seen (after 6 months in two patients) (Figure 18) (Bellmunt et al., 2016). The clinical benefit rate was 30% (defined as the rate of complete responses plus partial responses (PR) plus stable disease for ≥24 weeks (Balar et al., 2016b).

Figure 18: IMvigor 210 (Cohort 1) Duration of treatment and response by objective response status, cohort 1 15-month follow-up analysis, data cutoff: 4th July 2016 (Bellmunt et al., 2016)



CR, complete response; PD, progressive disease; PR, partial response

PFS cohort 1 (1L)

At the 15 month follow-up analysis, median PFS was 2.7 months (95% CI: 2.1–4.2).

Table 32: IMvigor 210 (Cohort 1) Progression-free survival, cohort 1 15-month follow-up analysis, data cutoff: 4th July 2016 (F. Hoffmann-La Roche Ltd, 2016b)

PFS (IRF-assessed; RECIST v1.1)	Cohort 1 15-month follow-up analysis (cutoff date: 4th July 2016)
	All patients (n=119)
No. of patients with event (%)	88 (73.9)
Median time to event (months)	2.7
95% CI	2.1, 4.2

CI, confidence interval; PFS, progression-free survival; IRF, independent review facility

OS cohort 1 (1L)

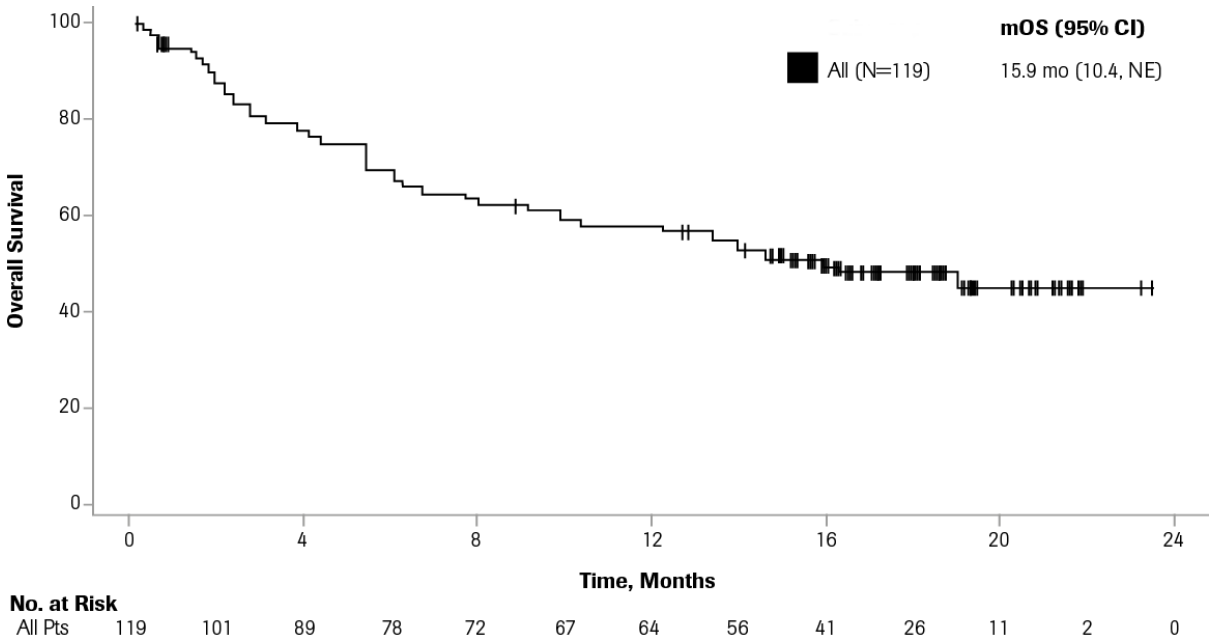
At the cohort 1 15 month follow-up analysis, the median OS was 15·9 months (95% CI: 10.4 to NE) (Table 33 and Figure 19) and the 12-month landmark survival was 57% (95% CI: 48–66) (Balar et al., 2016b).

Table 33: IMvigor 2010 (Cohort 1) Median OS and 12-month OS, cohort 1 15-month follow-up analysis, data cutoff: 4th July 2016 (Bellmunt et al., 2016)

OS (IRF-assessed; RECIST v1.1)	All patients n=119
Median OS (95% CI)	15.9 months (10.4, NE)
12-month OS rate (95% CI)	57.2% (48.2%, 66.3%)

CI, confidence interval; NE: Not estimable; OS, overall survival; RECIST, response evaluation criteria in solid tumours

Figure 19: IMvigor 210 (Cohort 1) Kaplan-Meier OS plot, cohort 1 15-month follow-up analysis, data cutoff: 4th July 2016 (Bellmunt et al., 2016)



NE, not estimable

Patients at risk of an event are displayed at indicated time point below the plot. Censored values are indicated with a plus (+) symbol.

Subgroup analysis cohort 1 (1L)

Outcomes were assessed in key clinical subgroups (Bellmunt et al., 2016, Balar et al., 2016b). Good response rates were seen across subgroups as defined by demographic and baseline characteristics. As reported for ORR above positive resposes were observed across all subgroups defined by IC status. These results demonstrate that atezolizumab is efficacious in a broad range of patients. However, given that IMvigor 210 is a single-arm study, results should be interpreted with caution (Balar et al., 2016b).

4.11.10.3 Efficacy results for cohort 2 (2L+)

Primary efficacy results for Cohort 2 are based on data presented in the Rosenberg et al. publication with a data cutoff date of 5th May 2015 (hereafter referred to as the cohort 2 primary analysis) and additional results shown are from the later cutoff date of 4th July 2016 (hereafter referred to as the cohort 2 20-month follow-up).

The median duration of follow up at the 4th July 2016 data cutoff was 21.1 months (range 0.2*–24.5 months, where * denotes a censored value) (F. Hoffmann-La Roche Ltd, 2016b).

ORR and DOR cohort 2 (2L+)

The cohort 2 primary analysis showed that compared with an ORR of 10% in historical control, treatment with atezolizumab resulted in a significantly improved ORR (as per RECIST v1.1) in the all-patient population (15.1%; 95% CI: 11.3–19.6, p=0·0058) and for each pre-specified IC subgroup (IC2/3: 27.0% [95% CI: 18.6–36.8)], p<0·0001; IC1/2/3: 18.3% [95% CI: 13.3–24.2], p=0·0004) (Table 34) (Rosenberg et al., 2016a). Table 34 shows the ORR per INV-assessed results. The cohort 2 20-month follow-up analyses of INV-assessed ORR remained consistent with the ORR reported in the cohort 2 primary analysis, in the all-patient population and in each IC subgroup (F. Hoffmann-La Roche Ltd, 2016b).

Table 34: IMvigor 210 (Cohort 2) Objective response rate by (IRF) PD-L1 status – RECIST v1.1 criteria by independent review, pre-planned cohort 2 primary analysis, data cutoff: 5th May 2015 (Rosenberg et al., 2016a, F. Hoffmann-La Roche Ltd, 2016b)

	All Patients (n = 311)	**IC2/3 (n = 100)**	**IC1/2/3 (n = 208)**
ORR per IRF RECIST v1.1[a] (95% CI)	15.1% (11.3–19.6)	27.0% (18.6–36.8)	18.3% (13.3–24.2)
CR rate per IRF RECIST v1.1 (95% CI)	3.9% (2.0–6.6)	8.0% (3.5–15.2)	5.3% (2.7–9.3)

CI, confidence interval; CR, complete response; IC, immune cells; ORR, objective response rate

[a]Objective response evaluable population: all treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1

Table 35: IMvigor 210 (Cohort 2) Objective response rate (INV) by PD-L1 status – RECIST v1.1 criteria by independent review, pre-planned cohort 2 primary analysis, data cutoff: 5th May 2015 (F. Hoffmann-La Roche Ltd, 2016b)

	All Patients (n = 311)	IC2/3 (n = 100)	IC1/2/3 (n = 208)
ORR per INV RECIST v1.1 (95% CI)	16.1% (12.2–20.6)	23.0% (15.2–32.5)	17.8% (12.8–23.7)
CR rate per INV RECIST v1.1 (95% CI)	3.2% (1.6–5.8)	5.0% (1.6–11.3)	4.3% (2.0–8.1)
ORR per INV immune-modified RECIST (95% CI)	18.3 (14.2–23.1)	26.0% (17.7–35.7)	21.2 (15.8–27.3)

CI, confidence interval; CR, complete response; IC, immune cells; INV, investigator; ORR, objective response rate; RECIST, response evaluation criteria in solid tumours

Overall, a high concordance rate (94.8%) was observed in the all-patient population following a concordance analysis between the IRF-assessed RECIST v1.1 and INV-assessed RECIST v1.1 tumour responses (F. Hoffmann-La Roche Ltd, 2016b).

At the cohort 2 20-month follow-up, the median treatment duration was 12 weeks (range, 0 to 104); and a total of 137 patients were treated beyond RECIST v1.1 progression. The ORR status at the cohort 2 20-month follow-up is reported in Table 36 (IRF-assessed) (Loriot et al., 2016). There was consistency in the IRF-assessed ORR between the cohort 2 primary analysis and cohort 2 20-month follow-up analyses, in the all-patient population (F. Hoffmann-La Roche Ltd, 2016b).

Table 36: IMvigor 210 (Cohort 2) Objective response rate (IRF), cohort 2 20-month follow-up analyses, data cutoff: 4th July 2016 (Loriot et al., 2016, F. Hoffmann-La Roche Ltd, 2016b)

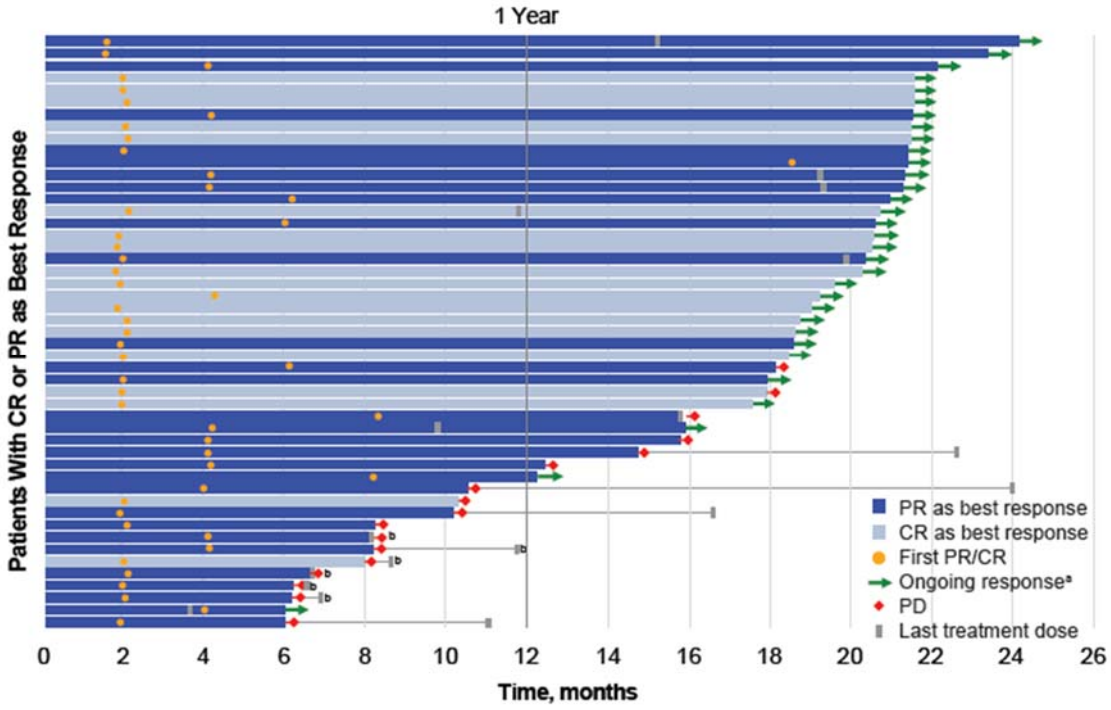
	All Patients (n = 310)
ORR per IRF RECIST v1.1[a] (95% CI)	15.8% (11.9–20.4)
CR rate per IRF RECIST v1.1 (95% CI)	6.1% (3.7–9.4)

ORR per immune-modified RECIST[b] (95% CI)	19.7% (15.4–24.6)

CI, confidence interval; CR, complete response; IC, immune cells; INV, investigator; ORR, objective response rate; RECIST, response evaluation criteria in solid tumours
Does not include [a] 17 or [b] 20 patients with missing/unevaluable responses. All treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1.

A swim lanes plot depicting the treatment and response duration is shown in Figure 20 (Loriot et al., 2016). The median time to response was 2·1 months (95% CI 2.0–2.2) (Rosenberg et al., 2016a).

Figure 20: IMvigor 210 (Cohort 2) Duration of treatment and response (Loriot et al., 2016)



CR, complete response; PD, progressive disease (IRF RECIST v1.1), PR, partial response
Objective response status is per IRF RECIST v1.1
[a] No PD or death
[b] Patient is deceased (timing not implied)

At the cohort 2 20-month follow-up analysis, the maximum DOR in the all-patient population increased compared with the primary analysis (22.6 months vs 8.3 months, respectively). In addition, 65.3% of the all-patients population demonstrated ongoing DOR at 12-month landmark analysis, (Table 37) (F. Hoffmann-La Roche

Ltd, 2016b), with majority of responders still progression-free at the time of the most recent analysis. This demonstrates the durable responses that patients experienced with atezolizumab in IMvigor 210 (Rosenberg et al., 2016a).

Table 37: IMvigor 210 (Cohort 2) Duration of response (IRF), cohort 2 20-month follow-up analysis, data cutoff: 4th July 2016 (F. Hoffmann-La Roche Ltd, 2016b)

Efficacy endpoint		All responders (n = 49)
DOR per IRF RECIST v1.1	**No. of patients with event (%)**	17 (34.7)
	No. of ongoing responders	32 (65.3)
DOR Landmark analysis at 12 months	**No. of patients at risk**	29
	Event–free rate, % (95% CI)	65.3 (51.5–79.0)

CI, confidence interval; DOR, duration of response; IC, immune cell; IRF, independent review facility; RECIST, response evaluation criteria in solid tumours

PFS cohort 2 (2L+)

In the cohort 2 20-month follow-up analysis, 274 / 310 (88.4%) of patients had an event of IRF-assessed disease progression, per RECIST v1.1, or death (Table 38) (F. Hoffmann-La Roche Ltd, 2016b).

Table 38: IMvigor 210 (Cohort 2) Progression-free survival (IRF), cohort 2 20-month follow-up analysis, data cutoff: 4th July 2016 (F. Hoffmann-La Roche Ltd, 2016b)

PFS (IRF-Assessed; RECIST v1.1)	All patients (n = 310)
No. of patients with event (%)	274 (88.4)
Median time to event, months (95% CI)	2.1 (2.1–2.1)

CI, confidence interval; IC, immune cell; IRF, independent review facility; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours

OS cohort 2 (2L+)

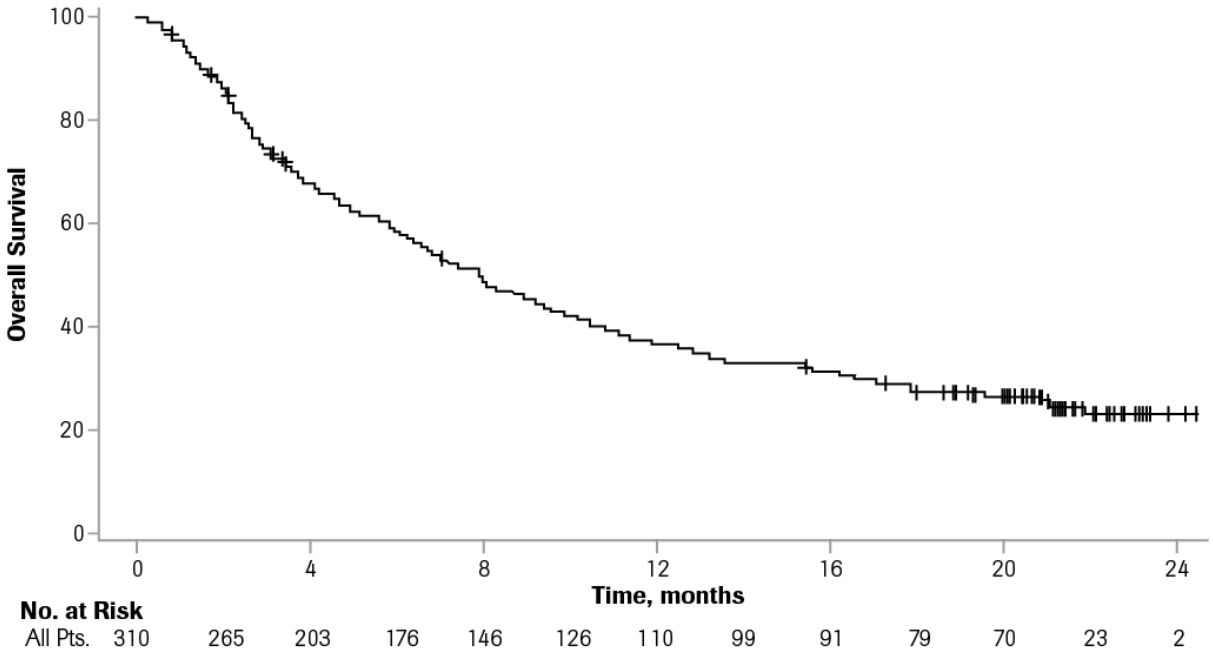
12-month survival rate was 36.9% in Cohort 2 (F. Hoffmann-La Roche Ltd, 2016b). Median OS for the cohort 2 20-month follow-up analysis is shown in Table 39. The KM curve is shown in Figure 21.

Table 39: IMvigor 210 (Cohort 2) Median OS and 12-month OS, cohort 2 20-month follow-up analysis, data cutoff: 4th July 2016 (Loriot et al., 2016, F. Hoffmann-La Roche Ltd, 2016b)

	All patients (n = 310)
Median OS, months (95% CI)	7.9 (6.7–9.3)
12-month OS rate (95% CI)	36.9% (31.4–42.3)

NE, not estimable; OS, overall survival. Patients at risk of an event are displayed at indicated time points below plot. Censored values are indicated with a plus (+) symbol.

Figure 21: IMvigor 210 (Cohort 2) Kaplan-Meier curve of OS in all patients (Loriot et al., 2016)



Patients at risk of an event are displayed at indicated time points below plot. Censored values are indicated with a plus (+) symbol.

Subgroup analysis cohort 2 (2L+)

Outcomes were assessed in key clinical subgroups (F. Hoffmann-La Roche Ltd, 2016b). Good response rates were seen across subgroups as defined by demographic and baseline characteristics. As reported for ORR above positive resposes were observed across all subgroups defined by IC status. These results demonstrate that atezolizumab is efficacious in a broad range of patients. However, given that IMvigor 210 is a single-arm study, results should be interpreted with caution(Balar et al., 2016b).

4.11.11 Summary of the PCD4989g study

4.11.11.1 Study design

Study PCD4989g is a multi-centre, first-in-human, open-label Phase Ia study. The primary objectives of the study were to assess the safety and tolerability of atezolizumab, to determine the maximum tolerated dose, to evaluate the dose limiting toxicity, and to identify a recommended Phase II dose of atezolizumab (F. Hoffmann-La Roche Ltd, 2015a).

The primary endpoint of the PCD4989g study was ORR based on INV-RECIST v1.1. Secondary endpoints included best overall response (BOR), DOR per RECIST v1.1, PFS per RECIST v1.1, OS and safety (F. Hoffmann-La Roche Ltd, 2015a).

4.11.11.2 Baseline characteristics

As of the clinical data cutoff on the 31st March 2016, the safety evaluable population with UC included 95 patients with locally advanced or metastatic UC, and was predominately white (74/95, 77.8%) and male (72/95, 75.8%) with a median age of 66.0 years (range: 36-89 years). The majority of the patients were ≥65 years old (56/95, 58.9%) (F. Hoffmann-La Roche Ltd, 2016c).

Baseline characteristics of the efficacy evaluable UC cohort are summarised in Table 40.

Table 40: PCD4989g Baseline characteristics (F. Hoffmann-La Roche Ltd, 2016c)

Baseline characteristic	Total (n=95)	
Age	Median	66.0
	Range	36–89
Gender	Male	72 (75.8%)
Baseline ECOG PS	0	37 (38.9%)
	1	58 (61.1%)
Visceral Metastases at study entry	Yes	74 (77.9%)
Liver metastases at study entry	Yes	35 (36.8%)
Haemoglobin level <10g/dL	Yes	18 (18.9%)
Prior Therapy (Adjuvant, Neoadjuvant)	0	1 (1.1%)
	1	0 (0%)
	2	17 (17.9%)
	3	15 (15.8%)
	4	14 (14.7%)
	5	17 (17.9%)
	≥6	31 (32.6%)
Prior Therapy with Platinum Based Regimen	Cisplatin-based	73 (76.8%)
	Carboplatin-based	37 (38.9%)
Time from prior chemotherapy (≤3 months)	Yes	39 (41.9%)

ECOG, Eastern Cooperative Oncology Group; PS, performance status

Note: Efficacy evaluable population = 95, safety evaluable population = 95, data cut-off 31st Mar 2016

4.11.11.3 Efficacy results

A total of 95 patients enrolled in the UC cohort and 94 were OR-evaluable with at least 12 weeks follow-up (F. Hoffmann-La Roche Ltd, 2016c).

The urothelial carcinoma tumour response results based on the 94 OR-evaluable patients, inclusive of the primary and sensitivity analyses of the primary and secondary efficacy endpoints, are presented below. The first tumour assessment occurred 6 weeks after starting treatment and then every 6 weeks for 24 weeks, and every 12 weeks thereafter until disease progression, death or initiation of further systemic cancer therapy, in accordance with the protocol schedule. ORR values are presented in Table 41 (F. Hoffmann-La Roche Ltd, 2016c).

Table 41: PCD4989g ORR, per RECIST v1.1 (F. Hoffmann-La Roche Ltd, 2016c)

Efficacy endpoint	All patients n=94
ORR per INV RECIST v1.1 (95% CI)	26.6% (18.01, 36.71)
CR rate per INV RECIST v1.1 (95% CI)	9.6% (4.47, 17.40)
ORR per IRF RECIST v1.1 (95% CI)	25.5% (17.09, 35.57)

CR, complete response; IC, tumour-infiltrating immune cells; INV,investigator; ORR, objective response rate; IRF, independent review facility; RECIST, Response Evaluation Criteria in Solid Tumours v1.1

Clinical cutoff date: 31st March 2016

Note: ORR analysis is based on n=94 efficacy evaluable patients with measurable disease at baseline

- Durable DOR was observed with a median DOR per INV-RECIST v1.1 of 22.1 months (95% CI: 12.12, NE)
- Overall median DOR on the basis of the IRF-RECIST v1.1 was not reached (95% CI: 27.598, NE)
- At 2 years, the survival rate was 30.3% (95% CI: 20.34, 40.25)
- Median PFS per INV RECIST v1.1 was 2.7 months (95% CI: 1.4, 4,3)
- Median PFS per IRF RECIST v1.1 was 1.8 months (95%CI 1.4,3.3)
- Median OS was 10.1 months (95% CI: 7.29, 16.99)

4.12 Adverse reactions

4.12.1 Adverse events from RCTs

No RCT evidence was identified. Please see Section 4.1 for further details

4.12.2 Summary table of adverse events

No RCT evidence was identified. Please see Section 4.1 for further details.

4.12.3 Additional adverse reactions

No RCT evidence was identified. Please see Section 4.1 for further details. Adverse event information for atezolizumab is provided from the Phase II study, IMvigor 210.

4.12.3.1 IMvigor 210: safety profile in patients with UC

Safety result from the July 2016 data-cut are available for Cohort 1 (15-month follow up analysis) and Cohort 2 (20-month follow-up analysis). These analyses demonstrated that atezolizumab was well tolerated with a low incidence of AEs leading to study drug withdrawal. The observed AEs were consistent with the known mechanism of action of atezolizumab and other immunotherapies, and the underlying disease. There were no new safety concerns identified with longer follow-up (F. Hoffmann-La Roche Ltd, 2016b).

Cohort 1

At the time of the 15-month follow-up analysis, all patients in Cohort 1 were treated for a median of 15 weeks and received a median of 6 doses. Of the 119 patients, 21% (25 patients) received study drug treatment for ≥1 year (F. Hoffmann-La Roche Ltd, 2016b).

Comparison of the primary analysis vs the 15-month follow-up analysis (4th July data cutoff) (Cohort 1)

Overall, 95.8% of patients experienced at least one AE; five grade 5 AEs (deaths) occurred, of which one AE (sepsis) was considered treatment-related by the treating investigator (Table 42). The safety analysis results of the 15-month follow up were consistent with the results of the primary analysis with no new safety concerns identified (F. Hoffmann-La Roche Ltd, 2016b).

Table 42: IMvigor 210 (Cohort 1) Overview of AEs (safety-evaluable population) (F. Hoffmann-La Roche Ltd, 2016b)

AE	Primary analysis 14th September 2015 cutoff date n=119	15-month follow-up analysis 4th July 2016 cutoff date n=119
AEs	115 (96.6%)	114 (95.8%)
Treatment-related AEs	76 (63.9%)	79 (66.4%)
SAEs	42 (35.3%)	45 (37.8%)
Treatment-related SAEs	9 (7.6%)	12 (10.1%)
Grade 3–4 AEs	51 (42.9%)	54 (45.4%)
Treatment-related Grade 3–4 AEs	14 (11.8%)	19 (16.0%)
Grade 5 AEs	4 (3.4%)	4 (3.4%)
Treatment-related Grade 5 AEs	1 (0.8%)	1 (0.8%)
AESIs	32 (26.9%)	37 (31.1%)
AESI (Grade 3-4)	6 (5.0%)	9 (7.6%)
AEs leading to study drug dose interruption	39 (32.8%)	41 (34.5%)
AEs leading to withdrawal from study drug	7 (5.9%)	9 (7.6%)

AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

Note: Safety summaries include all AEs that occur up to 30 days after the last dose of study drug, with the exception of treatment-related SAEs and AESIs for which no window was applied.

Common adverse events cohort 1 (1L)

The majority of patients (95.8%; 114/119 patients) experienced at least one AE (F. Hoffmann-La Roche Ltd, 2016b). The most commonly reported AEs (≥ 10%) included fatigue, decreased appetite, nausea, diarrhoea, anaemia, pruritus, blood creatinine increased, vomiting, constipation, oedema peripheral, urinary tract infection, back pain, pyrexia, arthralgia, cough, and rash (F. Hoffmann-La Roche Ltd, 2016b). Overall, these are expected events based on the underlying disease, and the known safety profile of atezolizumab (F. Hoffmann-La Roche Ltd, 2016b).

Grade 3–4 adverse events cohort 1 (1L)

Grade 3-4 AEs were experienced by 45.4% of patients (54/119) with the most commonly reported AEs (≥ 2.5%) being fatigue, anaemia, hyponatremia, blood creatinine increased, asthenia, renal failure, small intestinal obstruction, back pain,

urinary tract infection, decreased appetite, diarrhoea, ALT increased, AST increased, urosepsis and hypotension (F. Hoffmann-La Roche Ltd, 2016b).

Treatment-related adverse events cohort 1 (1L)

Treatment-related Grade 3-4 AEs were reported in 16.0% of patients, the most common of which (≥ 2.5%) were fatigue, alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased (Table 43) (F. Hoffmann-La Roche Ltd, 2016b).

Table 43: IMvigor 210 (Cohort 1) Treatment-related AEs (Bellmunt et al., 2016, Balar et al., 2016b)

AE[a] (n=119)	Any grade	Grade 3–4
Overall	79 (66%)	19 (16%)
Fatigue	36 (30%)	4 (3%)
Diarrhoea	14 (12%)	2 (2%)
Pruritus	13 (11%)	1 (1%)
Decreased appetite	11 (9%)	1 (1%)
Hypothyroidism	8 (7%)	0 (0%)
Anaemia	6 (5%)	2 (1%)
Chills	6 (5%)	0 (0%)
Nausea	6 (5%)	0 (0%)
Pyrexia	6 (5%)	0 (0%)
Rash	6 (5%)	1 (1%)
Vomiting	6 (5%)	0 (0%)
Rash, maculopapular	5 (4%)	0 (0%)
ALT increase	5 (4%)	4 (3%)
Arthralgia	5 (4%)	0 (0%)
AST increase	4 (3%)	3 (3%)
Blood bilirubin increase	4 (3%)	2 (2%)
Dyspnoea	4 (3%)	0 (0%)
Infusion-related reaction	4 (3%)	0 (0%)
Lymphocyte count decrease	4 (3%)	0 (0%)
Renal failure	2 (2%)	2 (2%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

[a] Reported in ≥ 4 patients (any grade) or ≥ 2 patients (Grade 3-4). Multiple occurrences of the same event were counted once at maximum severity.

Serious adverse events cohort 1 (1L)

Serious adverse events were experienced by 37.8% of patients (45/119). The most commonly reported SAEs (≥ 2.5%) included acute kidney injury, small intestinal obstruction, renal failure, sepsis, and diarrhoea, the majority of which were assessed as related to underlying disease. Treatment-related SAEs were reported in 10.1% of all comers, with the most frequently reported (≥ 2 patients) being diarrhoea (2.5%) and renal failure (1.7%) (F. Hoffmann-La Roche Ltd, 2016b).

Deaths cohort 1 (1L)

The majority of deaths were due to progressive disease (88.1%, 52 of 59 patients). Four patients experienced a Grade 5 AE (cardiac arrest, myocardial infarction, sepsis [investigator-assessed as related], respiratory failure) within 30 days of their last dose of study treatment. One additional death occurred more than 30 days after last dose of atezolizumab, which was due to respiratory distress. These Grade 5 AEs were reported at the primary analyses and no new information was received subsequently (F. Hoffmann-La Roche Ltd, 2016b).

Furthermore, there were two deaths due to other unspecified causes (not due to disease progression or an AE). One death was reported during the primary analyses and although the exact cause of death could not be determined, suspected thrombotic thrombocytopenia purpura and disseminated intravascular coagulation was reported (F. Hoffmann-La Roche Ltd, 2015b). For the death which occurred during the 15-month follow-up, no further details regarding the exact cause of death were available (F. Hoffmann-La Roche Ltd, 2016b).

AEs that led to dose interruption or treatment withdrawal cohort 1 (1L)

Overall, atezolizumab was well tolerated; 34.5% (41/119) of patients had an AE leading to dose interruption and 7.6% had an AE leading to treatment withdrawal. New events leading to treatment withdrawal reported since the primary analysis included one each of Grade 3 fatigue, Grade 3 rheumatoid arthritis, and Grade 2 autoimmune colitis.

Adverse events of special interest (AESI) cohort 1 (1L)

AESIs reported in ≥3 patients were: rash, hypothyroidism, ALT increase, AST increase, maculo-papular rash, bilirubin increase, colitis, dermatitis, and peripheral neuropathy (F. Hoffmann-La Roche Ltd, 2016b). Most AESIs were immune-mediated, as expected with atezolizumab, an immunoglobulin G1 monoclonal antibody that inhibits PD-L1 and potentiates the immune system.

Immune-mediated AEs cohort 1 (1L)

A quarter (25%) of all patients received steroids for an AE due to any cause; immune-mediated AEs requiring systemic corticosteroids are listed in Table 44 (Bellmunt et al., 2016). No patients were treated with non-corticosteroid immunomodulatory agents (e.g., infliximab, tocilizumab) for an immune-mediated AE (Bellmunt et al., 2016).

Table 44: IMvigor 210 (Cohort 1) Immune-mediated AEs (Bellmunt et al., 2016)

AE[a] (N=119)	Any grade	Grade 3–4
Overall	12%	7%
Rash	3%	1%
ALT increase	2%	2%
Blood bilirubin increase	2%	2%
Rhabdomyolysis	2%	1%
AST increase	1%	1%
Autoimmune colitis	1%	1%
Colitis	1%	1%
Diarrhoea	1%	1%
Liver disorder	1%	1%
Rheumatoid arthritis	1%	1%
Arthralgia	1%	0%
Arthritis	1%	0%
Hypothyroidism	1%	0%
Muscle spasms	1%	0%
Rash, maculopapular	1%	0%
Tenosynovitis	1%	0%

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase

[a] Occurring in any patient. Multiple occurrences of the same event were counted once at maximum severity.

Renal function cohort 1 (1L)

Renal function was assessed by change in estimated GFR (eGFR) and no major decline in median eGFR was observed on treatment in the overall patient population (Bellmunt et al., 2016).

Cohort 2 (2L+)

At the 20-month follow-up analyses, all patients in Cohort 2 had been treated for a median of 12.3 weeks and received a median of five doses. Of the 310 patients, 20% (62 patients) had received atezolizumab for >1 year (F. Hoffmann-La Roche Ltd, 2016b).

Comparison of the primary analysis vs the 20-month follow-up analysis cohort 2 (4th July data cutoff) (2L+)

The results of 20−month safety analysis were consistent with the results of the primary analysis with no new safety concerns identified (F. Hoffmann-La Roche Ltd, 2016b).

Table 45: IMvigor 210 (Cohort 2) Overview of AEs (safety-evaluable population) (F. Hoffmann-La Roche Ltd, 2016b)

AE	Primary analysis 5th May 2015 cutoff date N=311	20-month follow-up analysis 4th July 2016 cutoff date N=310[a]
AEs	298 (95.8%)	303 (97.7%)
Treatment-related AEs	203 (65.3%)	220 (71.0%)
SAEs	141 (45.3%)	144 (46.5%)
Treatment-related SAEs	33 (10.6%)	38 (12.3%)
Grade 3–4 AEs	154 (49.5%)	186 (60.0%)
Treatment-related Grade 3–4 AEs	46 (14.8%)	56 (18.1%)
Grade 5 AEs	2 (0.6%)	3 (1.0%)
Treatment-related Grade 5 AEs	0	0
AESIs	79 (25.4%)	93 (30.0%)
AESIs (Grade 3-4)	13 (4.2%)	20 (6.5%)
AEs leading to study drug dose interruption	83 (26.7%)	100 (32.3%)
AEs leading to withdrawal from study drug	10 (3.2%)	12 (3.9%)

AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

[a] As a result of updated data for cohort eligibility, two patients assigned to Cohort 2 (one within the IC0 subgroup and one within the IC1 subgroup) and one patient assigned to Cohort 1 (within the IC0 subgroup) as of 5 May 2015 were re-assigned to the alternate cohort as of the 14 September 2015 cutoff.

Note: Safety summaries include all AEs that occur up to 30 days after the last dose of study drug, with the exception of treatment-related SAEs and AESIs for which no window was applied.

Common adverse events cohort 2 (2L+)

The majority of patients (97.7%; 303/310 patients) experienced at least one AE, regardless of the cause. The most commonly reported AEs (≥ 10%) included fatigue, decreased appetite, nausea, constipation, urinary tract infection, pyrexia, oedema peripheral, diarrhoea, vomiting, back pain, dyspnoea, chills, arthralgia, anaemia and cough, haematuria, pruritus, abdominal pain, rash, pain in extremities, headache, and pain (F. Hoffmann-La Roche Ltd, 2016b). Overall, these are expected events based on the underlying disease, and the known safety profile of atezolizumab.

Grade 3–4 adverse events cohort 2 (2L+)

Grade 3–4 AEs were experienced by 60.0% of patients; the most commonly reported AEs (≥ 2.5%) were anaemia, urinary tract infection, fatigue, haematuria, hyponatremia, dehydration, dyspnoea, sepsis, pain, back pain, and abdominal pain (F. Hoffmann-La Roche Ltd, 2016b).

Treatment-related adverse events cohort 2 (2L+)

Treatment-related Grade 3-4 AEs were reported in 18.1% of patients, the most common of which (≥ 1.0%) were fatigue, ALT increase, AST increase, hypertension, lymphocyte count decrease, and pneumonitis (F. Hoffmann-La Roche Ltd, 2016b). There were no treatment-related Grade 3-4 AEs reported at a rate of ≥2.5% in cohort 2.

Table 46: IMvigor 210 (Cohort 2) Treatment-related AEs (F. Hoffmann-La Roche Ltd, 2016b)

AE (N=310)	Any grade	Grade 3–4
Overall	71.0%	18.1%
Fatigue	30.6%	1.6%
Diarrhoea	8.4%	0.3%
Pruritus	11.9%	0.3%
Decreased appetite	11.3%	0.6%
Hypothyroidism	2.6%	0.3%
Anaemia	2.3%	0.6%
Chills	10.6%	0%
Nausea	26.5%	1.9%
Pyrexia	22.3%	0.6%
Rash	11.6%	0.3%
Vomiting	19.4%	1.3%
Rash, maculopapular	3.2%	0%
ALT increase	5.2%	1.9%
Arthralgia	17.7%	1.0%
AST increase	5.2%	1.6%
Blood bilirubin increase	2.6%	0.6%
Blood alkaline phosphatase increase	5.2%	1.6%
Dyspnoea	0.3%	0%
Infusion-related reaction	0.6%	0%
Lymphocyte count decrease	1.6%	1.0%
Renal and urinary disorders	2.9%	0.6%

AE, adverse event; ALT, alanine aminotransferase; AST, Aspartate aminotransferase

Serious adverse events cohort 2 (2L)

SAEs were experienced by 46.5% of patients. Treatment-related SAEs were reported in 12.3% of all patients; the most frequently reported SAEs (≥ 3 patients) were pneumonitis (1.3%) and pulmonary embolism (1.0%) (F. Hoffmann-La Roche Ltd, 2016b).

Deaths cohort 2 (2L)

The majority of deaths were due to progressive disease (93.4%, 211/226 patient deaths). The incidence of deaths within and beyond 30 days from the last study treatment administration was 12.3% and 60.6%, respectively (F. Hoffmann-La Roche Ltd, 2016b).

Three patients experienced a Grade 5 AE (sub-ileus, pulmonary sepsis, cerebral haemorrhage) within 30 days of their last dose of study treatment. No Grade 5 AEs occurred after 30 days of last dose of atezolizumab were reported. None were assessed as related to study drug treatment by the investigator; two (sub-ileus and pulmonary sepsis) were previously reported at the primary analysis (F. Hoffmann-La Roche Ltd, 2016b).

AEs that led to dose interruption or treatment withdrawal cohort 2 (2L)

Overall, 32.3% of the patients (100/310) experienced an AE that led to dose interruption, with the majority of patients able to tolerate atezolizumab; AEs leading to treatment withdrawal were reported in 3.9% of patients. New events leading to treatment withdrawal reported since the primary analysis (CCOD: 5 May 2015) included one each of Grade 5 cerebral hemorrhage, Grade 3 pneumonitis, Grade 3 sepsis, Grade 3 colitis, Grade 2 colitis microscopic, and Grade 2 fatigue. The previously reported Grade 3 retroperitoneal haemorrhage was updated in the 20-month F/U analysis to a Grade 3 retroperitoneal infection (F. Hoffmann-La Roche Ltd, 2016b).

AESIs cohort 2 (2L)

AESIs reported in ≥3 patients were: rash, ALT increase, AST increase, hypothyroidism, maculo-papular rash, peripheral neuropathy, bilirubin increase, pneumonitis, increased transaminase, rash pruritic, and colitis (F. Hoffmann-La Roche Ltd, 2016b).. Most AESIs were immune-mediated, as expected with atezolizumab, an immunoglobulin G1 monoclonal antibody that inhibits PD-L1 and potentiates the immune system.

Immune-mediated AEs cohort 2 (2L)

In 63 patients treated with atezolizumab for ≥1 year, 13% experienced an immune-mediated AE of any grade, and 3% experienced a Grade 3–4 immune-mediated AE. In these patients, rash, acute kidney injury and influenza-like illness were the most common immune-mediated AEs of any grade (n=2 each) (Loriot et al., 2016). No patients were treated with non-corticosteroid immunomodulatory agents (e.g., infliximab, tocilizumab, rituximab, interleukin 2) for an immune-mediated AE (Loriot et al., 2016).

Phase I PCD4989G study

The safety results comprise data from patients in the UC cohort (n=95) who received atezolizumab over a median period of 8.6 months (range: 0.0–35.2 months; where 0.0 months reflects patients who received one dose of study treatment); 51.6% of patients were treated for less than 3 months as of 31st March 2016. The mean number of treatment doses received was 12.3 doses (F. Hoffmann-La Roche Ltd, 2016c).

The majority of patients (97.9%, 93/95) experienced at least one adverse event (AE) (regardless of attribution) during the course of study treatment (F. Hoffmann-La Roche Ltd, 2016c). Overall, Grade 3 or Grade 4 AEs were experienced by 50.5% (48/95) patients and 1.1% (1/95) experienced AEs resulting in death (Grade 5). For treatment-related AEs, 66.3% (63/95) of patients experienced AEs of any grade; 8.4% (8/95) experienced Grade 3 and 1.1% (1/95) experienced Grade 4 AEs. The most common treatment-related AEs (≥ 5% of patients, 5/95) were fatigue (19.9%, 17/95), asthenia (13.7%, 13/95), decreased appetite (12.6% (12/95), nausea (11.6%, 11/95), pruritus (11.6%, 11/95), rash (8.4%, 8/95), diarrhoea (7.4%, 7/95), and pyrexia (6.3%, 6/95) (F. Hoffmann-La Roche Ltd, 2016c).

4.12.4 Overview of safety of atezolizumab

4.12.4.1 Summary of IMvigor 210 safety results in patients with UC

In Cohort 1, patients tolerated first-line treatment with atezolizumab monotherapy well (Bellmunt et al., 2016). Overall, 41 (34%) patients had an adverse event leading to dose interruption, with no single adverse event predominating, and nine (8%) patients had an event leading to treatment withdrawal. Most treatment discontinuations (77 of 102) and deaths (52 of 59) were due to progression (Balar et al., 2016b).

In Cohort 2, atezolizumab for patients with mUC who have been treated with platinum chemotherapy was also well tolerated, with no treatment-related grade 5 AEs occurring on study even after approximately two years since last patient enrolled (Loriot et al., 2016). Most treatment-related adverse events were mild to moderate in nature, with fatigue among the most common any-grade adverse events (Rosenberg et al., 2016a). The incidence of grade 3–4 treatment-related adverse events was low, with fatigue being the most common, occurring in five (2%) patients (Rosenberg et al., 2016a).

The safety profile of atezolizumab remains consistent with other immunotherapies, and previous IMvigor 210 analyses (including among cohorts). No new safety concerns were identified with longer follow-up, including patients treated with atezolizumab beyond one year (F. Hoffmann-La Roche Ltd, 2016b).

4.13 Interpretation of clinical effectiveness and safety evidence

As described in section 3.3, outcomes in urothelial carcinoma are generally poor with limited therapeutic options and poor quality of life for patients who progress to more advanced disease. The lack of tolerable and effective treatment options has led to a high unmet medical need in this disease, particularly in the metastatic setting.

Data for atezolizumab in mUC is available from two studies: IMvigor 210, and the supportive phase I study (PCD4989g), which has longer follow-up and treatment exposure. Both studies showed consistently beneficial results, including clinically meaningful efficacy, and a well-tolerated and manageable safety profile that

compare favourably with the historical control outcomes with current treatment standards.

4.13.1 Principal (interim findings) from the clinical evidence

There have been no major advances in the treatment of metastatic urothelial bladder cancer in the past 30 years. Patient outcomes remain poor (Powles et al., 2014). Chemotherapy remains the standard of care, and there is a clear unmet need in the treatment options for patients with locally advanced or mUC. Principle findings from the evidence highlighting the clinical benefits and risks of atezolizumab monotherapy for the treatment of cisplatin-ineligible and previously treated patients are summarized below:

Atezolizumab offers a durable response across lines of therapy

The clinical benefit of atezolizumab is underscored by durable responses.

- **Cohort 1 (previously untreated metastatic disease) – ORR and DOR**

  - In the 15-month follow-up analysis, patients in Cohort 1 were treated for a median of 15 weeks and received a median of 6 doses. Of the 119 patients, 21% (25 patients) received study drug treatment for ≥1 year (F. Hoffmann-La Roche Ltd, 2016b).

  - Patients treated with atezolizumab had an ORR of 19.3% (95% CI: 12.66, 27.58) at the primary analysis. At the 15-month follow-up analysis, the ORR rose to 22.7% (95% CI: 15.52, 31.27) in all comer patients, and 19 of 27 (70%) responses were ongoing (Balar et al., 2016b). These objective response rates, as well as the duration of response of atezolizumab monotherapy observed in Cohort 1, are clinically meaningful.

  - ORRs and CRs were observed. Over time, with longer follow-up, all-patient ORRs have remained consistent and additional patients with CR have been observed (Bellmunt et al., 2016).

  - Durable clinical benefit has been observed, with a disease control rate ≥24 weeks of 30% (95% CI, 22–39) (Bellmunt et al., 2016).

- Median duration of response has not yet been reached and substantially exceeds that seen with conventional cytotoxic chemotherapy(Bellmunt et al., 2016)

- **Cohort 2 – ORR and DOR**

  - In Cohort 2, at the 20-month follow-up, the median treatment duration was 12 weeks (range, 0 to 104). The ORR was 15.8% (95% CI 11.9-20.4) (Loriot et al., 2016). Patients treated with atezolizumab had an ORR of 15.1% (95% CI: 11.3, 19.6) at the pre-planned primary analysis.

  - In Cohort 2 the maximum DOR in the all-patient population increased, from 8.3 months (primary analysis) to 22.6 months (20 month follow-up), and the median duration of response has not yet been reached. For the all-patient population, the estimated 1-year landmark event-free rate is 65.3% (F. Hoffmann-La Roche Ltd, 2016b). This demonstrates the durable responses that patients experienced with atezolizumab in IMvigor 210 (Rosenberg et al., 2016a). Again, these enduring responses would not be expected with the cytotoxic treatments currently used in clinical practice

  - Responses, including CRs, were observed in all PD-L1 subgroups; (Loriot et al., 2016). Additional PRs and CRs have been observed in the updated analyses (Loriot et al., 2016). Such persistent responses in the context of a favourable safety profile have consistently been observed across various studies including the phase I study, PCD4989g, for which the median DOR is 22.1 months (95% CI: 12.12, NE)

  - The responses observed represent statistically significant improvements compared to a historical control response rate of 10%, and over current available therapies for locally advanced and metastatic bladder cancer patients.

Atezolizumab offers a long term survival benefit in UC in cisplatin ineligible and in previously treated patients

PFS rates and OS rates are summarized below.

- Cohort 1 – PFS and OS (15 month follow up analysis)

In Cohort 1, the median progression-free survival was 2.7 months (95% CI 2.1–4.2) (Balar et al., 2016b), with a median overall survival of 15·9 months (95% CI, 10.4 to NE) (Balar et al., 2016b). The 12-month landmark survival was 57% (95% CI 48–66) (Balar et al., 2016b).

- Cohort 2- PFS and OS (20 month follow up analysis)

In Cohort 2, PFS was 2.1 months (95% CI 2.1,2.1) (F. Hoffmann-La Roche Ltd, 2016b), median overall survival was 7.9 months (95% CI 6.7-9.3), with a 12 month OS rate of 36.9% (31.4-42.0) (Loriot et al., 2016).

- phase I PCD4989g

At 2 years, OS was 30.3% (95% CI: 20.34, 40.25) for all mUC patients.

Atezolizumab has an established safety profile across lines of therapy in UC

Comparative safety data are not available for atezolizumab in mUC. However, an ongoing phase III clinical trial in NSCLC assesses atezolizumab as compared to docetaxel (Rittmeyer et al., 2016). These data are useful to explore the tolerability of atezolizumab as compared to taxane based chemotherapy in metastatic, advanced cancer, albeit in a differing tumour type. In this study there were fewer treatment-related adverse events with atezolizumab than with docetaxel, including grade 3 or 4 events (90 [15%] of 609 patients vs 247 [43%] of 578 patients.

Adverse events leading to treatment discontinuation occurred in 46 (8%) of 609 patients with atezolizumab and in 108 (19%) of 578 patients with docetaxel. There were no deaths related to atezolizumab and one related to docetaxel (respiratory tract infection).

- **Cohort 1**

- Treatment-related Grade 3-4 AEs were reported in 16.0% of patients, the most common of which (≥ 2.5%) were fatigue, ALT increase and AST increased (F. Hoffmann-La Roche Ltd, 2016b).

- Serious adverse events were experienced by 37.8% of patients (45/119). The most commonly reported SAEs (≥ 2.5%) included acute kidney injury, small intestinal obstruction, renal failure, sepsis, and diarrhoea, the majority of which were assessed as related to underlying disease. (F. Hoffmann-La Roche Ltd, 2016b).

- Overall, atezolizumab was well tolerated; 34.5% (41/119) of patients had an AE leading to dose interruption and 7.6% had an AE leading to treatment withdrawal(F. Hoffmann-La Roche Ltd, 2016b)

- **Cohort 2**

  - Treatment-related Grade 3-4 AEs were reported in 18.1% of patients, the most common of which (≥ 1.0%) were fatigue, ALT increase, AST increase, hypertension, lymphocyte count decrease, and pneumonitis (F. Hoffmann-La Roche Ltd, 2016b). There were no treatment-related Grade 3-4 AEs reported at a rate of ≥2.5% in cohort 2.

  - Treatment-related SAEs were reported in 12.3% of all patients; the most frequently reported SAEs (≥ 3 patients) were pneumonitis (1.3%) and pulmonary embolism (1.0%)(F. Hoffmann-La Roche Ltd, 2016b)

  - In 63 patients treated with atezolizumab for ≥1 year, 13% experienced an immune-mediated AE of any grade, and 3% experienced a Grade 3–4 immune-mediated AE. No patients were treated with non-corticosteroid immunomodulatory agents (e.g., infliximab, tocilizumab, rituximab, interleukin 2) for an immune-mediated AE (Loriot et al., 2016).

  - Overall, atezolizumab was well tolerated. 32.3% of the patients (100/310) experienced an AE that led to dose interruption, with the majority of patients able to tolerate atezolizumab; AEs leading to treatment withdrawal were reported in 3.9% of patients(Loriot et al., 2016). Overall, this data

demonstrates that atezolizumab provides a meaningful treatment option for patients who are cisplatin-ineligible.

Based on the overall results from IMvigor 210 and supporting PCD4989g study, atezolizumab presents a favourable benefit-risk as compared to historical controls (single agent chemotherapy) in a population with a high unmet medical need. The positive benefit-risk profile was not only observed in patients who expressed high levels of PD-L1 (IC2/3), but also in those who did not (IC0/1), suggesting all patients can derive benefit from atezolizumab treatment. Durable responses were observed with atezolizumab, including subsets of heavily pre-treated metastatic urothelial carcinoma patient population with pre-defined poor prognostic factors.

It is this durability of response - already seen with immunotherapies for other cancers such as melanoma, but not with conventional treatments for urothelial cancer - that marks out atezolizumab as a step-change in the treatment of UC. Atezolizumab offers the prospect of prolonged periods free of active disease to responding patients. Patients in atezolizumab-induced remission can expect to be generally unimpaired by serious treatment-related toxicity underscored by the low incidence of adverse events (AEs) leading to treatment withdrawal. Atezolizumab therefore represents a clinically significant innovative therapeutic option for the treatment of patients in the proposed UC indication

4.13.2 Strengths and Limitations of Clinical Evidence

The IMvigor 210 trial has populations which are largely reflective of the bladder cancer populations in the UK. The UK trial sites recruited well into both IMvigor 210, and the ongoing IMvigor 211 study indicating that both trial populations, and therefore results of these trials, will reflect UK practice. Despite any small differences across trials in the baseline populations, atezolizumab demonstrates a consistent efficacy and safety profile. The baseline characteristics of the patients enrolled in IMvigor 210 have been accepted by experienced treating clinicians as being generally reflective of the bladder cancer population, which is a largely elderly population often with co-morbidities.

The IMvigor 210 trial was designed to capture endpoints which are relevant to UK clinical practice, in particular objective response rates, with secondary endpoints of

progression free survival and overall survival, amongst others. ORR was measured using RECIST v1.1 criteria and modified RECIST criteria. Modified RECIST criteria are not yet standard practice, however RECIST 1.1 is a standard accepted worldwide assessment of response in solid tumours. Responses were measured by investigator and by independent review, and there was a high degree of concordance rates in ORR observed between investigator- vs. IRF-assessed ORR per RECIST V1.1 (Cohort 2 all comers: 92.6%) and investigator assessed ORR per RECIST V1.1 vs. mRECIST (Cohort 2 all comers: 97.7%).

As we have begun to understand immunotherapies across a number of different indications, it is becoming clear that although PFS is considered a standard measure of response for chemotherapies in solid tumours, it is less useful in assessing responses for immunotherapies. Nevertheless, PFS was included as a secondary endpoint in IMvigor 210. This reflects the fact that when the trials were designed, evidence of the use of PFS in immunotherapy trials was sparse, and PFS remained a useful measure for most standard chemotherapies. However, current clinical understanding is that PFS does not reflect the true value of immunotherapies. More useful markers of the benefit that immunotherapies bring to oncology are the duration of response and the OS rates. These are all measured as secondary endpoints within the study. The clinical community support, and have advised that these markers of response should be given higher emphasis within the interpretation of the trial results.

The most significant limitation of the data presented is the lack of a comparator within this large phase II trial, which is a function of the stage in its evidence base at which atezolizumab is being reviewed by regulatory authorities and NICE. Although current scientific opinion is that the response rate of current therapies lies within the range of 10-12% (Pimlack, 2016), there is no direct comparison within the clinical evidence for atezolizumab.

Active controlled phase III data in the 1L setting will be available for atezolizumab in the IMvigor 130 trial, which includes a direct comparison to chemotherapy (the current standard of care for these patients), in addition to a group receiving a combination of atezolizumab and chemotherapy. Results are not expected until

2020. Second line phase III data will be available through the ongoing IMvigor 211 study, with results expected in 2017.

However the unmet clinical need in this patient group and the excitement amongst the clinical community for the potential of the immunotherapy drugs in bladder cancer, has been recognized by medicines regulators in the US, Europe and UK, and has been pivotal in the drive to make these drugs available based on Phase II alone.

4.13.3 End-of-life criteria

Metastatic UC is recognized as having short survival duration. Atezolizumab is believed to meet end of life criteria, taking into account the extrapolated mean OS for atezolizumab and comparators. Due to the shape of treatment response, and long survival tail, median OS results do not accurately capture the survival gains for atezolizumab treated patients.

Table 47: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th><th>Cross reference</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>Median survival with or without treatment with systemic therapy 8-15 months</td><td>Section 3.2, Section 3.5.4</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>Due to the shape of treatment response, and long survival tail, median OS results do not accurately capture the survival gains for atezolizumab treated patients.

Significant long-term gains can be made, thus the mean OS results better reflect the clinical outcomes of patients.

Mean OS results are >3 months for atezolizumab as compared to all comparators, when taking results from the economic analysis, as shown in the table below

<table>
<tr><td></td><td>Mean</td><td>Median</td></tr>
<tr><td>Cohort 1</td><td></td><td></td></tr>
<tr><td>Atezolizumab</td><td>55.3 months</td><td>17.1 months</td></tr>
<tr><td>Gem + Carbo</td><td>25.1 months</td><td>8.5 months</td></tr>
<tr><td>Cohort 2</td><td></td><td></td></tr>
</table>
</td><td>Section 5.3</td></tr>
</table>

	Atezolizumab: 22.7 months; 7.9 months Docetaxel: 12.9 months; 7.6 months Paclitaxel: 12.2 months; 5.3 months BSC: 9.4 months; 4.4 months	
The treatment is licensed or otherwise indicated for small patient populations	Locally advanced or metastatic urothelial bladder cancer population (at diagnosis): 4-10% of 10,000 annual incidence (CRUK) – 400-1000 patients per year Internal estimates based on market research predict 864 patients would be eligible for treatment with atezolizumab.	Section 3.1 Section 3.5.4 Section 6

4.14 Ongoing studies

Table 48: Ongoing studies with atezolizumab

Study ID, Phase	Patient Population	Primary Objective	Estimated primary completion date
IMvigor211 (GO29294), Phase III	2-3L mUC	Compares atezolizumab with Chemotherapy (investigator's choice of one of vinflunine, docetaxel, or paclitaxel)	November 2017
IMvigor130 (WO30070), Phase III (planned)	1L cisplatin-ineligible mUC	Evaluate the safety and efficacy of atezolizumab with or without gemcitabine/carboplatin versus gemcitabine/carboplatin alone	June 2020
WO29635, Phase Ib/II	NMIBC	Evaluates the safety, pharmacokinetics, immunogenicity, PROs, and preliminary anti-tumor activity of atezolizumab administered as a single agent and in combination with BCG in patients with BCG-unresponsive NMIBC, and in combination with BCG in patients with BCG-relapsing, and VHR, BCG-naive NMIBC.	November 2020
IMvigor010 (WO29636), Phase III	MIBC Adjuvant PDL1 selected	Compares atezolizumab with observation as adjuvant therapy in patients with PDL1−selected	April 2022

BCG, Bacille Calmette-Guérin; MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma; NMIBC, non-muscle-invasive bladder cancer; PRO, patient-reported outcomes; VHR, very high risk

5 Cost effectiveness

Summary of Cost Effectiveness

- Cost-utility analyses were conducted to compare atezolizumab to the key comparators of interest – gemcitabine + carboplatin in 1L, and paclitaxel in 2L.
- Analyses comparing to the 2L comparators docetaxel and BSC were also conducted
- The analyses are consistent with the NICE reference case, and take the perspective of NHS England
- A three-state partitioned survival model was built and included the health-states PFS, PD and death. The time horizon is 20 years, which captures all relevant costs and benefits
- Drug costs, administration costs, supportive care costs and adverse event management are accounted for within the analyses
- Clinical benefits were derived from the IMvigor 210 study, and the ITC for comparators, and extrapolated to the 20 year time horizon
- For both PFS and time to treatment discontinuation extrapolation, the generalised gamma distribution was used. For OS extrapolation a mix-cure rate was used, with the cure-generalised gamma distribution. In the absence of robust long-term survival data in mUC, a cure fraction of 0% was used
- Benefits are expressed in QALYs, and atezolizumab provided a life-year and QALY gain over all comparators. Utility values were derived from prior HTA appraisals in mUC
- The resulting QALY gains and ICERs are:
- 1L
    - Atezolizumab = 2.69
    - Gemcitabine + carboplatin = 1.35
    - ICER = £44,158
- 2L
    - Atezolizumab = 1.23
    - Docetaxel = 0.76, ICER = £131,579
    - Paclitaxel = 0.71, ICER = £104,850
    - BSC = 0.55, ICER = £98,208

5.1 Published cost-effectiveness studies

An SLR was performed to identify cost-effectiveness evidence for patients with metastatic or locally advanced UC.

The following electronic databases were searched on the 16th September 2016: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Embase (Ovid), and the Cochrane Library, consisting of the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects (DARE), the HTA database, and the National Health Service Economic Evaluation Database (NHS EED).

Electronic searches were supplemented by hand searching the following sources: reference lists of included publications, conference proceedings over the last 3 years, previous HTA submissions, and the following websites: the European Quality of Life-5 Dimensions (EQ-5D) website, the HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA), and the National Institute for Health Research (NIHR) HTA website.

Full details of the search and hand searching methodology are provided in appendix 8.7. The SLR did not identify any economic evaluations relevant to the current HTA submission.

5.2 De novo analysis

5.2.1 Patient population

The de novo analysis will assess the use of atezolizumab in two populations: patients with mUC whose disease has progressed after prior chemotherapy (2L) and; patients for whom cisplatin-based chemotherapy is unsuitable as a first line treatment option (1L). These populations are at different points in their treatment pathway, and include differing comparators. As such two separate models will assess the cost-effectiveness in these populations.

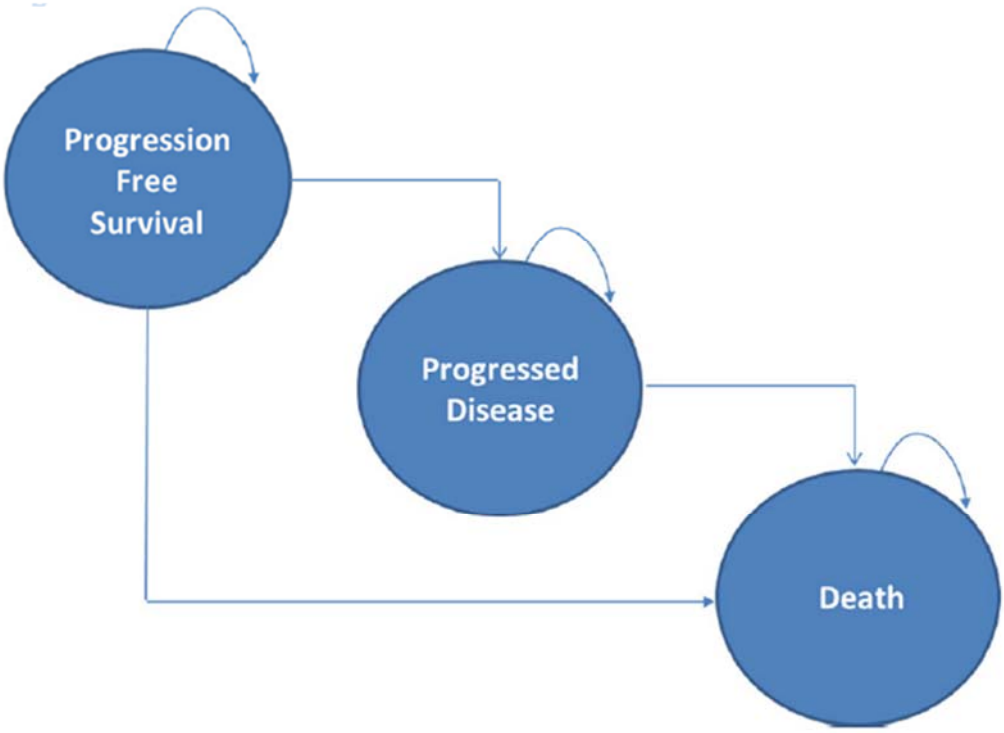
These populations are consistent with both the appraisal scope and anticipated Marketing Authorisation

5.2.2 Model structure

As stated above, two separate models were built to assess cost-effectiveness in the relevant populations. Model structures were identical, and the following information is applicable to both models.

A partitioned survival model with 3-states: ‘progression-free-survival’, ‘progressed disease’ and ‘death’ (Figure 22 below) has been developed.

Figure 22: State model schematic



This model was considered appropriate for the decision problem. The structure and health states are closely aligned with the clinical pathway identified in section 3. This model structure is consistent with the approaches used in earlier NICE appraisals of treatments for advanced or metastatic carcinoma, and the one prior appraisal of mUC (National Institute for Health and Care Excellence, 2013).

The primary aims of treatment in mUC are to reduce tumour burden, delay disease progression and prolong life.

The PFS health state captures patients who are responding to treatment either through reduced tumour burden, or stabilised disease. In this state patients would

normally be anticipated to have a higher quality of life compared to the PD health state. Use of the PD state is consistent with the anticipated Marketing Authorisation, which states: 'Treatment with atezolizumab should continue until loss of clinical benefit'. The model derives the proportion of patients in the PD health state as the difference between the PFS and OS curves.

The model does not assume any subsequent lines of anti-cancer therapy in either population, following progression on the intervention or comparators. Expert, treating physicians were consulted at an advisory board (details in section 1), who confirmed patients are unlikely to receive any further active anti-cancer treatment once their disease has progressed following treatment with atezolizumab in the 2L setting. This was validated by subsequent treatment information from cohort 2 within the IMvigor 210 study; where 42.7% of patients went onto receive radiotherapy following progression (assumed to be palliative radiotherapy). Gemcitabine was the following most prevalent subsequent treatment, at only 14.7%. (F. Hoffmann-La Roche Ltd, 2015b)

For cisplatin-ineligible patients, following 1L gemcitabine + carboplatin treatment failure, the NICE clinical guideline recommends either carboplatin + paclitaxel or gemcitabine + paclitaxel. Following atezolizumab failure in cohort 1 of the IMvigor 210 study, subsequent treatment information showed 54.3% and 40.0% of patients received gemcitabine and carboplatin respectively (F. Hoffmann-La Roche Ltd, 2015b). As these are first line treated patients, it is probable the majority of patients will go onto receive subsequent treatment. However, there is little incremental cost or efficacy impact of the choice of 2L therapy, so these have not been accounted for within the model.

Table 49: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	20 years	Sufficient to capture all meaningful differences in technologies compared. Expert clinical advice confirms time horizon appropriate.
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case
Discount of 3.5% for utilities and costs	Yes	NICE reference case
Perspective (NHS/PSS)	Yes	NICE reference case
NHS, national Health Service; PSS, personal social services; QALYs, quality-adjusted life years		

5.2.3 Intervention technology and comparators

Atezolizumab (the intervention) is implemented within the model, in accordance with the anticipated marketing authorisation. See section 5.5.3 for full details of assumed posology for comparators. In summary, comparator dosing is implemented in the model as follows:

1st Line:

Gemcitabine at 1000mg/m^2 days 1 and 8 of a 21 day cycle, and; carboplatin at 400mg/ m^2 day 1 of 21 day cycle.

2nd Line:

Docetaxel at a dose of 75mg/m^2 on day 1 of a 21 day cycle, or; paclitaxel at a dose of 80 mg/m^2 administered weekly.

BSC is assumed to be equal to supportive care costs.

Continuation Rules

Atezolizumab is anticipated to be licensed until loss of clinical benefit. The comparators are administered until disease progression. This is consistent with clinical practice. It is reasonable to assume the assessment of loss of clinical benefit - and so trigger for atezolizumab treatment discontinuation - will not require

additional resources or changes to current routine clinical practice. Section 5.5 includes further details of time on treatment assumptions.

5.3 Clinical parameters and variables

5.3.1 Incorporation of clinical data into the economic model

At the time of submission, clinical trial data for atezolizumab are available from IMvigor 210, a single arm, phase II study (F. Hoffmann-La Roche Ltd, 2015b, Rosenberg et al., 2016a). The study includes 2 cohorts: cohort 1 receiving atezolizumab as a 1st line treatment option when patients are cisplatin-ineligible, and; cohort 2 receiving atezolizumab 2nd line, after progression on chemotherapy. As outlined in section 4.11 this is considered the most appropriate source of clinical evidence for the intervention. The IMvigor 210 study is the data source for clinical outcomes, adverse events, treatment dose and duration of treatment with atezolizumab. An indirect treatment comparison was conducted (see section 4.10) to allow comparison of the intervention to the comparators of interest.

The model structure includes three health states, PFS, PD and death. PFS and OS outcomes are available directly from the IMvigor 210 study. These outcomes are also consistent with the appraisal scope.

The IMvigor 210 study was a multi-centre, international study, which included 22 UK patients, across 3 sites. Expert clinical advisors, including investigators taking part in this trial, confirm it is reasonable to assume responses seen in the study are the responses anticipated in UK clinical practice. Patients were recruited into the study once a clinical decision had been made to treat with immunotherapy. This same decision point will be made in clinical practice, and is consistent with the view that BSC is not an appropriate comparator in the 1L setting (see section 1.1). Clinical parameters are therefore incorporated using results from the IMvigor 210 study, without adjustment.

Controlled 2L data will be available in 2017 with a phase III clinical trial (IMvigor211), and in 2020 for 1L data (IMvigor 130 study). These studies will provide significant, additional evidence for patients in the 1 and 2L treatment setting.

5.3.2 Extrapolation of clinical data in the model

PFS and OS results from IMvigor 210 are extrapolated to the 20 year time-horizon. As life-time results are not available for all patients in the IMvigor 210 study, it is necessary to extrapolate the PFS and OS results to meet the 20 year time-horizon.

5.3.3 PFS Extrapolation: Atezolizumab

Atezolizumab 1L and 2L+

The established approach for extrapolation –fitting alternative distributions to the observed KM data from the trial through parameterisation –was undertaken. The following candidate distributions were fitted to the observed PFS data from the IMvigor 210 study: Exponential, Weibull, Log-logistic, Log-normal, Generalised gamma and Gompertz. The goodness of fit for these functions was assessed using Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and visual assessment of each fitted curve against the observed data. Based on the AIC and BIC statistics (Table 50 and Table 51), visual inspection and clinical plausibility, the Generalised gamma distribution was considered to be the most appropriate functional form, for both 1L and 2L. The extrapolation applied to trial data is illustrated in Figure 23 below for 1L and Figure 24 for 2L. Alternative extrapolations are explored in scenario analysis in section 5.8 and resulting curves are presented in appendix 8.8.

Table 50: Summary of parametric function goodness of fit for PFS (1L)

Parametric distribution	AIC	BIC
Exponential	369.38 (5)	372.16 (4)
Weibull	367.33 (4)	372.88 (5)
Log-normal	342.62 (2)	348.18 (2)
Generalised gamma	**336.23 (1)**	**344.57 (1)**
Log-logistic	343.30 (3)	348.86 (3)
Gompertz	371.38 (6)	376.94 (6)

Table 51: Summary of parametric function goodness of fit for PFS (2L+)

Parametric distribution	AIC	BIC
Exponential	1019.3 (5)	1023.1 (5)
Weibull	1012.1 (4)	1019.6 (4)
Log-normal	904.1 (3)	911.6 (3)
Generalised gamma	**856.5 (1)**	**867.7 (1)**
Log-logistic	887.9 (2)	895.4 (2)
Gompertz	1021.3 (6)	1028.8 (6)

Figure 23: Parametric (Gamma) and KM estimates for PFS (1L)

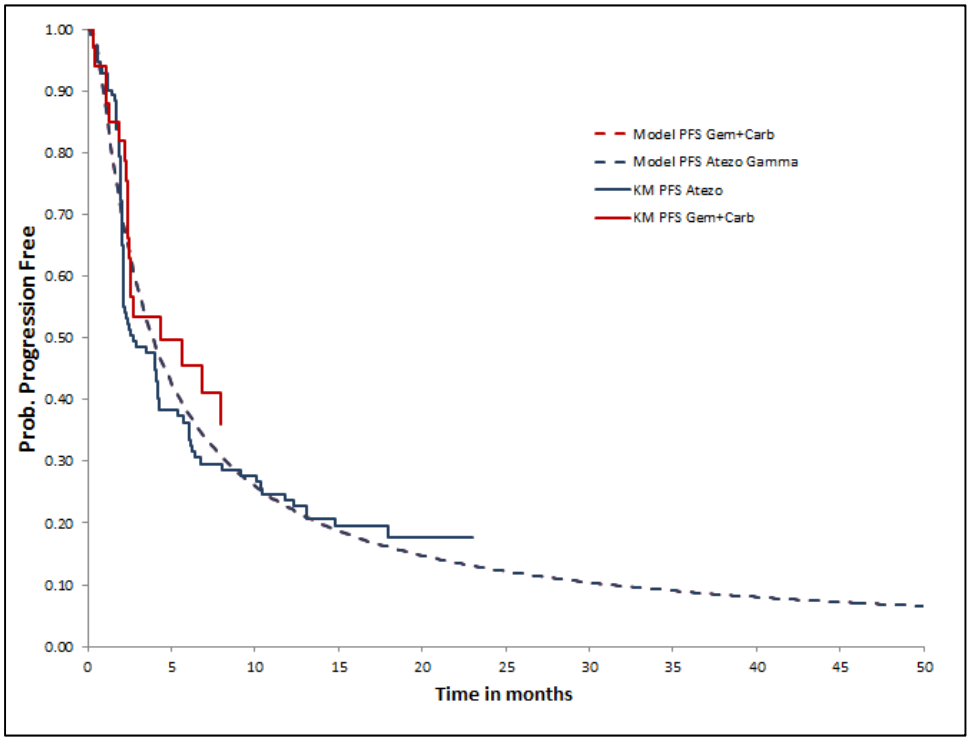
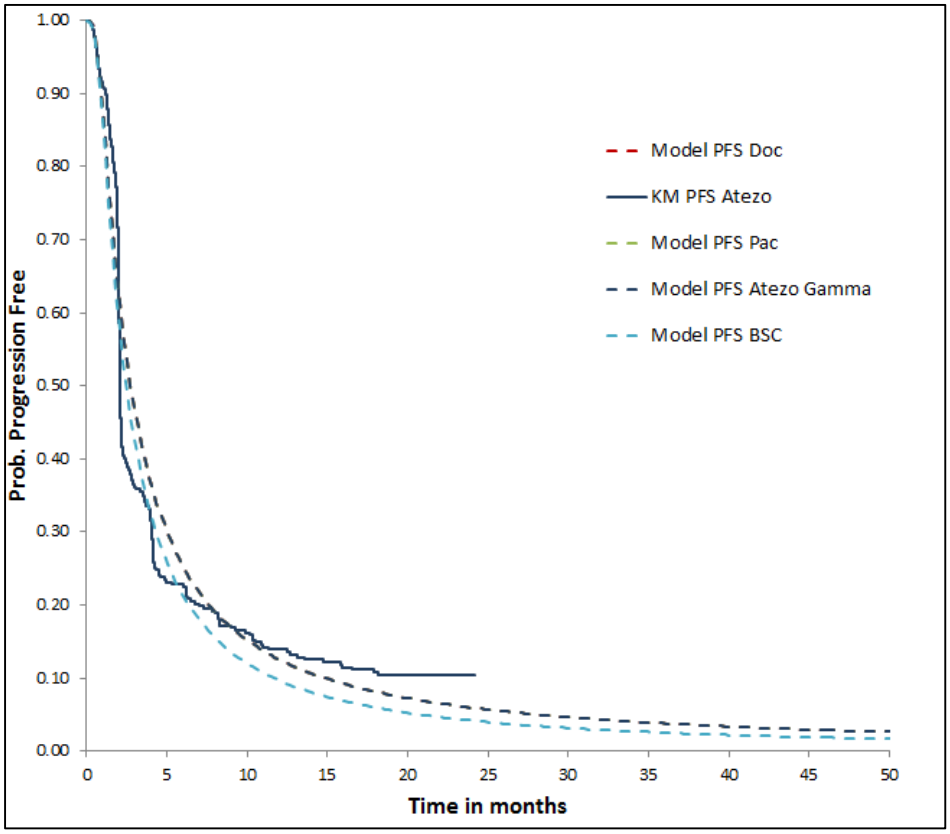


Figure 24: Parametric (Gamma) and KM estimates for PFS (2L+) (paclitaxel and docetaxel curves lie directly beneath atezolizumab curve)



The extrapolated PFS results for atezolizumab as compared to clinical trial results are shown in Table 52 below. Phase I results are included as the longest term follow up data, acknowledging the difference in study populations and so limited inference which can be taken with these phase I data.

Table 52: Comparison of modelled and trial results for PFS

	Median (model)	Median (trial)	12 month (model)	12 month (trial)
1L	3.9 months	2.7 months	22.5%	NR
2L+	2.76 months	2.1 months	12.6%	NR
Phase I study	n/a	1.84 months	n/a	22.11

5.3.4 PFS: Incorporating comparators

Fractional polynomial NMA

In order to extrapolate the treatment effect of all relevant comparators, results of the fractional polynomial NMA were incorporated into the economic model. The NMA is previously described in section 4.10.9. As described in that section, the outputs of the NMA are subject to significant uncertainty, given the limitations of data feeding into the NMA.

When applied within the economic model, extrapolated results of the NMA were clinically implausible, with PFS and OS curves crossing for docetaxel at 15 months, and paclitaxel at 24 months. This is likely due to the extremely small number of studies providing evidence for PFS within the NMA, those studies being of limited size and quality and the requirement of a predication model to provide comparative data. Evidence of the limitations of available data can be seen in Figure 25. The KM curves for PFS and OS taken directly from observed results of the Bamais et al. study of gemcitabine + carboplatin in 1L mUC can be seen to cross at approximately 10 months (Bamias et al., 2007).

Figure 25: PFS and OS KM curves for gemcitabine + carboplatin (Bamias et al.)

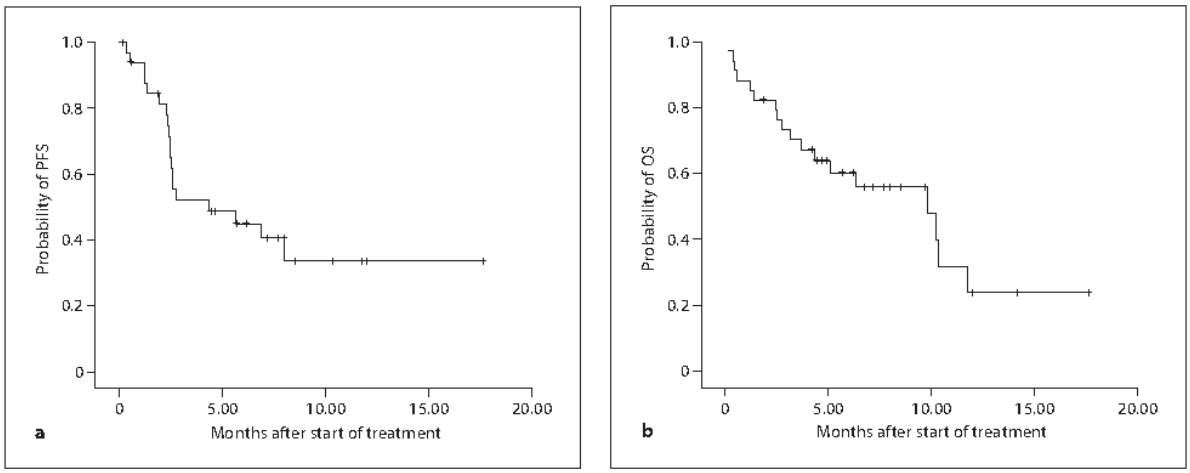


Fig. 1. Kaplan-Meier curves of PFS (**a**) and OS (**b**) of 34 patients treated with carboplatin/gemcitabine. + = Censored cases.

The following methods were explored in an attempt to resolve this effect in the model:

1. Use of the proportional hazards model
2. Capping of hazard ratios

1. Use of the proportional hazards model.

   As discussed in section 4.10.9, the proportional hazard assumption is highly likely to be violated. As such, use of this method is not appropriate. When implemented in the model, PFS is greater than OS for paclitaxel at all-time points, thus invalidating appropriateness of this method.

2. Capping hazard ratios

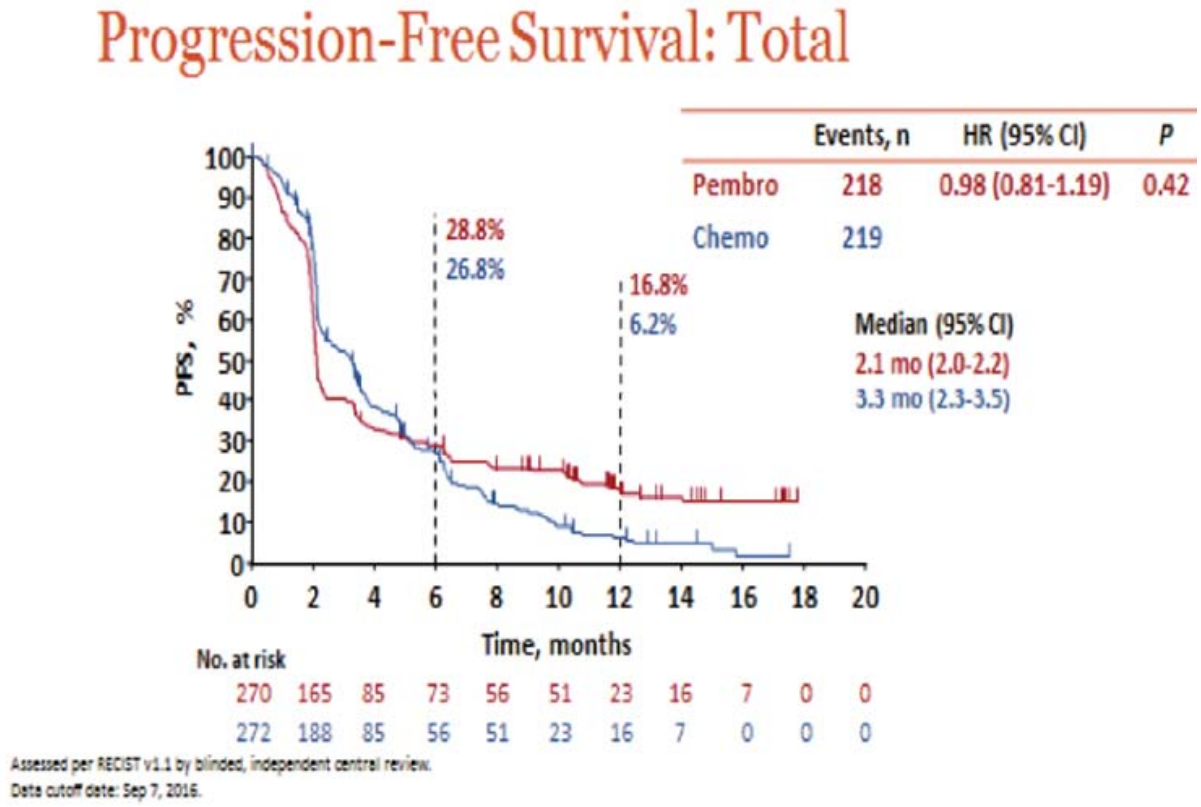
   The output of the fractional polynomial NMA model shows a linearly decreasing HR over time (vs atezolizumab). At the median follow up of IMvigor 210 (21.1 months) the HR compared to docetaxel is 0.03, which is the equivalent of a HR for atezolizumab vs. docetaxel of 33.33. To prevent the hazard ratio reaching this implausible value, it was limited to a minimum value and proportional hazards applied after this point. For example when the hazard ratio vs. atezolizumab reaches 0.8, which is at 2.76 months. However, as PFS and OS curves are fit independently there remained challenges with the 2 curves crossing, thus invalidating the appropriateness of this method.

Method for extrapolating comparator PFS (1L and 2L+)

As the previously described methods were deemed inappropriate, external literature was reviewed to explore alternative solutions.

At the Society for Immunotherapy of Cancer (SITC) Annual Meeting in November 2016, phase III clinical trial results were published for the immunotherapy pembrolizumab, in 2L mUC (KEYNOTE-045) (Bellmunt, 2016) [3]. These data demonstrated a non-significant HR of 0.98 for PFS, when comparing pembrolizumab to a blended comparator of docetaxel, paclitaxel and vinflunine (Figure 26 below).

Figure 26: PFS results of the KEYNOTE-045 trial (Bellmunt, 2016)



[3] The SLR to identify relevant clinical evidence for this appraisal (section 4.10.1) was completed prior to November 2016, in order to allow development of the NMA and incorporation of the results into the economic model ahead of this submission to NICE in January 2017. As such, this publication was not incorporated into the NMA, but has been subsequently identified.

In discussion with expert clinical advisors, it was proposed these data may be a useful surrogate for atezolizumab, until controlled pIII data are available in 2017.

There are several limitations to this approach including:

- The unsupported assumption of equivalent treatment effect of pembrolizumab and atezolizumab on PFS in mUC
- Use of relatively immature PFS results for pembrolizumab, from the KEYNOTE-045 study
- Incomplete publically available clinical trial information and results (thus limited scope for assessment of trial heterogeneity)
- Publically available PFS results providing only pooled analysis for comparators

Whilst PFS is acknowledged as a suboptimal measure of response with immunotherapies as discussed in section 4.13, the assumption of no relative benefit to PFS in patients vs. chemotherapy is not anticipated to be supported with long-term, mature pIII RCT results, which will capture the full PFS benefit contributed by the minority of patients with very long-lived disease remissions. Ongoing evidence suggests the method of elucidating PFS is the likely limitation of PFS results, as opposed to the clinical effect of immunotherapies (Tuma, 2011, Axel Hoos and Brent Blumenstein, 2010). (Ades, 2015)

However, in the absence of robust alternative data, the PFS HR of 0.98 from the pembrolizumab mUC trial (Bellmunt, 2016) was implemented in the model. This was achieved by making the PFS curves for docetaxel and paclitaxel equal to the PFS curve of atezolizumab. This should be acknowledged as a conservative assumption, as it takes no account of the benefit of immunotherapy (over chemotherapy) in the tail of the PFS curve. The same assumption was applied in the 1L model, making the PFS curves for gemcitabine + carboplatin equal to atezolizumab.

For the comparison to BSC in the 2L+ setting, a proportional hazard model was assumed using the HR from the fixed effects zero order fractional polynomial; 1.12 (CrI 0.91 to 1.37).

5.3.5 OS extrapolation: Atezolizumab

Experience with immunotherapy agents has increased over the last few years, with new indications in melanoma, lung cancer and renal cancer in the last 18 months. Data available for immunotherapy agents suggest the risk of death for patients treated with these drugs declines over time, with plausibility that some patients experience sustained response, and survival, over time. Clinical experts all assented the expectation is long term survival will be possible for some mUC patients, given the mechanism of action of atezolizumab.

At this time, long term evidence is not available from clinical trials. Furthermore, with relatively immature data from the IMvigor 210 study, use of traditional parametric survival analysis – which relies on the observed data for atezolizumab – will fail to account for this change in mortality rate and lead to an inappropriate 'flattening' of the survival curve tail.

Various methods have been utilised in previous immunotherapy appraisals, with NICE assessments highlighting both strengths and weaknesses of the approaches. An important consideration is the clinical plausibility of the resulting extrapolated survival curve.

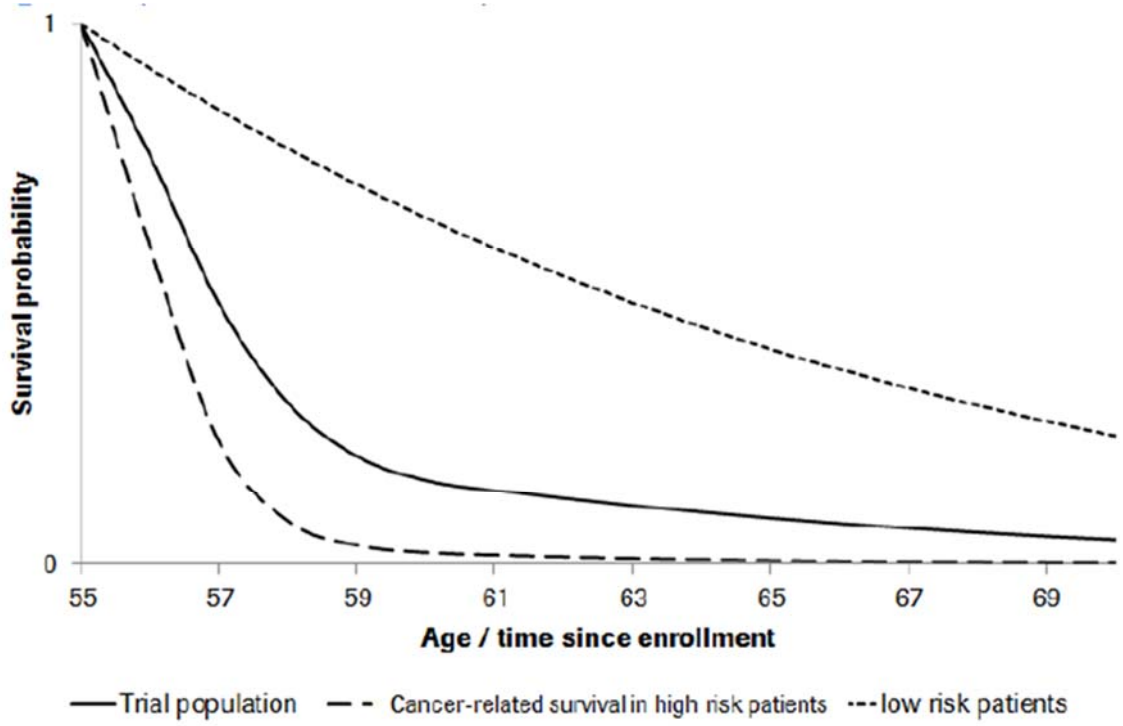
Mix-cure rate model

The OS estimates for this analysis were modelled using the mixture cure-rate methodology, as previously described in appraisal (National Institute for Health and Care Excellence, 2016a)

The mixture model accounts for the decrease in cancer-related mortality-risk over time. Statistically, this decrease in the cancer-related mortality-risk is accounted for by an estimation of the overall mortality risk at a given point in time, as a mixture between the cancer-related and background mortality risk. The estimation uses a dataset including the observed survival times in the IMvigor 210 trial and the background mortality risks from life-tables. The weight assigned to the background mortality is referred to as the "cured fraction". However this 'cure rate fraction', should not be interpreted as a clinical 'cure' from cancer. Rather, the proportion of patients for whom their disease is stable, and the risk of death attributable to cancer,

is equivalent to the risk of death from other causes. This can be interpreted as a proportion of patients whom are as likely to die of non-cancer causes as from cancer. These two populations (those with low risk of cancer related death, and those with high risk of cancer related death) are combined to produce an average survival for the whole population, illustrated in Figure 27 below.

Figure 27: Stylised illustration of cause-specific survival rates



The trial population survival is expressed as S(t), and incorporates the patients at high risk of cancer-related death [$S_c(t)$], and the patients at low risk [$S^b(t)$]. The 'cure fraction' is expressed as π

$$S(t) = S^b(t)\pi + (1-\pi)S^b(t)S_c(t)$$

In order to ascertain the 'cure fraction', long term survival data for mUC patients are required. Registry data are the most useful source for such data, however, exploration of available registries did not highlight suitable and robust data to validate an assumed 'cure fraction' in mUC.

Given the lack of robust, long term data in mUC, a strong assumption would be required to estimate a 'cure fraction' for implementation into the OS extrapolation.

Over time, it is anticipated clinical data for immunotherapies will support such a cure fraction. For the extrapolation of atezolizumab, it was assumed 0% of patients will be at a lower risk of death due to their disease. This is a conservative assumption, and when long-term data are available, this will be further explored.

The mix-cure method is still appropriate to use, even when assuming a 0% cure fractions. Incorporation of background mortality in the extrapolation of the observed survival data mean the tail of the survival curve will never be above that of background mortality. This prevents an implausible scenario whereby long-term atezolizumab treated mUC survivors have a reduced risk of death vs. that of the age matched general population. Use of the method within this submission also allow for examination in results of scenario analyses which assume a positive cure fraction.

Generating parametric models for OS from IMvigor210

The Exponential, Weibull, LogLogistic, LogNormal, Gompertz, Gamma and Generalized Gamma parametric models were fit to the IMvigor 210 results. The 'cure fraction' was set to 0%, as described above. The resulting AIC and BIC values for the 0% cure fraction are displayed in Table 53 and Table 54 below, for 1L and 2L+ respectively.

Table 53: Summary of parametric function goodness of fit for OS (1L)

Parametric distribution	AIC	BIC
Exponential	185.95 (7)	188.73 (7)
Weibull	183.46 (5)	186.23 (5)
Log-logistic	180.34 (4)	183.12 (4)
Log-normal	177.22 (2)	180.00 (2)
Gompertz	179.02 (3)	181.80 (3)
Gamma	184.23 (6)	187.01 (6)
Generalised gamma	**175.13 (1)**	**177.91 (1)**

Table 54: Summary of parametric function goodness of fit for OS (2L+)

Parametric distribution	AIC	BIC
Exponential	500.04 (7)	503.77 (7)
Weibull	498.35 (5)	502.09 (5)
Log-logistic	476.38 (3)	480.12 (3)
Log-normal	468.62 (2)	472.36 (2)
Gompertz	485.82 (4)	489.55 (4)
Gamma	499.8 (6)	503.54 (6)
Generalised gamma	**464.08 (1)**	**467.81 (1)**

According to visual fit and the AIC and BIC criterion (above), generalised gamma function was the most appropriate fit. The resulting curves were assessed as compared to available trial data, and discussed with expert clinical advisors. Table 55 demonstrates the model results correlate highly with trial data, thus validating the chosen parametric function.

Table 55: Comparison of modelled and trial results for OS (F. Hoffmann-La Roche Ltd, 2016b)

	Median (model)	Median (trial)	12 month (model)	12 month (trial)
1L	17.0 months	15.9 months	56.8%	57%
2L+	7.8 months	7.9 months	38.4%	36.9%
Phase I study		10.1 months		45.5%

Expert clinical advice suggested the proportion of 2L treated atezolizumab patients anticipated to be alive at 5, 10, and 20 years. Although robust evidence are not available to support this, these views are based on experience with immunotherapies to date and their expertise in clinical research. As seen in Table 56, these correlate highly with the extrapolated results of cohort 2 in the 2L model.

Table 56: Comparison of modelled and expert opinion results for OS

	5 year OS	10 year OS	20 year OS
Expert clinical advice	10-20%	5-10%	0-5%
Atezolizumab 2L+ model	9.5%	4.1%	1.1%

5.3.6 OS: Incorporating comparators

For the indirect comparison with comparators, results of the fractional polynomial model were incorporated. Using the fractional polynomial model, the HRs increase linearly over time, as the HR from the tail of the observed data continue in the same direction for the extrapolated tail. Left uncapped, these HRs result in clinically implausible values, as the relative efficacy of atezolizumab continually increases. For example, left uncapped, at 5 years the HR for docetaxel vs. atezolizumab is 11.86 (equivalent to 0.0843 for atezolizumab vs. docetaxel).

To avoid this clinical implausibility, the hazard ratios have been capped at the levels identified at time points corresponding to median follow up of cohorts 1 and 2. For cohort 2 this is 21.16 months, after this time point, all comparators are assumed to have proportional hazards. The HRs at this time point are shown in Table 57. The overall survival curves for each comparator are displayed in Figure 28 below.

Table 57: Comparator OS HR at 21.16 months (2L+)

	OS HR at 21.16 months comparator vs. atezolizumab	*OS HR at 21.16 months atezolizumab vs. comparator**	Proportion alive at 21.16 months
Docetaxel	2.12	*0.47*	16.8%
Paclitaxel	1.49	*0.67*	13.9%
BSC	1.66	*0.60*	9.6%
* Inverted HRs presented for illustrative purposes only (not employed in economic model)			

For cohort 1 median follow up was 17.2 months. However, at this time point the HR for gemcitabine + carboplatin vs. atezolizumab was 0.34 (equivalent to a HR of 2.94 for atezolizumab vs. gemcitabine + carboplatin). Rather than use this high atezolizumab treatment effect, the follow up duration for the comparator trial was utilised - 8 months. At this time the HR for gemcitabine + carboplatin vs. atezolizumab was 1.86 (equivalent to 0.54 HR for atezolizumab vs. gemcitabine + carboplatin). Overall survival curves for 1L are shown in Figure 29 below.

Figure 28: Parametric and KM estimates: OS, indirect comparison to comparators (2L+)

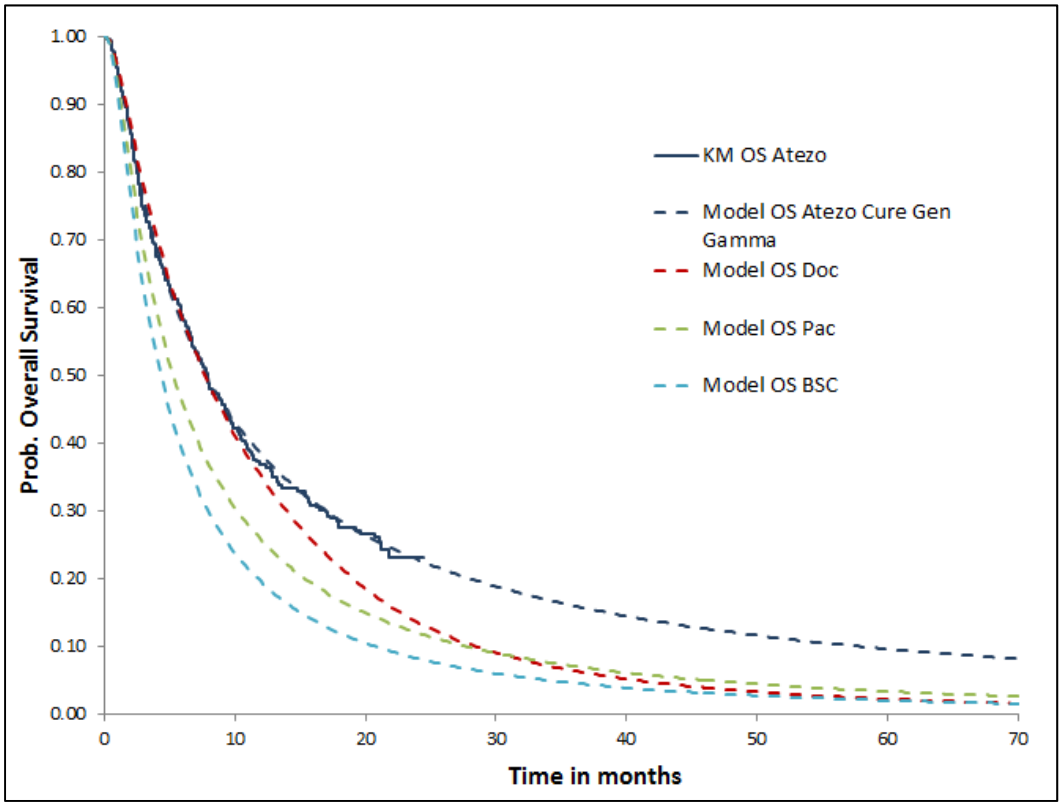
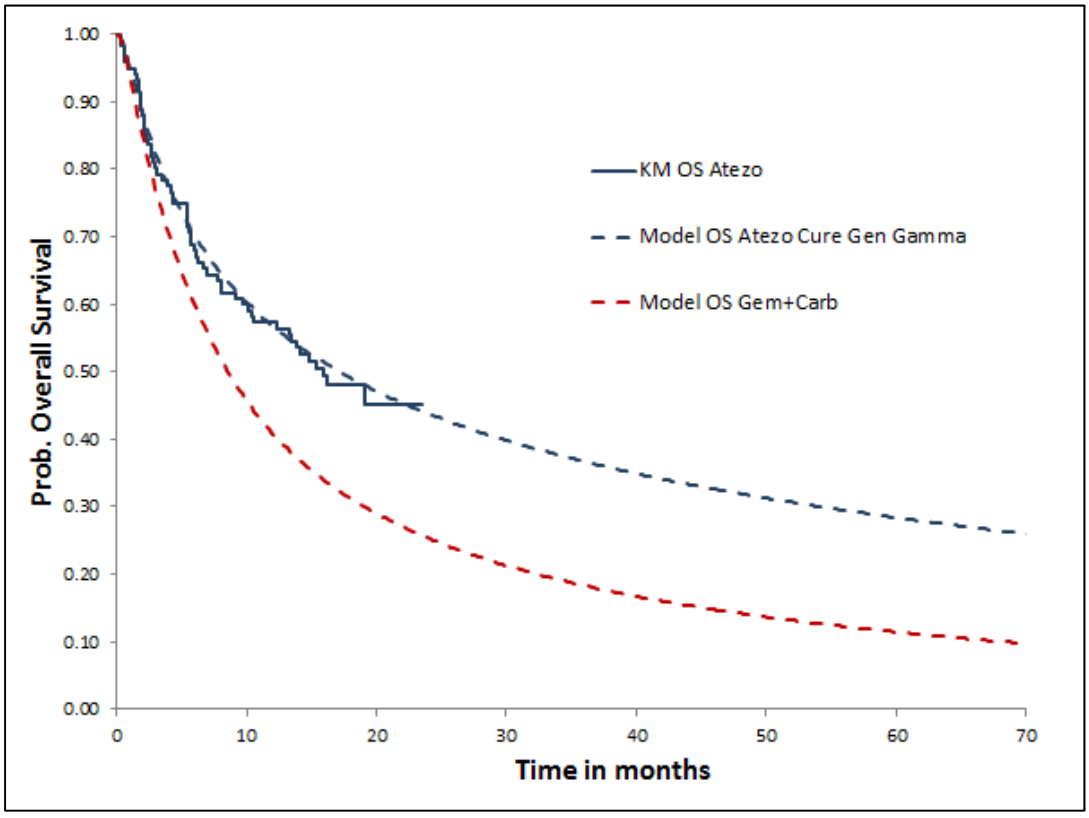


Figure 29: Parametric and KM estimates: OS, indirect comparison to comparators (1L)



5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

Health related quality-of-life data were not collected in the IMvigor 210 study. The phase III studies (IMvigor 211, and IMvigor 130) will provide quality-of-life data directly from 2L and 1L mUC patients treated with atezolizumab, including EQ5D.

5.4.2 Mapping

As no quality-of-life data are available from the IMvigor 210 study, mapping to utility values was not viable.

5.4.3 Health-related quality-of-life studies

A systematic review was conducted to identify HRQoL studies from the published literature relevant to the decision problem. The SLR was kept broad to identify utility values derived using any instrument, or mapping algorithms that would allow disease specific or QoL scores to be translated to utilities. Studies considered most appropriate were those which reported utility data for relevant health states, derived using methods consistent with the NICE reference case. Table 58 below details the inclusion and exclusion criteria applied in the search.

Table 58: Eligibility criteria for the HRQoL systematic review

Criteria	Include	Exclude	Justification
Population	Patients with advanced/metastatic urinary bladder cancer who have progressed after at least one prior chemotherapy regimen (or who are intolerant of cisplatin-based chemotherapy).	Paediatric patients or adult patients receiving first-line therapy	In line with draft NICE scope
Interventions	No restriction	-	In line with NICE reference case
Comparators	No restriction	-	In line with NICE reference case
Outcomes	• Utilities derived either directly (e.g. using TTO or SG) or through generic preference-based instruments (e.g. EQ-5D, HUI2, HUI3, SF-6D, AQoL, QWB) for relevant health states • Mapping studies which allow disease-specific HRQoL	-	In line with NICE reference case

Criteria	Include	Exclude	Justification
	measures to be converted to preference-based utilities • Studies reporting generic or disease-specific QoL outcomes in patients undergoing surgery or receiving chemotherapy		
Setting/study design	No restriction	-	In line with NICE reference case
Language of publication	English, including English abstracts of foreign publications	-	-
Date of publication	No restriction	-	-
Countries/global reach	No restriction	-	-

AQoL, assessment of quality of life; EQ-5D, European quality of life; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; QoL, quality of life; QWB, quality of well-being scale; SF, short form; SG, standard gamble; TTO, time trade-off

The following electronic databases were searched on the 16th September 2016: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Embase (Ovid), and the Cochrane Library, consisting of the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects (DARE), the HTA database, and the National Health Service Economic Evaluation Database (NHS EED).

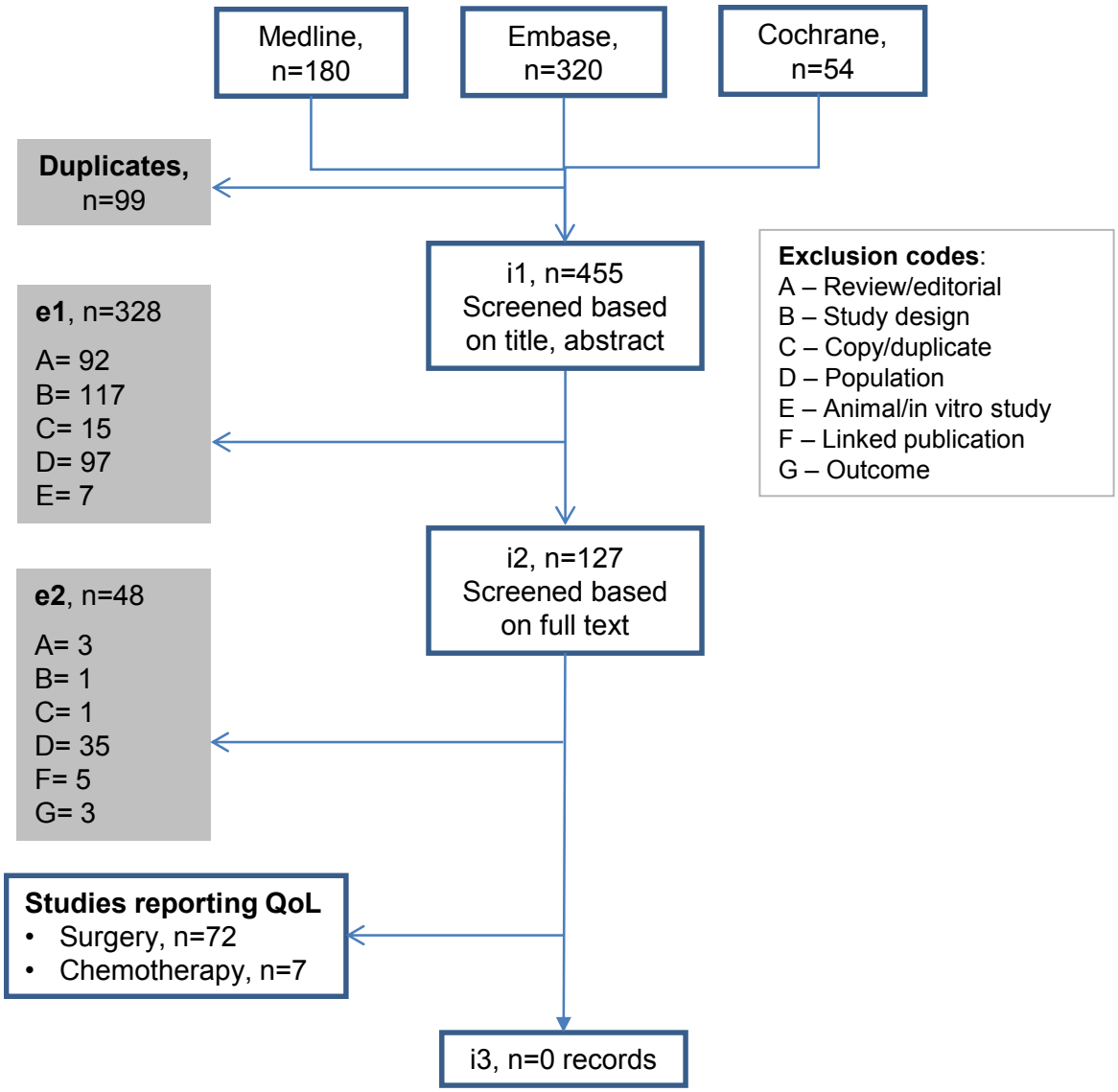
Electronic searches were supplemented by hand searching the following sources: reference lists of included publications, conference proceedings over the last 3 years availability, previous HTA submissions, and the following websites: the European Quality of Life-5 Dimensions (EQ-5D) website, the HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA), and the National Institute for Health Research (NIHR) HTA website.

Full details of the search and hand searching methodology are provided in appendix 8.9.

In total, 554 citations were identified through the electronic database searches. Upon removal of duplicates, 455 titles and abstracts were reviewed. A total of 127 references were deemed to be potentially relevant and were ordered for full publication review. However, upon full publication review, all 127 references were

excluded. Hand searching yielded no additional relevant publications. This resulted in no relevant studies for final inclusion in the health state utility values (HSUV) review, reporting utilities for the population of interest. The flow of studies through the review is presented in the PRISMA flow diagram in Figure 30.

Figure 30: HRQoL data SLR PRISMA flow diagram



Given the paucity of data available, the results were re-reviewed. Any publication reporting general QoL data for patients with urothelial/bladder cancer regardless of line of therapy or stage of disease was re-evaluated. Publications reporting QoL data in patients receiving chemotherapy (n=7) are summarised in Table 59 below.

However none of these studies were consistent with the reference case, as such were not included.

Table 59: Studies reporting QoL in patients receiving chemotherapy for mUC

Author, study design, country	Inclusion criteria	Line of therapy	Treatment	Follow-up	Tool used for measuring QoL	QoL assessment outcome
(Albers et al., 2002b) Open-label, non-randomised multicentre phase II trial Germany	Patients with cisplatin-refractory transitional cell carcinoma	Second line	Gemcitabine monotherapy	Mean (range), 8.4 months (0-25.3)	10-point scale Spitzer index 7-point pain scale	*Non-responders* **Spitzer index, mean (SD)** • Before treatment: 7.8 (2.4) • End of treatment: 6.7 (2.2) **Pain values, mean (SD)** • Before treatment: 5.3 (1.8) • End of treatment: 4.8 (1.5) *Responders* **Spitzer index, mean (SD)** • Before treatment: 8.0 (1.6) • End of treatment: 8.1 (2.5) **Pain values, mean (SD)** • Before treatment: 4.3 (1.9) • End of treatment: 5.8 (1.3), p<0.05
(Gerullis et al., 2012) Non-randomised, open-label phase II trial Germany	Patients with advanced or metastatic TCCU of the urinary bladder or upper urinary tract with disease progression following first-line platinum therapy	Second line	Temsirolimus IV at 25 mg weekly for 8 consecutive weeks	NR	"Global Health Status" section of the EORTC-QLQ-C30 questionnaire Assessment every four weeks	• Start of treatment: 7.68 • End of treatment: 5.00
(Gontero et al., 2012)	Patients with intermediate-risk NMIBC	NR	• BCG 1/3 dose weekly for 6 weeks • GEM 2,000	12 months	EORTC-QLQ-C30	After completion of the induction cycle, the GEM-group showed improved QoL in cognitive and emotional functioning (p<0.05)

Author, study design, country	Inclusion criteria	Line of therapy	Treatment	Follow-up	Tool used for measuring QoL	QoL assessment outcome
RCT NR			mg/50cc weekly for 6 weeks			After 1 year, the GEM-group showed a significantly improved QoL in cognitive functioning ($p<0.05$) as well as less symptom distress regarding nausea and vomiting ($p=0.001$)
(Lida et al., 2016b) Observational study NR	Patients with metastatic urothelial cancer	Third line	GEM and PTX for two 21-day cycles	NR	SF-36	QoL score did not significantly decrease compared with pre-treatment score
(Miyata et al., 2015) Observational study Japan	Patients with cisplatin-resistant urothelial cancer	Second line	GEM, PTX and sorafenib	NR	• SF-36 • VAS for pain	The bodily pain score of the SF-36 decreased significantly following treatment compared with baseline ($p=0.012$) The VAS score decreased significantly following treatment compared with baseline ($p=0.001$)
(Niegisch et al., 2016) Observational study Germany	Patients with cisplatin-resistant urothelial cancer	Second line	• GEM/PTX • PTX/everolimus	NR	EORTC QLQ- C30	An increased pain symptom scale ($p<0.001$) and a lower emotional functional scale ($p<0.01$) was reported in patients with urothelial cancer failing on cisplatin compared with normative data for patients suffering from metastatic malignancies. No significant differences were reported between patients with and without an objective response during treatment.
(Wei et al., 2014) Observational study	Patients undergoing intravesical treatment for NMIBC	NR	• Pirarubicin 40 mg weekly for six weeks followed by monthly for 12	6 weeks	Chinese version of the EORTC QLQ-C30	**Global health status**, **mean (SD)**[†] • Before instillation: 83.3 (11.8) • After instillation: 74.5 (17.2) **Social functioning, mean (SD)**[†]

Author, study design, country	Inclusion criteria	Line of therapy	Treatment	Follow-up	Tool used for measuring QoL	QoL assessment outcome
China			months			• Before instillation: 100 (0) • After instillation: 83.6 (15.4) **QoL index score, mean (SD)**† • Before instillation: 1.79 (1.88) • After instillation: 3.34 (0.99) **CLSS score, mean (SD)**† • Before instillation: 1.79 (1.88) • After instillation: 4.98 (3.27)

BCG, Bacillus Calmette–Guérin; EORTC-QLQ; European Organisation for Research and Treatment of Cancer-Quality of life questionnaire; GEM, gemcitabine; IV, intravenous; PTX, paclitaxel; QoL, quality of life; NMIBC, non-muscle-invasive bladder cancer; SD, standard deviation; RCT, randomised controlled trial; SF, short-form; TCCU, transitional cell carcinoma of the urothelial tract; VAS, visual analogue sore; CLSS, Core Lower Urinary Tract Symptom Score ; NR, not reported

As no studies were identified which met the eligibility criteria, independent cost-utility analyses and relevant previous HTA submissions reporting sufficient information were extracted. This information was identified during the economic evaluation review (section 5.1). These data were reviewed to understand how previous analyses in this indication have approached the modelling of utilities, given the paucity of available data.

The countries in which the economic analyses were based included: the USA, Canada, UK and Australia. The populations modelled in the analyses included the following:

- Patients with advanced or metastatic TCC of the urothelium who have failed a prior platinum-containing regimen
- Patients with NMBIC
- Patients with high-risk T1G3 TCC
- Patients with locally advanced or metastatic bladder cancer

All of the analyses acknowledged the lack of appropriate utilities for patients with bladder cancer, and obtained values through mapping or preference-based or direct elicitation from a proxy population

Results of these are presented in Table 60 below.

Table 60: Summary of sources of utility data in prior economic evaluations

Study, country	Population considered in the analysis	Source of utility data	Population from which utilities were derived	Instrument(s) used to derive utilities	Method of valuation	Health states	Mean HSUV (SD) [range]	Summary of relevance of utilities for informing HTA submission and limitations
Previous cost-utility analyses								
(Green et al., 2013) US	Patients with low-risk carcinoma NMIBC	Utility data for bladder cancer obtained from similar, previously published analyses: • Kulkarni, 2007 (Kulkarni et al., 2007b) • Kulkarni, 2009 (Kulkarni et al., 2009)	See Kulkarni 2007 (Kulkarni et al., 2007b) and Kulkarni 2009 (Kulkarni et al., 2009) extraction	See Kulkarni 2007 (Kulkarni et al., 2007b) and Kulkarni 2009 (Kulkarni et al., 2009) extraction	NA	TURBT	-0.1	• Preference-based method was not used to derive utilities and the methodology is not clearly reported • See Kulkarni 2007 (Kulkarni et al., 2007b) and Kulkarni 2009 (Kulkarni et al., 2009) extraction
						Cystoscopy	0.997	
						Fulguration	-0.05	
(Kulkarni et al., 2007a, Kulkarni et al., 2009) Canada	The base case patients consisted of a 60 year old, otherwise well, compliant and sexually potent man with newly diagnosed high-risk T1G3 TCC; the T1G3 diagnosis was assumed to be bladder-confined and based on a TURBT	Uncomplicated, post-cystectomy health state: • Utilities derived directly in the study All other health states: • Tufts-New England Medical Center CEA	Uncomplicated, post-cystectomy health state: • Urologists and urology trainees described health states for patients with high-risk T1G3 bladder cancer All other health states: • Populations with	Uncomplicated, post-cystectomy health state: • Direct SG method All other health states: • NR	NA	Cystectomy	0.80 (SE 0.16) [0.5-1.0]	• Preference-based method was not used to derive utilities and the methodology is not clearly reported • It is unclear if the utilities used for the uncomplicated post-cystectomy health state are a true reflection of patients with bladder cancer, as they were derived
						Gastrointestinal complication after cystectomy	0.97 (SE 0.194) [0.69-1.0]	
						Genitourinary complication after cystectomy	0.93 (SE 0.186) [0.57-1.0]	
						Impotence after cystectomy	0.91 (SE 0.182) [0.69-1.0]	
						Metastases responsive to chemotherapy	0.62 (SE 0.124) [0.31-0.93]	
						Metastases unresponsive to chemotherapy	0.30 (SE 0.06) [0.13-0.62]	
						Surveillance cystoscopy	0.997 (SE 0.05)	

	containing muscularis propria, indicating an adequate resection	registry (link to source broken)	similar health issues (no further details reported)				[0.95-1.0]	from HCPs • For all other health states, patients with similar health issues were used to derive utilities; as limited details of this population are provided it unclear how representative they are of the population being modelled
						Post-cystectomy state	0.96 (SE 0.192) [0.72-1.0]	
						Cystectomy complication	-0.3 (SE 0.06) [-0.5 to -0.02]	
						Chemotherapy	-0.36 (SE 0.072) [-0.9 to -0.2]	
						Chemotherapy complication	-0.54 (SE 0.108) [-0.76 to -0.32]	
						BCG therapy – induction	-0.02 (SE 0.004) [-0.3 to 0]	
						BCG complication	-0.2 (SE 0.04) [-0.4 to 0]	
						TURBT for low-risk Ta lesions	-0.1 (SE 0.02) [-0.03 to -0.09]	
(Lee et al., 2012) US	Patients with NMIBC who have been untreated with perioperative intravesical chemo-therapy	Health state utilities for NMIBC obtained from: • Kulkarni, 2009 (Kulkarni et al., 2009)	See Kulkarni 2007 (Kulkarni et al., 2007b) and Kulkarni 2009 (Kulkarni et al., 2009) extraction	See Kulkarni 2007 (Kulkarni et al., 2007b) and Kulkarni 2009 (Kulkarni et al., 2009) extraction	NA	NR	NR	• Preference-based method was not used to derive utilities and the methodology is not clearly reported • See Kulkarni 2007 (Kulkarni et al., 2007b) and Kulkarni 2009 (Kulkarni et al., 2009) extraction
(Robinson et al., 2004) UK	Patients with locally advanced or metastatic bladder cancer	Derived directly in the study	Unclear	Direct TTO method	NA	NR	NR	• Preference-based method was not used to derive utilities and the methodology is not clearly reported • The population from which utilities were derived is unclear, therefore it is unknown how representative the utilities would be of the population being modelled

Stevenson (Stevenson et al., 2014) US	Patients with stage II or III bladder cancer (tumour invading muscle but not extending to pelvic or abdominal wall, and no evidence of nodal involvement or distant metastasis) treated with RC or NAC	Major events and complications experienced by the study cohort were assigned a standard literature-based utility; some utilities were extrapolated from studies involving patients with similar conditions and complications (sources not reported)	Unclear – study cohort and patients with similar conditions or complications from other studies	NR	NR	Cystectomy (short-term)	0.80	• Preference-based method was not used to derive utilities and the methodology is not clearly reported • The population from which utilities were derived is unclear, therefore it is unknown how representative the utilities would be of the population being modelled
						Post-cystectomy (urinary diversion) state	0.96	
						TURBT	0.90	
						Chemotherapy	0.64	
						Disease recurrence or progression	0.62	
						Prolonged ileus	0.65	
						Small bowel obstruction with conservative management	0.65	
						Small bowel obstruction with surgical intervention	0.55	
						Total peripheral nutrition	0.65	
						Atrial fibrillation/arrhythmia	0.99	
						Delirium	0.51	
						UTI	0.73	
						Fluid collection/abscess with conservative management	0.64	
						Fluid collection/abscess with surgical intervention	0.64	
						Fever NOS	0.64	
						Pneumonia	0.85	
						Urinary obstruction requiring PCN or stent	0.75	
						DVT	0.67	
						PE	0.62	
						Impotence	0.90	
						Incontinence	0.76	
						Neutropenia	0.64	
						Acute illness	0.64	
						Severe illness and hospitalisation	0.53	
						Acute sepsis	0.47	
						Kidney infections	0.66	
						Urinary or faecal fistula	0.68	
						Death	0	
Previous HTA submissions								

(National Institute for Health and Care Excellence, 2013) UK	Adult patients with advanced or metastatic TCC of the urothelium who have failed a prior platinum-containing regimen receiving vinflunine + BSC or BSC as second-line therapy	Pre-progression: • Study 302 Post-progression: • van den Hout, 2006 (van den Hout, 2006)	Pre-progression: • Patients with advanced TCC of the urothelium who have progressed after a platinum-containing regimen from Study 302 Post-progression: • Terminally-ill patients with painful bone metastases or poor-prognosis NSCLC	Pre-progression: • EORTC-QLQ-C30 item #30 data from Study 302 was mapped using a regression model relating this measure to utility from a TTO analysis in a sample of US cancer patients (O'Leary, 1995 (O'Leary et al., 1995)) Post-progression: • EQ-5D	Pre-progression: • NA Post-progression: • UK tariff, TTO (Dolan, 1997 (Dolan, 1997))	Pre-progression health state	0.65 (SE 0.014)	• Pre-progression health state: the preferred EQ-5D was not used to derive utilities • Post-progression health state: although the preferred EQ-5D was used to derive utilities and UK societal preferences were applied, utilities were derived from an unrelated population
						Post-progression health state	0.25 (SE 0.009)	
(Pharmaceutical Benefits Advisory Committee, 2015) Australia	Patients with advanced or metastatic TCC of the urothelial tract after failure of a prior platinum-containing regimen receiving vinflunine + BSC or BSC alone	Study 302	Patients with advanced TCC of the urothelium who have progressed after a platinum-containing regimen from Study 302	EORTC-QLQ-C30 scores from Study 302 were transformed to utilities using the Rowen, 2011 (full reference not reported) mapping algorithm	NA	NR	NR	• A preference-based method was not used to derive utilities • However, given the paucity of evidence, these methods may be considered acceptable for informing economic evaluation

BCG, Bacillus Calmette–Guérin; BSC, best supportive care; CEA, cost-effectiveness analysis; DVT, deep vein thrombosis; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, European quality of life-5 dimensions; ERG, evidence review group; HTA, health technology assessment; NA, not applicable; NAC, neoadjuvant chemotherapy; NICE, National Institute for Health and Care Excellence; NMIBC, non-muscle-invasive bladder cancer; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PCN, percutaneous nephrostomy; RC, radical cystectomy; SE, standard error; SG, standard gamble; TCC, transitional cell carcinoma of the urothelial tract; TTO, time trade-off; TURBT, Transurethral Resection of Bladder Tumours; UTI, urinary tract infection; NR, not reported; PE, pulmonary embolism

5.4.4 Adverse reactions

In discussion with expert clinical advisors, it was confirmed AEs and tolerability significantly impact the quality-of-life for many mUC patients receiving treatment with currently available therapies. The type, and frequency, of adverse events experienced with immunotherapies has not, thus far, shown evidence of significant negative impact on patient QoL (National Institute for Health and Care Excellence, 2017a, National Institute for Health and Care Excellence, 2017b, National Institute for Health and Care Excellence, 2017c).

However, incorporating the effect of AEs on HRQoL into the economic model is highly challenging due to the limited data for HRQoL in mUC and lack of comparative data. To avoid the use of unsupported assumptions for the effect of AEs on HRQoL, no dis-utilities have been accounted for within the model. This is a conservative approach, given the anticipated improvement in tolerability of atezolizumab (based on results from the IMvigor 210 study), compared to the tolerability of existing therapies.

As EQ5D results will be collected in all treatment arms of the phase III studies, this will provide significantly more evidence for the impact of AEs on HRQoL.

5.4.5 Incorporation of HRQoL into the economic model

The economic model includes the health states PFS, PD and death. However, it is recognised that progression, as measured via the RECIST criteria, does not always signify loss of clinical benefit for patients being treated with atezolizumab. This is observed by the extended treatment duration vs. PFS in cohort 2 of the IMvigor 210 study, with 12 weeks median time on treatment, vs. 9 week median PFS. It is recommended atezolizumab patients remain on treatment until loss of clinical benefit or unmanageable toxicity. As such, it is appropriate to assume that patients on treatment are receiving clinical benefit, including HRQoL benefit. Therefore, HRQoL is implemented in the economic model via ‘on treatment’ or ‘off treatment’ states. For comparators, time on treatment is equal to PFS, thus ‘on treatment’, ‘off treatment’ is equivalent to ‘PFS’ and ‘PD’ health states.

Should this approach not be taken, the model contains an inconsistency in which cost is being generated for atezolizumab patients beyond progression, without any resulting HRQoL benefit being accounted for.

5.4.6 Health-related quality-of-life data used in cost-effectiveness analysis

As discussed previously, there are no HRQoL data available for mUC patients treated with atezolizumab. EQ5D data will be available with the IMvigor 211 study, and later with the IMvigor 130 study.

A review of the literature did not highlight any suitable data to be used in proxy. As such, assumptions from prior HTA reviews of immunotherapies (in NSCLC and melanoma) and treatments for mUC (vinflunine) were considered. Expert clinical advisors considered utility values from the prior NICE vinflunine appraisal to be too low for those expected with atezolizumab, and suggested values from prior immunotherapy NICE appraisals in NSCLC to be more representative (Table 61).

Notwithstanding this advice, utility values from prior mUC cost-utility analyses were preferred over NSCLC analyses, in order to remain consistent with the decision problem. Considering the experts guidance that the NICE vinflunine values were too low, utility values used in the Australian Pharmaceutical Benefits Advisory Committee (PBAC) cost-utility analysis for vinflunine were assessed and used for the base case of this analysis. These values were mapped from EORTC results for mUC patients having received vinflunine, and are reported in Table 62 (Pharmaceutical Benefits Advisory Committee, 2015). Utility values are assumed constant over time, with patients coming off treatment as the trigger for a reduction in HRQoL. No adjustment has been made to the HRQoL, including disutility due to AEs, or age adjustment. Alternative utility values were explored in scenario analyses.

Table 61: Summary of utility values across mUC and NSCLC immunotherapy appraisals

State	Vinflunine NICE	Nivolumab non-squamous NSCLC NICE submission*	Vinflunine PBAC
PFS	0.65	0.739	0.75
PD	0.25	0.688	0.71
* appraisal ongoing			

Table 62: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
On treatment	0.75 (0.150)	5.4.6	Derived from mUC patients in vinflunine Australian PBAC assesssment
Off treatment	0.71 (0.142)	5.4.6	Derived from mUC patients in vinflunine Australian PBAC assesssment

PBAC: Pharmaceutical Benefits Advisory Committee

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

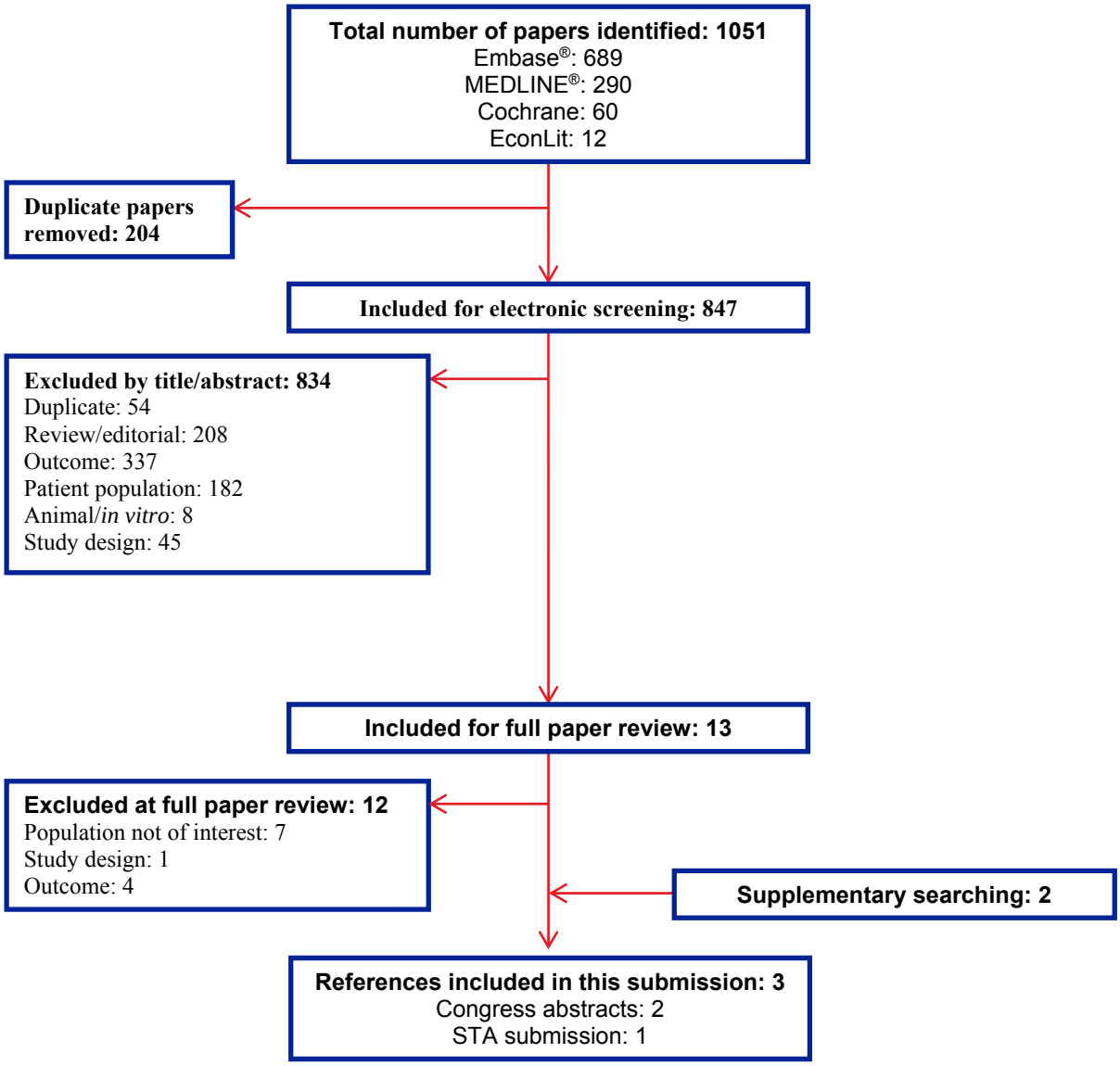
A SLR was conducted to identify published evidence regarding the resource use and costs associated with the management and treatment of advanced (or metastatic) urothelial carcinoma. Detailed descriptions of the search strategy, search terms and abstraction methods are provided in appendix 8.10. Briefly, searches of the MEDLINE® and MEDLINE® In-Process, Embase® , Cochrane Library, and EconLit, databases were conducted in Ovid and were limited to studies published in English between 1 January 2001 and 1 December 2016, and the search was not restricted by geographic location. Additionally, hand-searches were carried out of relevant congresses and manufacturer submissions and evidence review group/assessment reports from NICE. Table 63 reports the eligibility criteria of the searches.

Table 63: Cost and resource use search eligibility criteria

Population	Patients with advanced or metastatic urothelial carcinoma Adults ≥ 18 years
Interventions	Not restricted by intervention
Outcomes[b]	• Direct costs (including any intervention costs, costs to the payer) • Total costs • Resource use • Cost drivers
Study design	Not restricted by study design
Date restrictions	1 January 2001 to 1 December 2016
Language restrictions	English language
Country	Not restricted however evidence relevant from a UK payer perspective will be prioritized

The results of the screening and selection of relevant studies are presented in Figure 31 below.

Figure 31: Cost and resource use PRISMA flow diagram



In total, 15 studies met the broad inclusion criteria of the SLR, and three were considered relevant as per the eligibility criteria in Table 63. (Seal, 2015, Huillard, 2016, National Institute for Health and Care Excellence, 2013)

An overview of the findings from these studies is presented in Table 64, with brief descriptions below. A list of studies which met the inclusion criteria of the SLR but were not considered relevant to support the submission is included in appendix 8.10 along with a rationale for the non-inclusion. However, whilst these studies provide qualitative information regarding healthcare cost and resource use, none provide UK

specific quantitative data which can be used as parameter inputs for economic analysis.

A study reported by Seal *et al*., (Seal, 2015) evaluated the cost of care among patients diagnosed with metastatic or non-metastatic cancer in the US. Retrospective data from two large integrated claims databases were used, consisting of records spanning between July 2008 and December 2010. Patients receiving chemotherapy or patients with a diagnosis of any other cancer in the 6-month period prior to the index date (date of diagnosis) were excluded from the analysis. Data of interest included all-cause costs for the 6-month period prior to and after diagnosis of metastatic bladder cancer, and the proportion of costs attributable to medical services, inpatient and emergency visits.

Huillard *et al*., (Huillard, 2016) reported findings from a retrospective cohort study of patients with localised or metastatic bladder cancer in their last month of life . A retrospective review of the electronic medical records of all hospitalised adults who died from bladder cancer between 2010 and 2013 in France identified 8,766 patients with metastatic or locally advanced disease, 53.1% of whom had at least one comorbidity. Data of interest included the proportion of patients admitted to an intensive care unit and the utilisation of supportive medical care in the last month of life.

Estimates of healthcare resource use associated with the treatment of patients with advanced urothelial cancer in the UK were identified in the manufacturer's submission for the NICE technology appraisal of Vinflunine for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract who have failed a prior platinum-containing regimen (National Institute for Health and Care Excellence, 2013). The methods employed by the manufacturer to identify resource use evidence to inform the submission included a targeted review of the literature and interviews with expert advisors, including oncologists, nurses and clinical coding specialists. In the absence of sufficient evidence identified by the manufacturer's literature review, resource use was estimated by the clinical experts (the number of clinical experts interviewed was not reported). The findings from these interviews highlighted difficulties in identifying a typical care pathway for patients with urothelial cancer, although the ERG considered the estimates of cost

and resource use to be reasonable. Medical resource use associated with pre- and post-progression health states was reported, and included the number of general practitioner, nurse, health visitor, dietician, and oncologist (consultant and non-consultant) visits per month, the use of pain medication, and the use of prophylaxis for constipation during each cycle of chemotherapy.

Table 64: Cost and resource use studies (n=3)

Reference	Year	Country of study	Available cost/resource use data	Cost reference year (currency)	Patient population	Results (with assessment of relevance to UK)
(National Institute for Health and Care Excellence, 2013)	2010	UK	Resource use associated with pre- and post-progression health states (estimated based on interviews with clinical experts)	NA	Resource use was estimated for adults with advanced or metastatic transitional cell carcinoma of the urothelial tract who have failed a prior platinum-containing regimen	Estimates of healthcare resource use for pre- and post-progression health states: *Pre-progression: BSC* • GP home consultation/month: 1 • Community nurse specialist home visit/month: 4 • Health home visitor/month: 1 • Dietician/month: 1 • Consultant led (oncologist) follow-up visit/month: 1 • Palliative radiation therapy: o Dose per fraction (mean) (Gys): 4 *Post-progression: BSC* • GP home consultation visit/month: 1 • Community nurse specialist home visit/month: 4 • Health home visitor/month:1 • Dietician/month: 1 • Non-consultant (oncologist) follow-up visit/month: 1 • Pain medication (morphine sulphate 1mL daily)/month: 30 • Hospice care services/month: 1 • Palliative radiation therapy: • Dose per fraction (mean) (Gys):4 • Palliative chemotherapy • Number of cycles: 2 Resource use was assumed not be vary by treatment (based on expert opinion) Cost of constipation prophylaxis (one week of laxatives therapy) was assumed with each cycle of chemotherapy,

Reference	Year	Country of study	Available cost/resource use data	Cost reference year (currency)	Patient population	Results (with assessment of relevance to UK)
						consistent with expert recommendations As resource use was reported for relevant health states in the current economic model (pre- and post-progression) and based on interviews with oncologists and nurses from UK clinical practice, the findings were considered relevant to this submission
(Huillard, 2016)	2016	France	Admissions to ICU and supportive medical care received by patients in the last month before death (based on a retrospective review of electronic medical records)	NA	All hospitalized adults (≥ 20 years) who died from bladder cancer between 2010 and 2013 in France, including 8,766 patients (50.1%) who had a metastatic or locally advanced disease	Proportion of patients utilising healthcare resources in the last month before death: • admissions to ICU: 20.6% • chemotherapy: 13.4% • artificial nutrition: 6.9% • invasive ventilation: 2.4% • dialysis: 2.6% • hemodynamic support: 4.0% Although the study was based on patients in hospitals in France, and the generalisability of the findings to UK clinical practice is unknown, the study provides useful information regarding admissions to ICU and the utilisation of medical care in the last month of life in a large cohort of patients who died from metastatic bladder cancer
(Seal, 2015)	2015	US	Total all-cause costs associated with the 6-month period prior to and after diagnosis of metastatic bladder cancer, and the proportion of costs attributable to	2013 (USD)	Adult patients with a diagnosis of malignant neoplasm of the bladder, including 3,161 patients with metastatic disease (2,179 from one database, and 982) from the	Costs associated with the 6-month period prior to and after diagnosis of metastatic bladder cancer: • total 6-month cost prior to diagnosis (range): $6,766–$7,831 • total 6-month cost post-diagnosis (range): $40,695–$45,817 • proportion of total costs during the post-diagnosis period attributable to medical services: 94.8%–96.5% • proportion of total costs during the post-diagnosis period attributable to inpatient and emergency department costs: 50.4%–52.5%

Reference	Year	Country of study	Available cost/resource use data	Cost reference year (currency)	Patient population	Results (with assessment of relevance to UK)
			medical services, inpatient and emergency services (based on a retrospective review of two integrated claims databases)		other)	As the study was based on claims data in the US, and there was a lack of information reported regarding patient characteristics, the generalisability of the findings to UK clinical practice is unknown. Despite these limitations, the data was considered relevant to this submission as the findings provide an indication of the proportion of total costs in the 6-month period before and after diagnosis attributable to medical services, and inpatient and emergency department visits

5.5.2 Source for cost and resource use inputs

There are no payment-by-results tariffs which are directly applicable to atezolizumab in mUC or other indications.

The SLR described in 5.5.1 did not identify any studies which directly quantify costs and healthcare resource use for advanced or metastatic UC, treated with chemotherapy or immunotherapy in the NHS. As such, previous NICE appraisals were considered to be the most appropriate source for healthcare costs and resource use. The values were validated by expert clinical advisers.

One prior NICE appraisal was available for mUC (National Institute for Health and Care Excellence, 2013), and several prior NICE oncology appraisals were available for immunotherapy agents specifically targeting the PD1-PDL1 interaction. Expert clinical advisors suggested NSCLC was the most appropriate disease to use as an analogue for mUC, in the absence of robust data for the latter. As such appraisal were additionally used as sources of information, in combination with the vinflunine appraisal,TA272 (National Institute for Health and Care Excellence, 2017c, National Institute for Health and Care Excellence, 2017a).

5.5.3 Intervention and comparators' costs and resource use

Drug dosage, drug costs, treatment duration and administration costs all contribute to the overall cost and resource use associated with the intervention and comparators'. Information as outlined below is available in the following sections.

5.5.4: Drug dose and costs

5.5.5: Treatment duration

5.5.6: Administration costs

For dosing per m^2, the average body surface area of patients in cohort 1 and 2 of the IMvigor 210 study were used respectively for the 1L and 2L models. Given the absence of robust data, no dose modifications, or treatment breaks are assumed for atezolizumab or the comparators.

5.5.4 Drug dose and costs

Published list prices for the comparators (gemcitabine plus carboplatin, docetaxel and paclitaxel) are not representative of the price paid within the NHS, as these products are generically available. As such, prices for comparators were taken from the drugs and pharmaceutical electronic market information (eMit)(Department of Health, 2016a). Scenario analyses include use of list price for these products (section 5.8.3). As there are several branded products available with differing list prices, a non-weighted average was taken to derive a list price for each comparator product (for scenario analyses only). A summary of costs and doses is found in Table 65 below.

None of the comparator regimens are licensed for use in mUC, as such dose information was taken from 4 sources: licensed doses of the comparators for other indications; the ongoing phase III clinical trials of atezolizumab (IMvigor 130: gemcitabine plus carboplatin in 1L & IMvigor 211: docetaxel or paclitaxel in 2L); the 'North West London Cancer Network, Bladder cancer/transitional cell carcinoma - Regimens Approved' (hereafter referred to as 'Guidelines') (London Cancer Alliance, 2013), and; expert clinical advice.

Gemcitabine plus carboplatin

Gemcitabine in combination with carboplatin is not licensed for use in mUC. Dose information for gemcitabine in mUC is consistent across the Guidelines and IMvigor 130 at 1000mg/m^2 on days 1 and 8 of a 21 day cycle. Carboplatin dose as per the Guidelines and IMvigor 130 study, states: Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25], on day 1 of a 21 day cycle. Mean glomerular filtration rate (GFR) is not available for Cohort 1 of the IMvigor 210 study. As such the alternative licensed dose of 400 mg/m^2 is utilised, expected to be broadly consistent with the target AUC dosing, and with minimal impact on the overall drug costs assumed in the model.

Two trials fed into the ITC to generate parameter inputs for gemcitabine in combination with carboplatin, both with differing dosing regimens. One of the trials (Bamias et al., 2007), utilised a biweekly dose of both gemcitabine and carboplatin. As such, the dose used to generate the drug and administration cost inputs may be

an underestimation based on the clinical outcomes from this study, thus representing a conservative approach.

Paclitaxel

The dose of paclitaxel in the ongoing, atezolizumab phase III clinical trial (IMvigor 211) is 175 mg/m^2 IV on day1 of each 21-day cycle. However, expert clinical advice, and UK Guidelines (London Cancer Alliance, 2013) confirmed that standard UK practice is for patients to receive 80mg/m^2 weekly, to improve tolerability. As such, this dosage and frequency of infusion is utilised in the base case.

Docetaxel

The dose used in the phase III clinical trial is consistent with the recommended dose of docetaxel at 75mg/m^2, day 1 of each 21 day cycle.

Atezolizumab

The anticipated dose of atezolizumab is 1200mg on day 1 of each 21 day cycle.

Best supportive care

No drug cost is accounted for within BSC. As such, costs for this comparator are assumed to be accrues only from health-state costs.

Table 65: Dose and drug costs for intervention and comparators

	Dose	Source	List price	eMit price
1L				
Gemcitabine	1000mg/m^2 IV over 30 mins Day 1 and 8 of each 21 day cycle for maximum 6 cycles	SmPC, Guideline, pIII trial dose	200mg vial £31.60	200mg vial £3.99
Carboplatin	400mg /m^2 IV over 15 to 60 mins Day 1 of each 21 day cycle for maximum 6 cycles	SmPC,	50mg vial £21.74	50mg vial £3.57
Atezolizumab	1200mg IV over 60 mins for first infusion, thereafter 30 mins Day 1 of each 21 day cycle	Draft SmPC	1200mg vial £3807.69	n/a
2L				
Paclitaxel	80 mg/m^2 IV over 60 mins Weekly	Guideline, expert clinical advice	30mg vial £99.12 150mg vial £442.28	30mg vial £3.41 150mg vial £11.50
Docetaxel	75 mg/m^2 IV over 60 mins Day 1 of each 21-day cycle	SmPC, pIII trial	140mg vial £900.00	140mg vial £17.77
BSC	n/a	n/a	n/a	n/a
Atezolizumab	1200mg IV over 60 mins for first infusion, thereafter 30 mins Day 1 of each 21 day cycle	Draft SmPC	1200mg vial £3807.69	n/a

5.5.5 Treatment duration

Comparators:

As per clinical practice, the comparators are assumed to be administered until disease progression or unacceptable toxicity. In the absence of available data on time to treatment discontinuation (TTD) with the comparators, PFS will be used as a

proxy for time on treatment. Please see section 5.3 for detailed information regarding PFS extrapolation and parameter inputs.

Atezolizumab:

Atezolizumab is anticipated to be licensed for use until loss of clinical benefit or unmanageable toxicity. Results from the IMvigor 210 study, and clinical trial evidence from other indications for atezolizumab, suggests that patients may continue to receive treatment beyond disease progression. As such, PFS is not a good surrogate for treatment duration as it is likely to underestimate the true treatment duration expected in clinical practice, and as such, treatment cost.

Consequently, TTD was taken directly from the IMvigor 210 study. As the study is ongoing, and not all patients had discontinued treatment at the most recent July 2016 study data cut, it was necessary to extrapolate the study results such that treatment duration could be estimated beyond the trial period. Parametric distributions were fitted to the TTD KM curves, independently for 1L and 2L treatment cohorts, and assessed for their goodness of fit to the data using the AIC / BIC statistics, and graphical assessment of each function.

Table 66 and Table 67 provide the AIC and BIC goodness of fit results for the functions used to model TTD, for 1L and 2L respectively. The rank of the goodness of fit is shown in brackets, with one indicating best fit and six worst. Based on the AIC statistic, the best fit overall would be obtained with a Weilbull function for 1L and a Log-logistic function for 2L. However the AIC statistics only reflect the parametric distribution fit to observed data and do not allow conclusions to be drawn regarding the appropriateness of the tail of the distributions. Considering the AIC combined with visual examination of the extrapolation, a generalised gamma is deemed the most appropriate option for both 1L and 2L. The resulting extrapolations are displayed in Figure 32 and Figure 33 below

Table 66: AIC and BIC for TTD with ranks in brackets (1L)

Parametric distribution	AIC	BIC
Exponential	487.76 (5)	490.54 (5)
Weibull	461.67 (1)	467.23 (1)
Log-normal	470.67 (4)	476.22 (4)
Gamma	**463.37 (2)**	**471.71 (3)**
Log-logistic	463.44 (3)	468.99 (2)
Gompertz	489.76 (6)	495.32 (6)

Table 67: AIC and BIC for TTD with ranks in brackets (2L+)

Parametric distribution	AIC	BIC
Exponential	1371.7 (5)	1375.4 (5)
Weibull	1248.9 (3)	1256.3 (2)
Log-normal	1258.3 (4)	1265.8 (4)
Gamma	**1247.3 (2)**	**1258.5 (3)**
Log-logistic	1246.2 (1)	1253.6 (1)
Gompertz	1373.7 (6)	1381.1 (6)

Figure 32: Extrapolated TTD (1L)

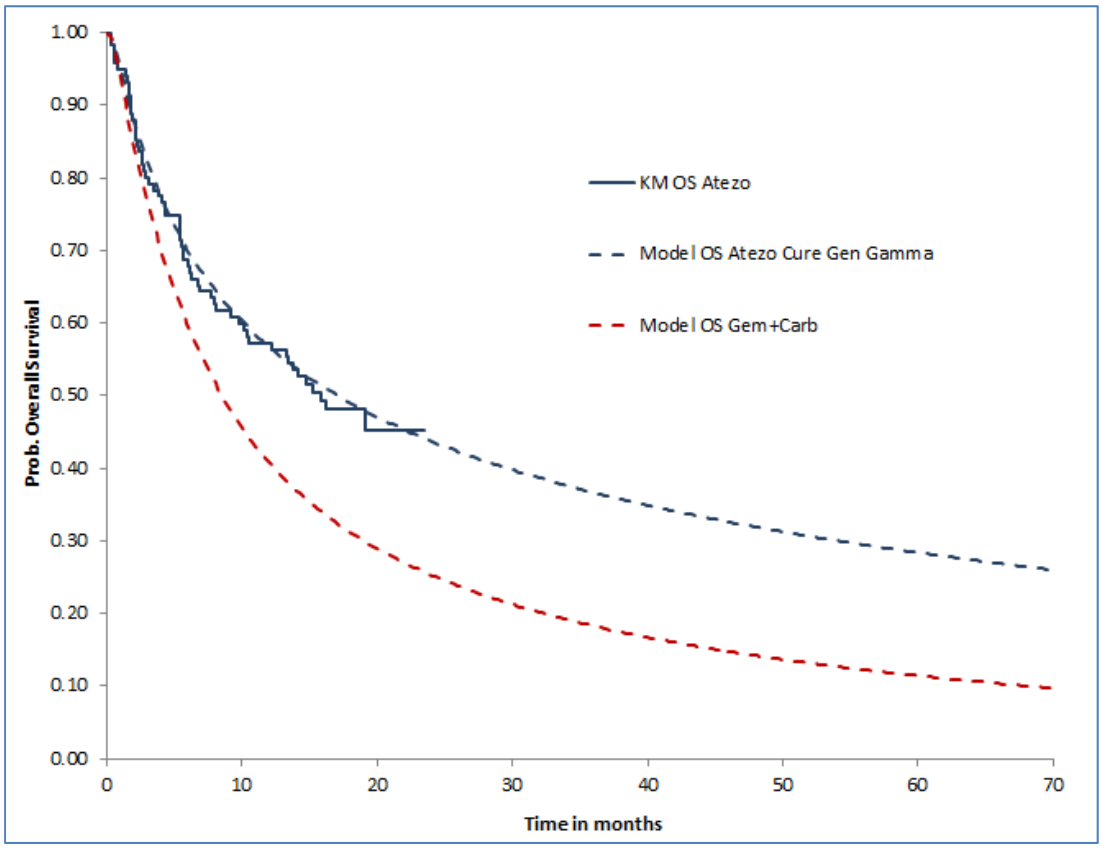
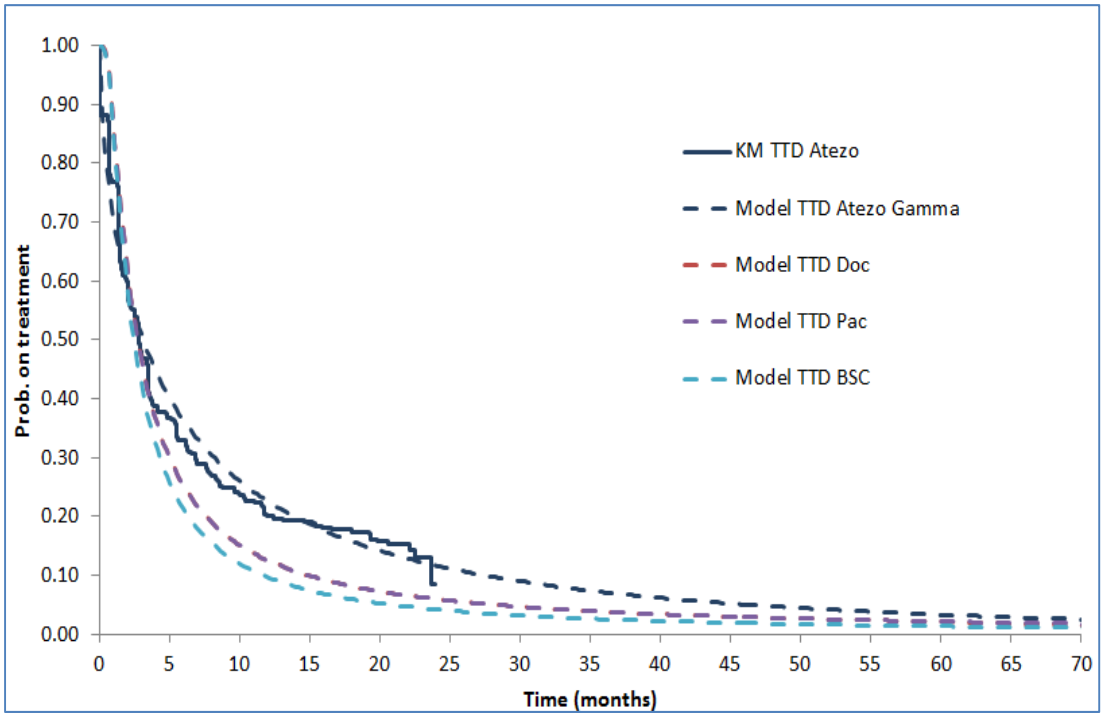


Figure 33: Extrapolated TTD (2L+)



5.5.6 Administration costs

Atezolizumab and all comparators are administered via IV infusion, over either 30 or 60 minutes duration. NHS reference codes have been designated from tariff codes in the NHS OPCS-4 Chemotherapy Regimens List and High Cost Drugs List 2016 (Health and social care information centre, 2016).

Table 68: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient Setting	SB12Z	£199	NHS reference costs 2014-15
Docetaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB12Z	£199	NHS reference costs 2014-15
Paclitaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB14Z	£304	NHS reference costs 2014-15
Gemcitabine and carboplatin	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB13Z	£265	NHS reference costs 2014-15

5.5.7 Health-state unit costs and resource use

Specific UK cost and resource use data for the relevant health states were not available for mUC. The SLR, as described in section 5.5.1, did not identify literature with directly applicable resource use costs for the UK.

As described in section 5.5.2, prior NICE appraisals were deemed to be the most appropriate source for resource use data. The one prior mUC NICE appraisal identified in the search was that of vinflunine (National Institute for Health and Care Excellence, 2013). Health-state resource use for this appraisal was elucidated

through expert clinical advice, and were deemed appropriate by the ERG and NICE Appraisal Committee.

In the absence of alternative published data for resource use in mUC, it was deemed preferable to remain consistent with information used in prior decision making for the disease. As such, resource utilisation by heath state were taken from the vinflunine submission, and are as described in Table 69 below. The allocated unit cost for each parameter has been updated to most recent price levels (2015/16 NHS Reference Costs and 2016 PSSRU costs) (Department of Health, 2016b) (Curtis, 2016).

Table 69: Resource utilisation and cost by health-state

	Frequency per month	Unit cost	Per cycle cost	Source for cost
Pre-progression				
GP consultation	1	£36	£8.31	Curtis 2016
Community nurse visit	4	£38	£28	Community health services – district nurse Service code NO2AF 2015-16 costs
Health home visit	1	£40	£9.23	Curtis 2016
Dietician	1	£81	£18.69	Community health services - dietitian Service code A03 2015-16 costs
Oncologist consultation (consultant)	1	£163	£37.62	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
Total			**£111.85**	
Post-progression				
GP consultation	1	£36	£8.31	Curtis 2016
Community nurse visit	4	£38	£38	Community health services – district nurse Service code NO2AF 2015-16 costs
Health home visit	1	£40	£9.23	Curtis 2016
Dietician	1	£81	£18.69	Community health services - dietitian Service code A03 2015-16 costs
Hospice care	70% of patients	£1119	£30.13	Curtis 2016 (Assumed proportion from vinflunine apprailsal TA272, assumed 6 months survival)
Oncologist consultation (non-consultant)	1	£100	£23.08	Non-consultant led - Medical oncology. Service code 370 2015-16 costs

Pain medication	30 (Daily)	£3.69	£0.85	eMIT £1.23 per 10mg/1ml morphine sulfate solution for infection – 10 pack
Palliative radiation therapy		£283		SC47Z: Preparation for simple radiotherapy with imaging and simple calculation (outpatient)
		£105		SC22Z: Deliver a fraction of treatment on a megavoltage machine (outpatient)
Proportion of patients	42.70%			Vinflunine appraisal TA272
Number of courses	1.9			Vinflunine appraisal TA272
Total dose		£314.78	£12.11	Over assumed 6 month survival
Palliative chemotherapy		£277		Outpatient – Procure cheomotherapy drugs for regimens in Band 2 – SB02Z
Proportion of patients	30%			Vinflunine appraisal TA272
Number of cycles (of 21 days)	2			Vinflunine appraisal TA272
Total dose		£27.70	£6.39	Over assumed 6 month survival
Total cost			**£146.79**	

5.5.8 Adverse reaction unit costs and resource use

The IMvigor 210 study provides the type and rate of AEs for atezolizumab in mUC. As this is a single arm study, the rate of AEs is not available for comparators from this same source. As such, the studies included within the ITC provide the rate of AEs for comparators.

All grade ≥3 treatment related AEs with an incidence of ≥1% in any of the studies are included in the base case analyses. AE treatment costs are calculated per episode, using the National Schedule of Reference Costs (2015/16) where possible. (Department of Health, 2016b)

Where there were gaps in the data, costs were sourced from prior NICE submissions in mUC or NSCLC and inflated to current price levels (as a disease analogue as per expert clinical advice).

Table 70: Adverse event costs

Adverse event	Cost	Reference
alanine aminotransferase increase	£163.00	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
aspartate aminotransferase increase	£163.00	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
Anemia	£329.92	HRG 2015/16 (Day case SA04G,H,J,K,L (Iron Deficiency Anaemia, average of CC scores)
blood bilirubin increased	£163.00	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
diarrhoea	£114.00	non-consultant led first visit - gastroenterology - service code 301
Electrolyte abnormalities	£163.00	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
Fatigue	£3082.59	Nivolumab NSCLC appraisals ID811 and ID900 (National Institute for Health and Care Excellence, 2017a, National Institute for Health and Care

		Excellence, 2017b)
Febrile neutropenia	£362.66	Nivolumab NSCLC appraisals ID811 and ID900 (National Institute for Health and Care Excellence, 2017a, National Institute for Health and Care Excellence, 2017b)
Leucopenia	£362.22	Nivolumab NSCLC appraisals ID811 and ID900 (National Institute for Health and Care Excellence, 2017a, National Institute for Health and Care Excellence, 2017b)
hypophosphataemia	£163.00	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
Infection	£163.00	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
Peripheral neuropathy (sensory or motor)	£139.12	HRG service code 191, pain management
Renal failure	£310.00	Acute Kidney Injury with Interventions, with CC Score 0-5. Currency code LA07k
Thrombocytopenia	£362.66	Nivolumab NSCLC appraisals ID811 and ID900 (National Institute for Health and Care Excellence, 2017a, National Institute for Health and Care Excellence, 2017b)

5.5.9 Miscellaneous unit costs and resource use

No additional costs were identified

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Parameter inputs can be found in Table 71 below.

Table 71: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Patient age (1L)	71.8	Fixed	4.11.5
Patient agre (2L)	65.6	Fixed	4.11.5
Discount rate (costs)	3.5%	Fixed	5.2.2
Discount rate (efficacy)	3.5%	Fixed	5.2.2
Time horizon	20 years	Fixed	5.2.2
Utility values			
On treatment	0.75	Beta distribution 0.150 standard error	5.4.7
Off treatment	0.71	Beta distribution 0.142 standard error	5.4.7
Parametric survival curves			
PFS atezolizumab	Generalised gamma	Multivariate normal distribution	5.3.3
PFS comparators	Generalised gamma	Multivariate normal distribution	5.3.4
OS atezolizumab	Cure generalised gamma	Multivariate normal distribution	5.3.5
OS compartors	Cure eneralised gamma	Multivariate normal distribution	5.3.6
Parametric survival tail for treatment duration			
TTD atezolizumab	Generalised gamma	Multivariate normal distribution tail	5.5.5
TTD comparators`	Equal to PFS	Multivariate normal distribution tail	5.5.5
Treatment costs			
Atezolizumab 1200mg	£3807.69	Fixed	5.5.4
Docetaxel	Table 65	Fixed	5.5.4
Paclitaxel	Table 65	Fixed	5.5.4
Gemcitabine + carboplatin	Table 65	Fixed	5.5.4
Administration atezolizumab	£199 Table 68	Log-normal distribution	5.5.6
Administration docetaxel	£199 Table 68	Log-normal distribution	5.5.6
Administration paclitaxel	£304 Table 68	Log-normal distribution	5.5.6
Administration gemcitabine	£265 Table 68	Log-normal distribution	5.5.6
Administration	£265	Log-normal distribution	5.5.6

carboplatin	Table 68		
Health state costs			
Cost of PFS	£111.85 See Table 69	Log-normal distribution	5.5.7
Cost of PD	£146.79 Table 69	Log-normal distribution	5.5.7
Adverse event			
Individual AE costs	Table 70	Log-normal distribution	5.5.8

5.6.2 Assumptions

The de novo model used a range of assumptions, details of which can be found throughout section 5 of this submission. Key assumptions are detailed in Table 72 below

Table 72: Key assumptions within economic model

Area	Assumption	Justification
Time horizon	20 years	Appropriate to capture all associated costs and benefits
Clinical efficacy and safety	Efficacy and safety results for atezolizumab seen in the IMvigor 210 study are transferable to UK population	The IMvigor 210 study included UK patients. Expert clinical advice suggests the outcomes seen from the study are expected in UK patients.
HRQoL	Use of utility values from Australian PBAC appraisal of vinflunine	Most appropriate data available in the absence of HRQoL data from IMvigor 210. HRQoL was taken directly from patients receiving vinflunine and mapped to utilities.
Treatment duration	Atezolizumab treatment duration is based on time on treatment results of the IMvigor 210 study Comparator treatment duration is based on PFS	IMvigor 210 results suggest patients in 2L continue to received treatment beyond progression Treatment duration results are not available for comparators, and as treatment is until progression, PFS is a

		suitable proxy.
Resource use	As per section 5.5.5	Assumptions based on prior appraisals, and feedback received from ERG appraisal reviews.
Indirect treatment comparison	Various assumptions	See section 4.10
PFS	Comparator PFS is equal to atezolizumab	Conservative assumption due to scarcity of data. Anticipated to be modified with the availability of phase III data.

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Base-case results of the economic model are presented below. These results include the proposed list price for atezolizumab, which has not yet been submitted to the Department of Health.

Atezolizumab 1L provided a QALY gain of 2.69, and life-year gain of 3.74, at a total drug cost of £47,857, and total overall cost of £77,211. The comparator relevant for 1L, gemcitabine in combination with carboplatin, provides 1.35 QALY gain and 1.84 life-year gain, at a total cost of £18,106. The resulting ICER is £44,158 / QALY.

Atezolizumab 2L provided a QALY gain of 1.23, and life-year gain of 1.69, at a total drug cost of £56,997, and total overall cost of £71,868. The most relevant comparator based on clinical practice in England is paclitaxel, which provided a gain of 0.71 QALYs and 0.96 life years, at drug costs of £483 and total costs of £16,606. The resulting ICER for atezolizumab compared to paclitaxel is £104,850 / QALY. For ICERs as compared to other 2L comparators please see Table 74 below.

Table 73: Base-case results (1L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£77,211	3.74	2.69				
Gemcitabine + carboplatin	£18,106	1.84	1.35	£59,106	1.91	1.34	£44,158
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 74: Base-case results (2L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£71,868	1.69	1.23				
Docetaxel	£9,439	1.04	0.76	£62,430	0.65	0.47	£131,579
Paclitaxel	£16,606	0.96	0.71	£55,262	0.73	0.53	£104,850
BSC	£4,836	0.75	0.55	£67,032	0.94	0.68	£98,208
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

5.7.2 Clinical outcomes from the model

As described in section 5.3 above, clinical inputs for atezolizumab and the comparators are associated with significant uncertainty. As data for atezolizumab are available only from a single arm, phase II study, this presents significant challenge deriving comparative efficacy data. Confounding this is the weak evidence base available for comparators. For example, OS and PFS data for the key 2L comparator paclitaxel are only available from a 34 patient study. As the model inputs are subject to uncertainty, this leads to unavoidable uncertainty in the model outputs.

Additional uncertainty comes from the relative immaturity of the IMvigor 210 study, particularly when considering the expectation of durable responses in a significant proportion of patients, as demonstrated by immunotherapies in the metastatic setting of other indications. It was necessary to extrapolate from the end of the observed study data to obtain survival for a lifetime horizon.

Comparison of results from the model to observed data from the IMvigor 210 study, and phase I study allow some assessment of the accuracy of the modelled survival. Results for PFS and OS from the model, are compared to trial data in Table 75 and Table 76 respectively. Although PFS is overestimated within the model as compared to the IMvigor 210 study, the model is more accurate in its OS estimates, thus supporting the approach taken to OS extrapolation. Additionally the extrapolated 5 and 10 year OS results for 2L were validated by clinical experts as being clinically plausible (Table 77).

Table 75: Summary of PFS model results compared with observed clinical data

	Median PFS (model)	Median PFS (trial)	12 month PFS (model)	12 month PFS (trial)
IMvigor cohort 1 (1L)	3.9 months	2.7 months	22.5%	NR
IMvigor cohort 2 (2L)	2.76 months	2.1 months	12.6%	NR
Phase I study	n/a	1.84 months	n/a	22.11

Table 76: Summary of OS model results compared with observed clinical data

	Median OS (model)	Median OS (trial)	12 month OS (model)	12 month OS (trial)
IMvigor cohort 1 (1L)	17.0 months	15.9 months	56.8%	57%
IMvigor cohort 2 (2L)	7.8 months	7.9 months	38.4%	36.9%
Phase I study		10.1 months		45.5%

Table 77: Comparison of modelled and expert opinion results for OS

	5 year OS	10 year OS	20 year OS
Expert clinical advice	10-20%	5-10%	0-5%
Atezolizumab 2L model	9.5%	4.1%	1.1%

The movement of patients through the model health states over time are illustrated below for 1L (Figure 34 and Figure 35) and 2L+ (Figure 37, Figure 38, Figure 39, and Figure 40).

From these figures it can be seen patients spend a greater amount of time in the PFS state, and experience longer OS when receiving atezolizumab, as compared to comparators. Figure 36 and Figure 41 shows aggregated results for all health states for the comparisons in 1L and 2L respectively.

Figure 34: Markov trace for health states over time: atezolizumab (1L)

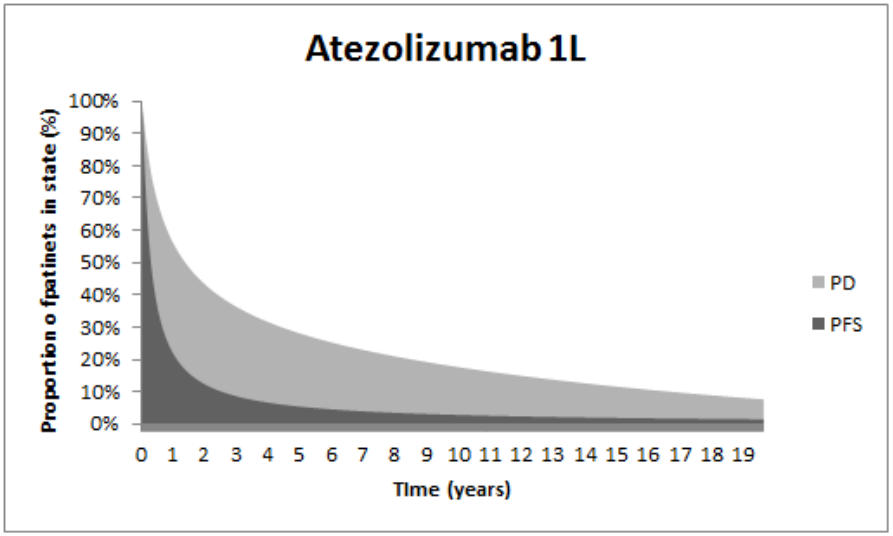


Figure 35: Markov trace for health states over time: gemcitabine + carboplatin (1L)

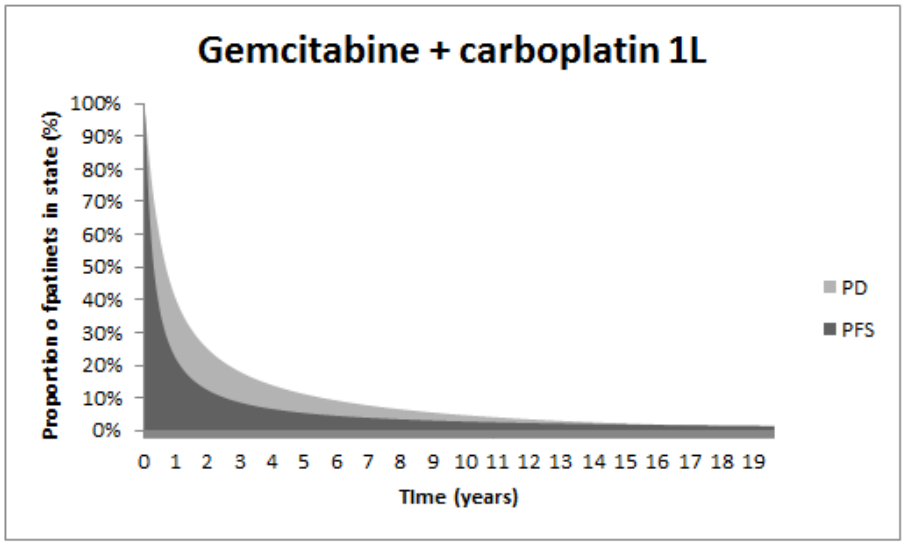


Figure 36: Markov trace: combined for all results (1L) (Model: GemPFS curve lies directly over Model: Atezolizumab PFS cure)

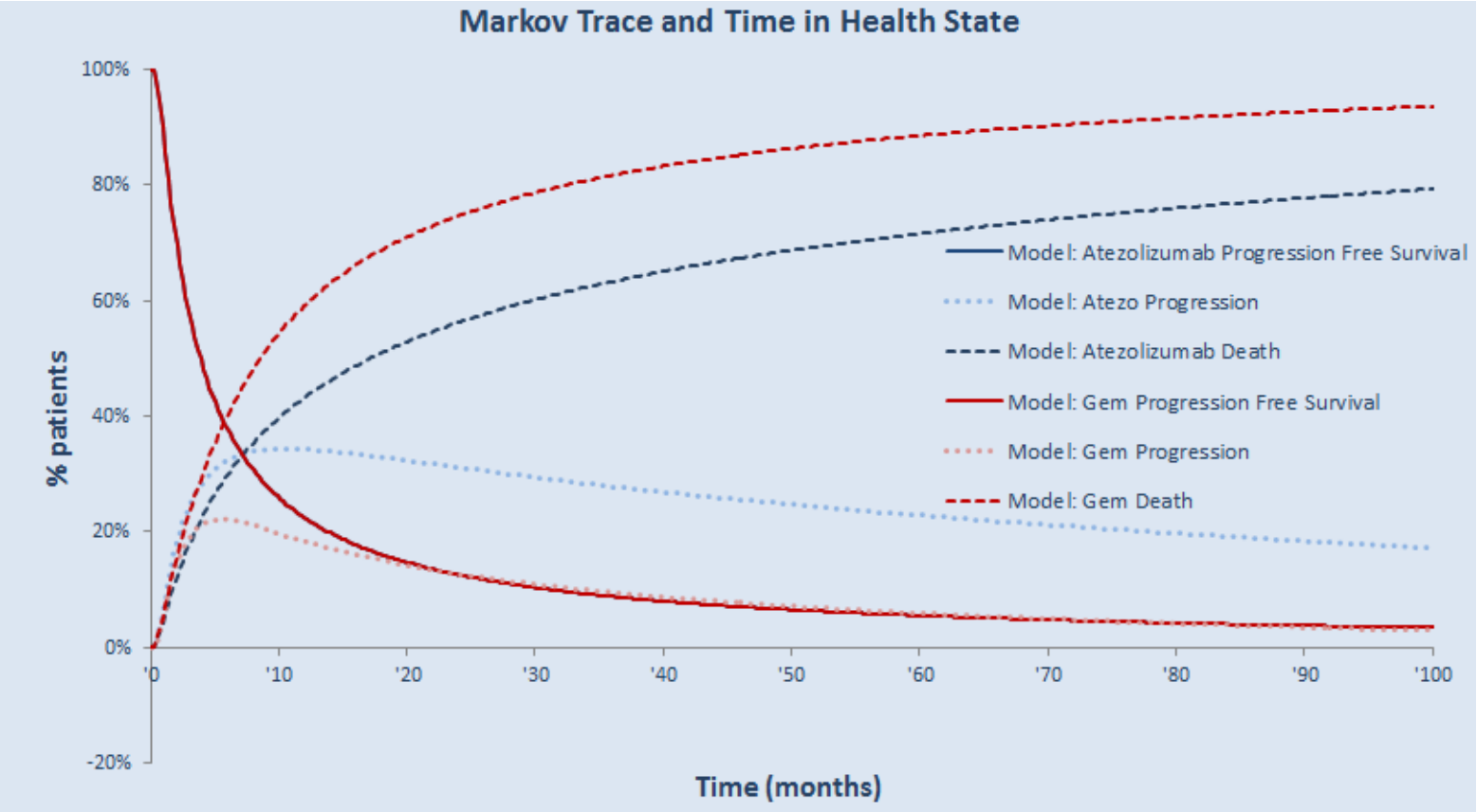


Figure 37: Markov trace for health states over time: atezolizumab (2L)

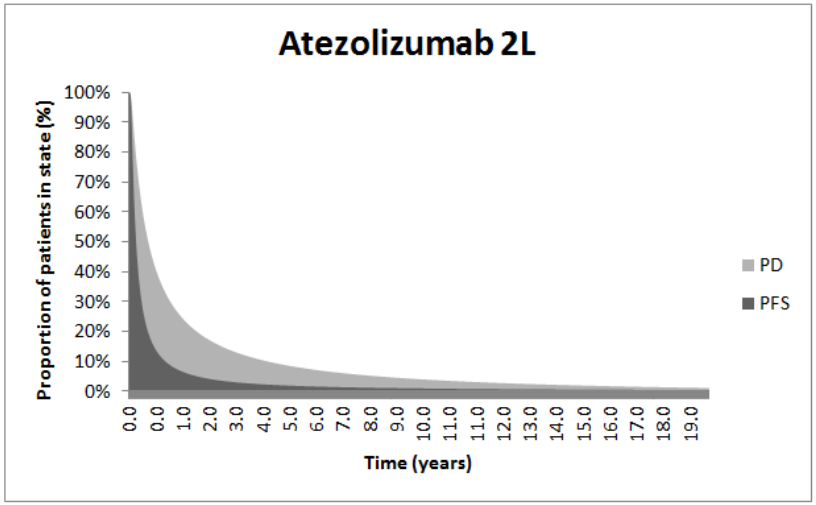


Figure 38: Markov trace for health states over time: docetaxel (2L)

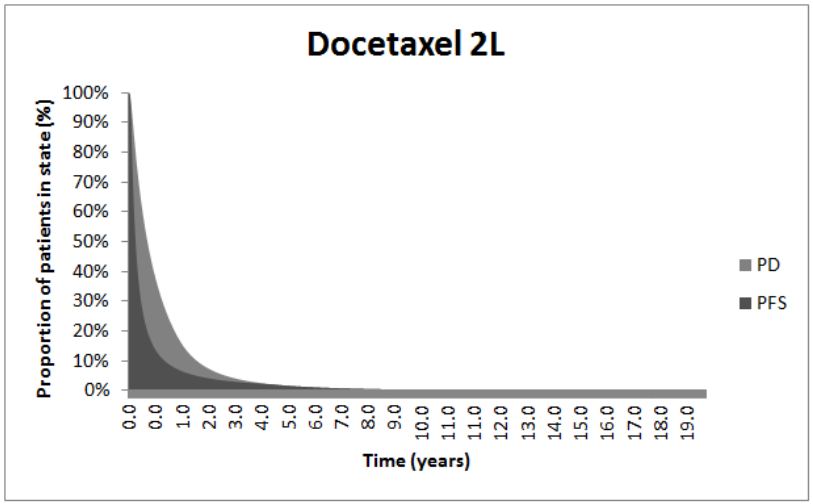


Figure 39: Markov trace for health states over time: paclitaxel (2L)

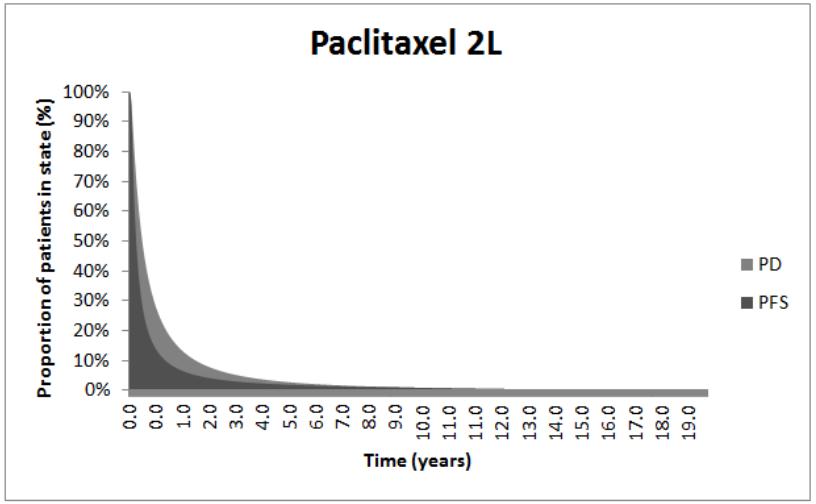


Figure 40: Markov trace for health states over time: BSC(2L)

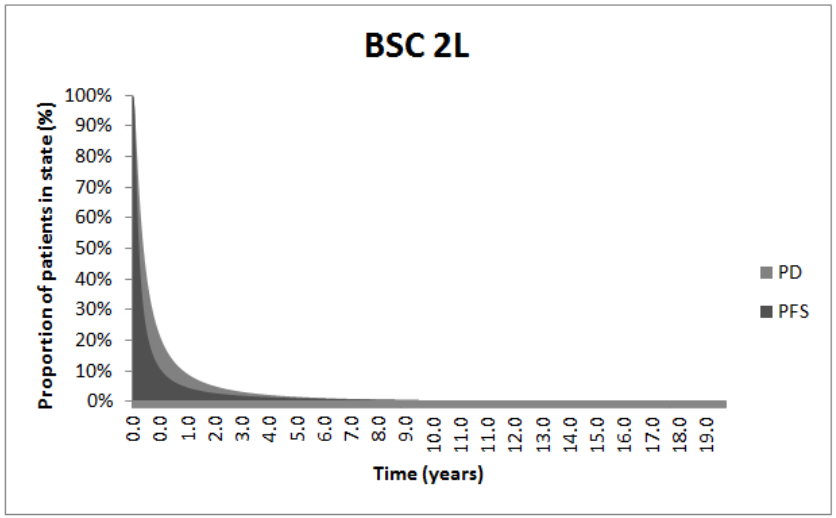
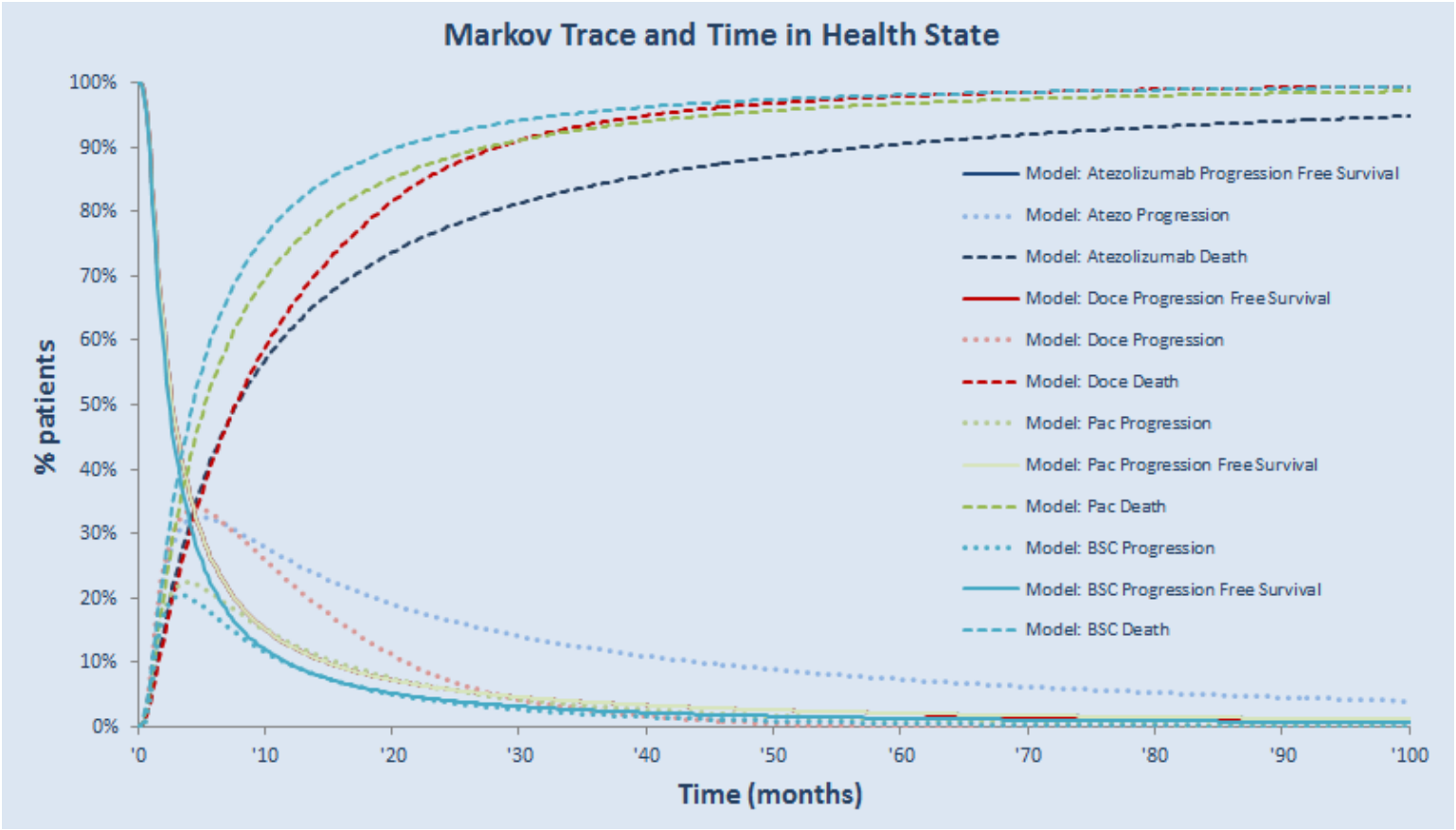


Figure 41: Markov trace: combined for results for all comparators (2L) (Model Pac curve lies directly over Model atezolizumab and docetaxel curves)



5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

The QALY gain disaggregated by health states allows exploration of which health state is driving QALY gain. Table 78 shows the results for the 1L comparison to gemcitabine + carboplatin. The 2L comparisons are shown in Table 79 (docetaxel) Table 80 (paclitaxel) and Table 81 (BSC).

In all comparators, the majority of incremental QALY gain for atezolizumab is achieved when patients are off treatment in the PD health state. These results are as expected, given the relatively modest PFS benefit achieved with atezolizumab, as compared to the substantial survival gain anticipated with immunotherapy treatments.

Table 78: Summary of QALY gain by health state: comparison to gemcitabine + carboplatin (1L)

Health state	QALYs: atezolizumab	QALYs gemcitabine + carboplatin	Increment	% absolute increment QALYs
PFS	0.53	0.83	-0.3	-22%
PD	2.16	0.52	1.64	122%
Total	2.69	1.35	1.34	100%

Table 79: Summary of QALY gain by health state – comparison to docetaxel (2L+)

Health state	QALYs: atezolizumab	QALYs docetaxel	Increment	% absolute increment QALYs
PFS	0.63	0.44	0.19	40%
PD	0.60	0.32	0.28	60%
Total	1.23	0.76	0.47	100%

Table 80: Summary of QALY gain by health state – comparison to paclitaxel (2L+)

Health state	QALYs: atezolizumab	QALYs paclitaxel	Increment	% absolute increment QALYs
PFS	0.63	0.47	0.17	32%
PD	0.60	0.24	0.36	68%
Total	1.23	0.71	0.53	100%

Table 81: Summary of QALY gain by health state – comparison to BSC (2L+)

Health state	QALYs: atezolizumab	QALYs BSC	Increment	% absolute increment QALYs
PFS	0.63	0.37	0.26	38%
PD	0.60	0.18	0.42	62%
Total	1.23	0.55	0.68	100%

A breakdown of the difference in costs can be found below. Table 82 for 1L, and Table 83, Table 84and Table 85 for 2L comparisons, show the breakdown of costs by health states. Cost breakdown by resource use is found in Table 86 for 1L and Table 87, Table 88 and Table 89 for 2L comparisons.

Table 82: Summary of costs by health state: comparison to gemcitabine + carboplatin (1L)

Health state	Cost atezolizumab	Cost gemcitabine + carboplatin	Increment	% absolute increment
PFS	£57,006	£12,513	£44,493	75%
PD	£20,205	£5,592	£14,613	25%
Total	£77,211	£18,106	£59,106	100%

Table 83: Summary of costs by health state: comparison to docetaxel (2L+)

Health state	Cost atezolizumab	Cost docetaxel	Increment	% absolute increment
PFS	£63,777	£5,956	£57,822	93%
PD	£8,091	£3,483	£4,608	7%
Total	£71,868	£9,439	£62,430	100%

Table 84: Summary of costs by health state: comparison to paclitaxel (2L+)

Health state	Cost atezolizumab	Cost paclitaxel	Increment	% absolute increment
PFS	£63,777	£13,994	£49,784	90%
PD	£8,091	£2,612	£5,479	10%
Total	£71,868	£16,606	£55,262	100%

Table 85: Summary of costs by health state: comparison to BSC (2L+)

Health state	Cost atezolizumab	Cost BSC	Increment	% absolute increment
PFS	£63,777	£2,896	£60,881	91%
PD	£8,091	£1,940	£6,151	9%
Total	£71,868	£4,836	£67,032	100%

Table 86: Summary of predicted resource use by category of cost (1L)

Cost Item	Cost atezolizumab	Cost gemcitabine + carboplatin	Increment	% absolute increment
Treatment	£47,857	£619	£47,238	80%
Administration	£2,501	£3,572	-£1,070	-2%
Adverse events	£199	£1,874	-£1,676	-3%
Supportive care (PFS)	£6,449	£6,449	0	0%
Supportive care (PD)	£20,205	£5,592	£14,613	25%
Total	£77,211	£18,106	£59,106	100%

Table 87: Summary of predicted resource use by category of cost – docetaxel (2L+)

Cost Item	Cost atezolizumab	Cost docetaxel	Increment	% absolute increment
Treatment	£56997	£238	£56,760	91
Administration	£2,979	£2,084	£895	1%
Adverse events	£95	£232	-£137	0%
Supportive care (PFS)	£3,706	£3,402	£304	1%
Supportive care (PD)	£8,091	£3,483	£4,608	7%
Total	£71,868	£9,439	£62,430	100%

Table 88: Summary of predicted resource use by category of cost – paclitaxel (2L+)

Cost Item	Cost atezolizumab	Cost paclitaxel	Increment	% absolute increment
Treatment	£56,997	£483	£56,514	102%
Administration	£2,979	£9,842	-£6,863	-12%
Adverse events	£95	£48	£47	0%
Supportive care (PFS)	£3,706	£3,621	£85	0%

Supportive care (PD)	£8,091	£2,612	£5,479	10%
Total	£71,868	£16,606	£55,262	100%

Table 89: Summary of predicted resource use by category of cost – BSC (2L+)

Cost Item	Cost atezolizumab	Cost BSC	Increment	% absolute increment
Treatment	£56,997	0	£56,997	85%
Administration	£2,979	0	£2,979	5%
Adverse events	£95	0	£95	0
Supportive care (PFS)	£3,706	£2,896	£810	1%
Supportive care (PD)	£8,091	£1,940	£6,151	9%
Total	£71868	£4,836	£67,032	100%

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted using 1000 samples, to assess uncertainty surrounding variables. The distributions and sources to estimate parameters can be found in section 5.6. Analyses are based on the proposed list price of atezolizumab, and the eMIT drug prices for comparators.

Results of the PSA should be interpreted with caution, as they are unlikely to be reliable. The high level of uncertainty in the fractional polynomial model and prediction model provides a skewed output for OS. This subsequently impacts other model outputs. For example, at extreme draws in the probabilistic analysis , >20% of the paclitaxel cohort and >7% of the docetaxel cohort are alive at 20 years.

Results of the PSA compared to deterministic results for 1L and 2L are presented in Table 90 and Table 91 below.

Scatterplots in Figure 42 and Figure 43 show iterations for 1L and 2L respectively. Cost effectiveness acceptability curves for 1L and 2L are shown in Figure 44 and Figure 45

Table 90: PSA results compared to base-case (1L)

	Costs		QALYs		ICER	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Atezolizumab	£77,211	£82,893	2.69	2.775		
Gemcitabine + carboplatin	£18,106	£20,605	1.35	1.467	£44,158	£47,593

Table 91: PSA results compared to base-case (2L)

	Costs		QALYs		ICER	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Atezolizumab	£77,211	£74,165	1.23	1.26		
Docetaxel	£9,439	£10,621	0.76	0.82	£131,579	£143,144
Paclitaxel	£16,606	£18,075	0.71	0.83	£104,850	£129,333
BSC	£4,836	£5,637	0.55	0.58	£98,208	£101,247

Figure 42: Scatterplot of PSA results for cost effectiveness plane (1L)

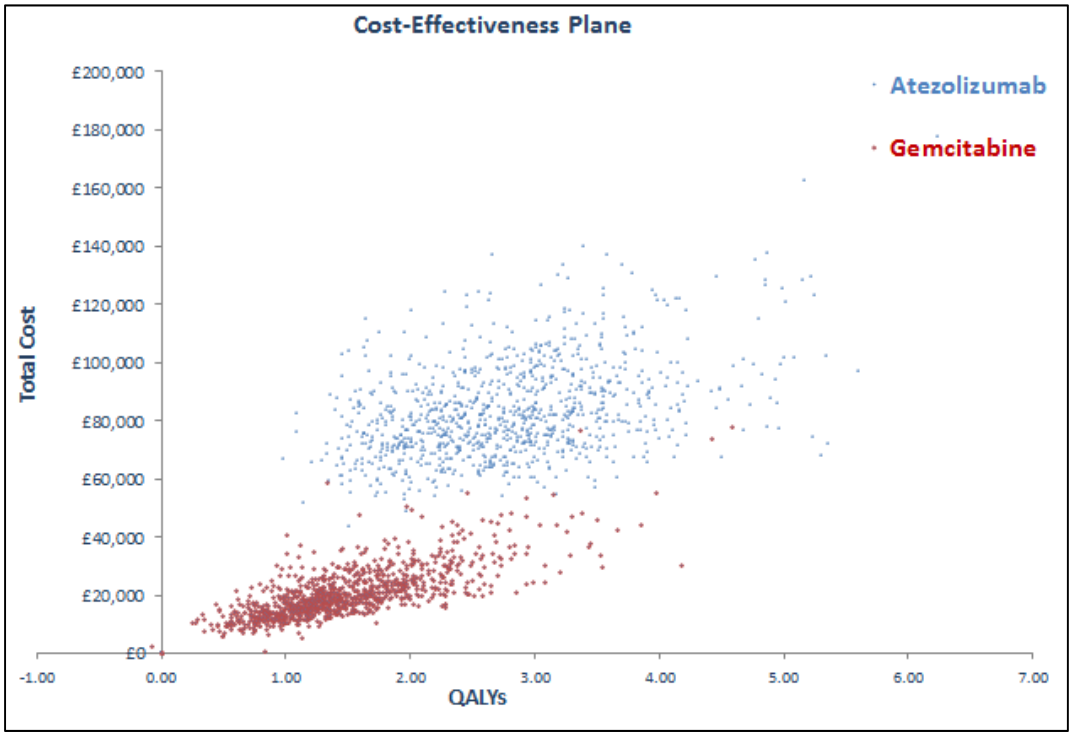


Figure 43: Scatterplot of PSA results for cost effectiveness plane (2L)

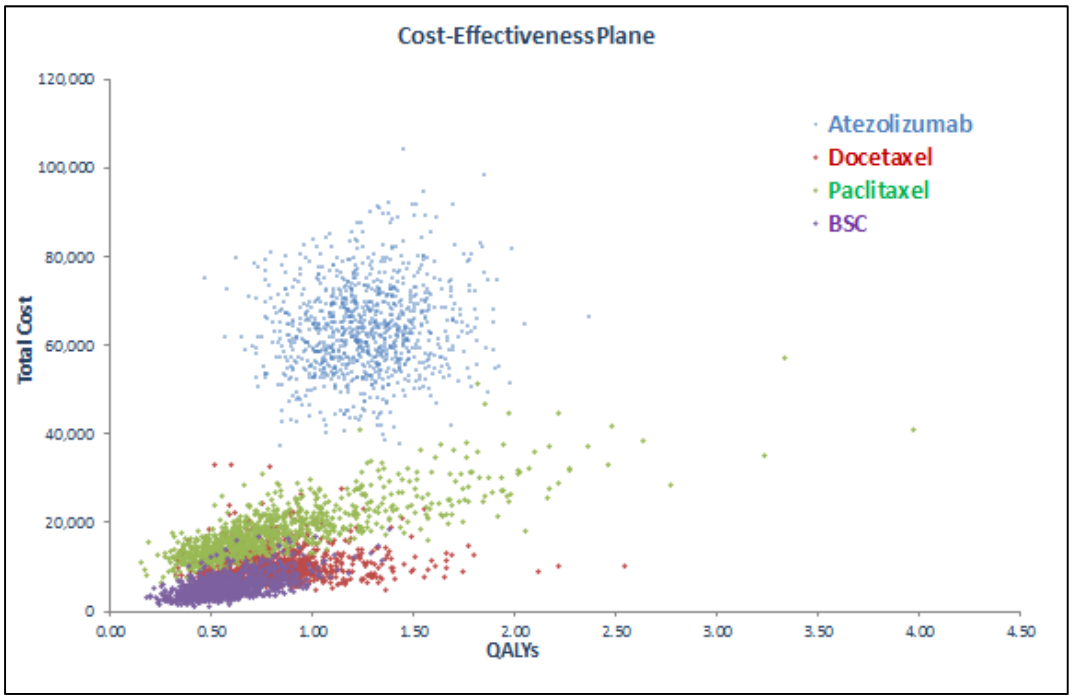


Figure 44: Cost-effectiveness acceptability curve (1L)

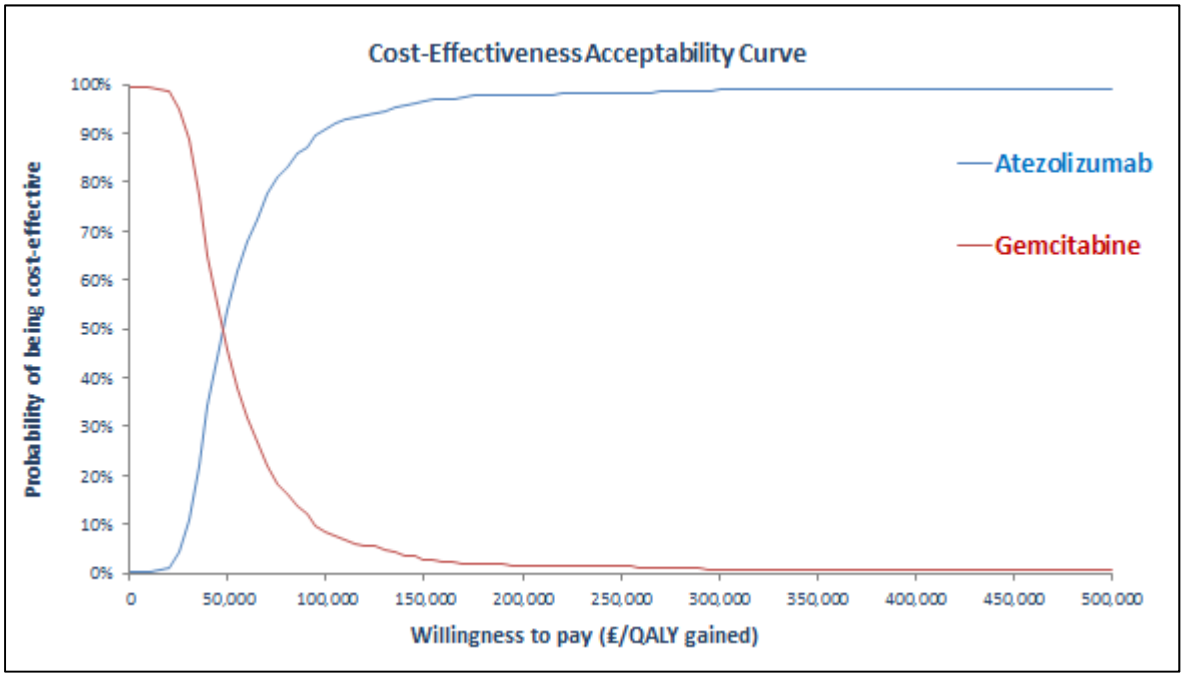
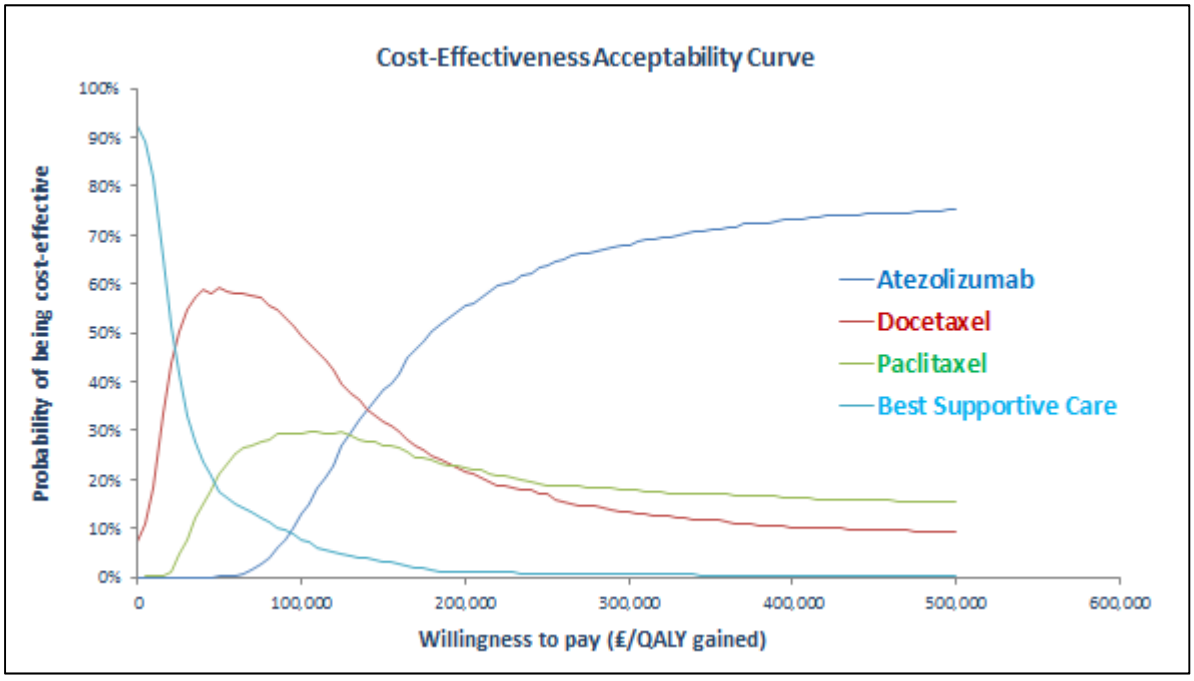


Figure 45: Cost-effectiveness acceptability curve (2L)



5.8.2 Deterministic sensitivity analysis

The choice of parameters to include in univariate analysis was considered *a-priori*, and further informed by the results in section 5.7, with focus on the parameters providing greatest impact on the percentage increment in costs or QALYs, thus having the greatest impact on the resulting ICER. The parameter values used in the analyses, and rationale for choice can be found in Table 92 below. Results of the analyses are displayed in Figure 46 for 1L, and Figure 47, Figure 48, and Figure 49 for 2L.

These results are further explored and discussed in 5.8.3, scenario analysis below.

Table 92: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value	Rationale for value range
Monthly cost of atezolizumab	£5500	+ 50%	- 50%	
Atezolizumab on treatment utility	0.750	0.653	1	Lower value: Prior NICE mUC appraisals Higher value: Maximum utility value
Comparator on treatment utility	0.750	0.653	1	Lower value: Prior NICE mUC appraisals Higher value: Maximum utility value
Off treatment utility	0.71	0.5	1	Lower value: 50% of possible utility value Higher value: 100% of possible utility value
Atezo off treatment supportive care costs	£146.79	+50%	-50%	
Comparator off treatment supportive care costs	£146.79	+50%	-50%	

Figure 46: Comparison to gemcitabine + carboplatin univariate sensitivity analysis (dark blue = lower value; light blue = higher value) (1L)

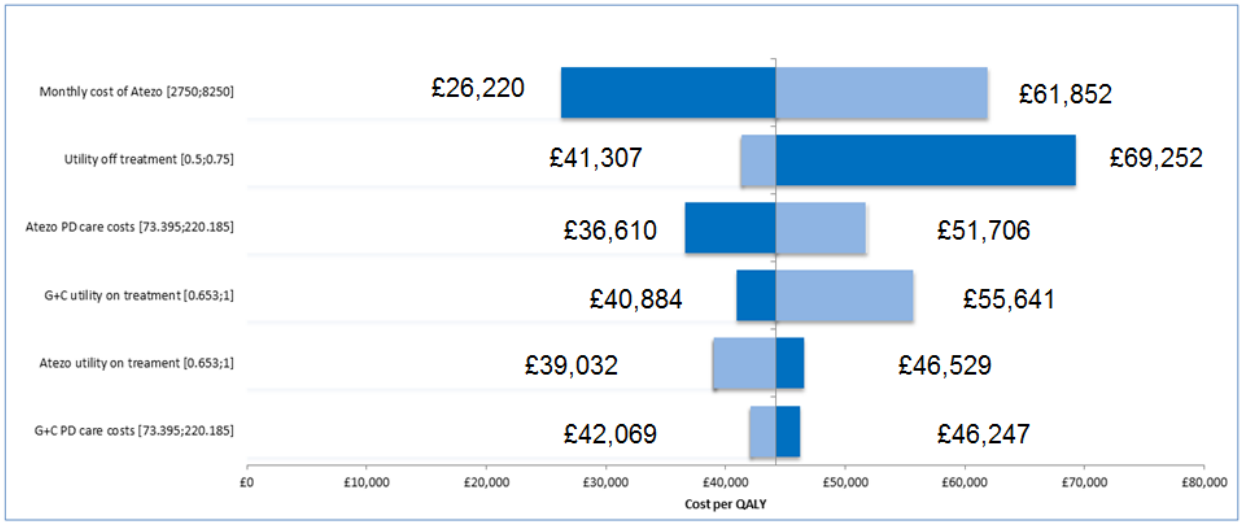


Figure 47: Comparison to docetaxel univariate sensitivity analysis (dark blue = lower value; light blue = higher value) (2L+)

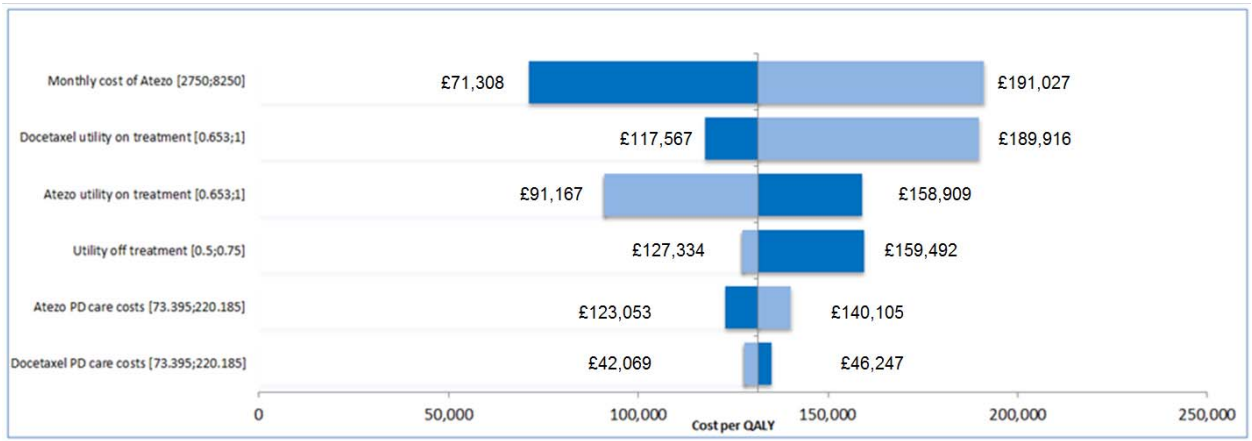


Figure 48: Comparison to paclitaxel univariate sensitivity analysis (dark blue = lower value; light blue = higher value) (2L+)

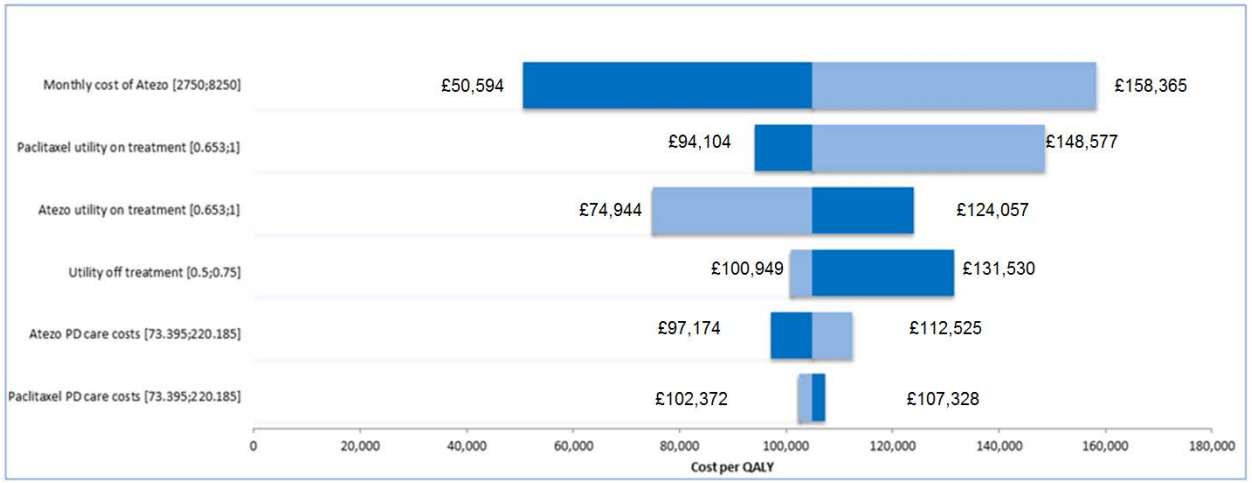
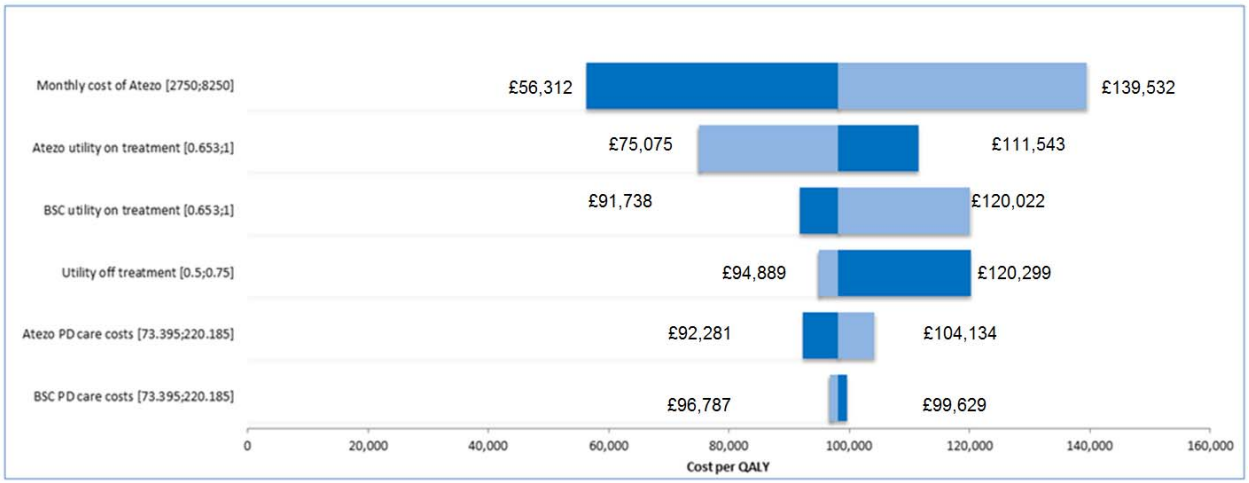


Figure 49: Comparison to BSC univariate sensitivity analysis (dark blue = lower value; light blue = higher value) (2L+)



5.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around structural assumptions of the model. Results are shown in Table 93 (1L) and Table 94 (2L) for the following scenarios exploring parameter changes:

- Drug costs for comparators
- Alternative OS cure-rates
- Alternative PFS parametric distributions
- PFS as a proxy for TOT for atezolizumab
- On treatment utilities
- Off treatment utilities
- Time horizons of 10 years
- Cost discount rate (1.5% rather than 3.5%)
- Effects discount rate (1.5% rather than 3.5%)

The scenarios indicate there are conditions at which the ICER is below the acceptable threshold.

Table 93: Resulting ICER vs gemcitabine + carboplatin from scenario analyses (1L)

Scenario	Parameter	Value	ICER vs. gemcitabine + carboplatin
Base case	Comparator price	eMIT drug prices	£44,158
		List prices	£41,309
Base case	Cure rate	0%	
		1%	£44,026
		2%	£43,891
		3%	£43,754
Base case	Distribution PFS	Gamma	£44,158
		Log-normal	£44,075
		Log-logistic	£44,139
Base case	Comparator relative effect	Equal to atezolizumab	

	PFS		
Base case	Treatment duration assumption	Actual treatment duration	£44,158
		Until progression	£64,365
Base case	Time horizon	20	£44,158
		10	£58,992
		15	£48,563
Base case	On treatment utility (all products)	0.750	£44,158
	Atezo on treatment utility	0.800	£43,028
	G+C on treatment utility	0.653	£40,884
Base case	Off treatment utility	0.710	£44,158
		0.500	£69,252
		0.750	£41,307
Base case	Discount rate – effects and costs	3.5% for both	£44,158
	Discount rate - costs	1.5% (3.5% for effects)	£46,807
	Discount rate – effects	1.5% (3.5% for costs)	£37,859
	Discount rate – effects and costs	1.5% for both	£40,130

Table 94: Resulting ICERs vs docetaxel, paclitaxel or BSC from scenario analyses (2L)

Scenario	Parameter	Value	ICER vs. docetaxel	ICER vs. paclitaxel	ICER vs. BSC
Base case	Comparator price	eMIT drug prices	£131,579	£104,850	£98,208
		List prices	£108,819	£72,477	£98,208
Base case	Cure rate	0%	£131,579	£104,850	£98,208
		1%	£126,277	£101,507	£95,403
		2%	£121,364	£98,369	£92,708
		3%	£116,805	£95,430	£90,115
Base case	Distribution PFS	Gamma	£131,579	£104,850	£98,208
		Log-normal	£131,509	£108,757	£97,819
		Log-logistic	£131,427	£109,624	£97,581
Base case	Comparator relative effect	Equal to atezolizumab	£131,579	£104,850	£98,208

	PFS				
		FP	£132,250	£99,996	£98,273
Base case	Treatment duration assumption	Actual treatment duration	£131,579	£104,850	£98,208
		Until progression	£102,982	£78,727	£78,028
Base case	Time horizon	20	£131,579	£104,850	£98,208
		10	£158,410	£119,719	£109,318
		15	£139,012	£109,279	£101,541
Base case	On treatment utility (all products)	0.750	£131,579	£104,850	£98,208
	Atezo on treatment utility	0.800	£120,864	£97,100	£92,507
	Comparator on treatment utility	0.653	£117,567	£94,104	£91,738
Base case	Off treatment utility	0.710	£131,579	£104,850	£98,208
		0.500	£159,492	£131,530	£120,299
		0.750	£127,334	£100,949	£94,889
Base case	Discount rate – effects and costs	3.5% for both	£131,579	£104,850	£98,208
	Discount rate - costs	1.5% (3.5% for effects)	£136,976	£108,999	£102,067
	Discount rate – effects	1.5% (3.5% for costs)	£116,599	£95,227	£89,962
	Discount rate – effects and costs	1.5% for both	£121,382	£98,995	£93,497

5.8.4 Summary of sensitivity analyses results

As discussed in sections 4 and 5 above, the available evidence base for both atezolizumab and comparators are limited, thus creating significant uncertainty when assessing the resulting ICERs. This uncertainty is a function of the potential regulatory approval of atezolizumab based in phII trial results, and the unmet need in

patients with mUC – both of which are based on the lack of effective, licensed, and evidence based treatments for this condition. Assumptions and extrapolations were required to generate comparative evidence, for a life-long time-horizon.

Sensitivity analyses allow determination of the main drivers of the economic analysis, and exploration of alternative parameter inputs. However, the fundamental limitations of the data are unable to be resolved through sensitivity analyses, and will only be rectified with the availability of controlled phase III data (as discussed in section 1 and Table 1).

The base-case ICER in 1L is below the acceptable threshold for a treatment considered under the end-of-life criteria, and as can be seen in Table 93, remains below the threshold in the majority of scenarios explored. The main drivers of the economic analysis for this population are the price of atezolizumab and the utility of patients in the progressed disease state.

The base-case ICER based on the proposed list price of atezolizumab in 2L mUC is above the acceptable threshold vs. all comparators. As can be seen in the deterministic analysis, and scenario analysis, the ICER is most sensitive to the price of atezolizumab.

Results of the PSA must be interpreted with caution. In order to incorporate comparative evidence for the appraisal comparators, various assumptions were made. These include capping the steadily decreasing HRs for atezolizumab vs. comparators for OS. As a result of these corrections, distributions are skewed, thus presenting challenges for conducting the PSA.

5.9 Subgroup analysis

No subgroup analyses were performed. Clinical benefit was observed in all subgroups of patients in the IMvigor 210 study. As such no analyses were conducted on restricted populations as compared to the anticipated indication.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

As discussed in section 1, clinical experts were consulted to validate the appropriate methodological and clinical assumptions had been made, and that model outputs were clinically plausible.

Key aspects discussed included:

- The overall model structure and health states within the model
- Prediction model
- NMA methodology
- OS and PFS extrapolation, and anticipated long-term outcomes
- Utility value assumptions
- Resource use included in the model

Experts agreed that clinical and economic evidence in mUC is limited, as such assumptions and extrapolation of data were unavoidable. Expert clinical advice suggested significantly more robust data will be available for atezolizumab with the IMvigor 210 study, which will resolve some assumptions required in the model.

Internal quality control and validation of the 1L and 2L models was conducted by an external consultancy - ICON. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of 'pressure tests' were conducted, using extreme values. The results of the model using these values were then compared to expected outputs to assess functionally accuracy.

5.11 Interpretation and conclusions of economic evidence

Although multiple treatment options are available for earlier stages of bladder cancer, advanced metastatic disease remains an area of extremely high unmet need with little innovative drug development in the last two decades. Consequently there are not only limited therapeutic options, but also limited economic research. Few economic, patient utility, and healthcare resource analyses have been conducted in mUC. Due to this limited economic literature, a de novo analysis was required to appraise the cost-effectiveness of atezolizumab.

The IMvigor 210 study provides strong evidence on the efficacy of atezolizumab in mUC. Based on the unmet need in this area, and the recognized potential for immunotherapies in oncology, regulatory filling was accepted on the basis of this phII trial. Such an evidence base does, however, present challenges for HTA appraisal. This is compounded when considered in the context of a poor evidence base for existing approaches to the management of patients with mUC. However, the methods employed in this economic analysis allowed for the building of a connected network from single arm studies, in order to conduct an indirect treatment comparison.

Whilst these data limitations required various assumptions and extrapolations, the long-term atezolizumab outcomes predicted by the model were considered plausible by clinical experts. The major data uncertainty is the clinical performance of comparators, as compared to atezolizumab. It is likely the model overestimates outcomes with comparators, as it was necessary to assume PFS results as equal to atezolizumab, and to cap the OS HRs after certain time-points.

Much of this uncertainty will be resolved with the availability of phase III clinical trials for atezolizumab, in 2L (IMvigor 211, results available in 2017) and 1L (IMvigor 130, results available in 2020). These two studies will provide comparative data, which will provide significantly greater certainty around the ICERs

Strengths:

The IMVigor 210 and 211 studies recruited patients from the UK. The economic analysis accurately captures aspects relevant to clinical practice in England and Wales, and the results are generalisable to patients with mUC.

The model structure captures clinically relevant health states and outcomes for mUC patients, and analyses use methods which follow recent appraisals for immunotherapies (national institute for Clinical Excellence, 2015). Clinical experts validated the atezolizumab long-term survival outcomes seen in the model are anticipated to be seen in clinical practice. The model accurately matched atezolizumab available observed data for OS.

Weaknesses:

The main weaknesses of the analyses are the clinical efficacy data feeding into the economic models. For atezolizumab, the clinical efficacy will be further assessed in large, confirmatory phase III clinical trials. For comparators there is a lack of robust clinical evidence. All comparators, except BSC, will be assessed in the phase III studies of atezolizumab, thus providing significantly more robust data for economic analysis.

The lack of utility values for mUC, with either atezolizumab or comparators is also a weakness of the analysis. EQ5D results will be available from the phase III clinical studies of atezolizumab.

6 Assessment of factors relevant to the NHS and other parties

6.1.1 Patients eligible for treatment in England

Based on the potential for atezolizumab in the management of mUC to be considered as an appropriate treatment for inclusion on the CDF, this budget impact analysis is focussed on assessment of a patient population in England.

Patients eligible for treatment with atezolizumab are those with locally advanced or mUC after prior chemotherapy or who are considered cisplatin ineligible. The incidence of metastic bladder cancer in the UK is reported from Cancer Research UK, (CRUK, 2017a) and was 10, 063 in 2014. However this number reports only new patients, and does not account for existing patients.

Estimation of patient numbers therefore relies on internal Roche assumptions derived from market research, as highlighted below.

Table 95: Estimation of eligible patient numbers: 2017

	Proportion	Patient Numbers	Source
Total metastatic or advanced urothelial carcinoma prevalence		7076	Roche assumption
Proportion of UK population in England	84%	5944	ONS population estimates
1L	[redacted]	[redacted]	Roche assumption
Eligible 1L population (cisplatin-ineligible patients only)	50.0%	[redacted]	De Santis et al.
2L+ population	66.7%	[redacted]	
Total eligible for treatment		[redacted]	
Treatment rate	[redacted]	[redacted]	Roche assumption
Market share	[redacted]	864	Roche assumption

6.1.2 Market share assumptions

Although there are currently limited treatment options available for mUC patients, it is not estimated all eligible patients will receive atezolizumab. Consideration is also given to new immunotherapy agents, anticipated to be licensed for use in mUC. Table 95 above includes the estimated proportion of patient share for atezolizumab in mUC.

6.1.3 Resource impact

Introduction of atezolizumab in the mUC treatment pathway is not anticipated to significantly impact NHS resource use or capacity. Compared to current standard of care in England, no additional tests or monitoring are required for treatment with atezolizumab. Atezolizumab has shown benefit in patients expressing all levels of PDL1 biomarker. As such, no additional diagnostic tests are required. Should additional diagnostic tests have been required, this would introduce an additional step in the treatment pathway, thus having cost and resource implications.

Current active treatment options in mUC are administered via IV infusion, at either weekly, or three weekly intervals. All treatments are weight based doses, thus requiring per-patient, reconstitution. Administration of atezolizumab is via IV infusion at a fixed dose every 3 weeks. This is an equal to, or lower impact on hospital infusion services, with flat dosing limiting pharmacy impact, and resulting in no vial wastage.

6.1.4 Estimated budget impact

Unit costs for budget impact were derived from the total year 1 costs generated in the economic analysis. This accounts for drug acquisition costs, administration costs, supportive care costs and AE management. Incremental budget impact for the first 5 years is displayed below in Table 96 for 1L and Table 97 for 2L+. Year 1, 2017, assumes a full calendar year of drug availability. As paclitaxel is the most relevant comparator in 2L+, the budget impact as compared to paclitaxel is included.

Table 96: Budget impact of atezolizumab (1L)

	Value	2017 (assumes full year)	2018	2019	2020	2021
Metastatic / advanced UC		7076	7078	7086	7100	7110
England proportion	84%	5944	5946	5952	5964	5972
1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin-ineligible	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of G+C	£8,989	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 97: Budget impact of atezolizumab (2L)

	Value	2017 (assumes full year)	2018	2019	2020	2021
Metastatic / advanced UC		7076	7078	7086	7100	7110
England proportion	90%	5944	5946	5952	5964	5972
1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of paclitaxel	£9,464	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The budget impact analyses utilise year one costs only, and apply this costs for each subsequent year. This does not account for the reducing proportional cost of treating patients after year one, and assumes 100% of patients are new each year in the analysis.

7 References

ABIDA W 2015. First line treatment and prognostic factors of metastatic bladder cancer for platinum eligible patients. *Hematology Oncology Clin North Am,* 29**,** 3319-28.

ADAMO, V., MAGNO, C., SPITALERI, G., GARIPOLI, C., MAISANO, C., ALAFACI, E., ADAMO, B., ROSSELLO, R., SCANDURRA, G. & SCIMONE, A. 2005. Phase II study of gemcitabine and cisplatin in patients with advanced or metastatic bladder cancer: long-term follow-up of a 3-week regimen. *Oncology,* 69**,** 391-8.

ADES, F. Y., NISE. 2015. WHO, RECIST, and immune-related response criteria: is it time to revisit pembrolizumab results? *Ecancermedicalscience,* 9.

AGARWAL, N., BELLMUNT, J., MAUGHAN, B. L., BOUCHER, K. M., CHOUEIRI, T. K., QU, A. Q., VOGELZANG, N. J., FOUGERAY, R., NIEGISCH, G., ALBERS, P., WONG, Y. N., KO, Y. J., SRIDHAR, S. S., TANTRAVAHI, S. K., GALSKY, M. D., PETRYLAK, D. P., VAISHAMPAYAN, U. N., MEHTA, A. N., BEER, T. M., STERNBERG, C. N., ROSENBERG, J. E. & SONPAVDE, G. 2014. Six-month progression-free survival as the primary endpoint to evaluate the activity of new agents as second-line therapy for advanced urothelial carcinoma. *Clin Genitourin Cancer,* 12**,** 130-7.

AKAZA, H., NAITO, S., USAMI, M., MIKI, T., MIYANAGA, N. & TANIAI, H. 2007. Efficacy and safety of gemcitabine monotherapy in patients with transitional cell carcinoma after Cisplatin-containing therapy: a Japanese experience. *Jpn J Clin Oncol,* 37**,** 201-6.

ALBERS, P. Randomized phase III trial of 2nd line gemcitabine/paclitaxel chemotherapy in patients with advanced bladder cancer: Temporary versus maintenance treatment (German Association of Urologic Oncology (AUO) Trial AB 20/99). ASCO, 2008.

ALBERS, P., PARK, S. I., NIEGISCH, G., FECHNER, G., STEINER, U., LEHMANN, J., HEIMBACH, D., HEIDENREICH, A., FIMMERS, R. & SIENER, R. 2011. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol,* 22**,** 288-94.

ALBERS, P., SIENER, R., HARTLEIN, M., FALLAHI, M., HAEUTLE, D., PERABO, F. G., STEINER, G., BLATTER, J. & MULLER, S. C. 2002a. Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. *Onkologie,* 25**,** 47-52.

ALBERS, P., SIENER, R., MICHAEL, R., FECHNER, G., KOBALZ, L., HEIDENREICH, A., STEFAN, M., BANNOWSKY, A., EHLERT, C. & GOLINSKI, C. 2002b. Randomized phase II trial of gemcitabine and paclitaxel with or without maintenance treatment in patients with cisplatin refractory transitional cell carcinoma [abstract]. *Proceedings of the American Society of Clinical Oncology* [Online], 21 (Pt 1). Available: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/590/CN-00694590/frame.html.

AMERICAN CANCER SOCIETY. 2015. *Bladder Cancer* [Online]. Available: http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics [Accessed 13th Jan 2017].

AXEL HOOS, A. M. M. E., SYLVIA JANETZKI, F. STEPHEN HODI, RAMY IBRAHIM, APARNA ANDERSON, RACHEL HUMPHREY, & BRENT BLUMENSTEIN, L. O., JEDD WOLCHOK 2010. Improved Endpoints for Cancer Immunotherapy Trials. *JNCI J Natl Cancer Inst*.

BAJORIN, D. F., DODD, P. M., MAZUMDAR, M., FAZZARI, M., MCCAFFREY, J. A., SCHER, H. I., HERR, H., HIGGINS, G. & BOYLE, M. G. 1999. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol,* 17**,** 3173-81.

BALAR, A. V., GALSKY, M. D., LORIOT, Y., DAWSON, N. A., NECCHI, A., SRINIVAS, S., JOSEPH, R. W., VAISHAMPAYAN, U. N., SRIDHAR, S. S., QUINN, D. I., DRAKAKI, A., DURAN, I., ROSENBERG, J. E., POWLES, T., HOFFMAN-CENSITS, J. H., CUI, N., MARIATHASAN, S., THASTROM, A. C., ABIDOYE, O. O. & BAJORIN, D. F. 2016a. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): Primary analysis of IMvigor210 cohort 1. *J Clin Oncol, ASCO Meeting Abstracts,* 34**,** LBA4500.

BALAR, A. V., GALSKY, M. D., ROSENBERG, J. E., POWLES, T., PETRYLAK, D. P., BELLMUNT, J., LORIOT, Y., NECCHI, A., HOFFMAN-CENSITS, J., PEREZ-GRACIA, J. L., DAWSON, N. A., VAN DER HEIJDEN, M. S., DREICER, R., SRINIVAS, S., RETZ, M. M., JOSEPH, R. W., DRAKAKI, A., VAISHAMPAYAN, U. N., SRIDHAR, S. S., QUINN, D. I., DURÁN, I., SHAFFER, D. R., EIGL, B. J., GRIVAS, P. D., YU, E. Y., LI, S., KADEL, E. E., III, BOYD, Z., BOURGON, R., HEGDE, P. S., MARIATHASAN, S., THÅSTRÖM, A., ABIDOYE, O. O., FINE, G. D. & BAJORIN, D. F. 2016b. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *The Lancet*.

BAMIAS, A., LAINAKIS, G., KASTRITIS, E., ANTONIOU, N., ALIVIZATOS, G., KOUREAS, A., CHRISOFOS, M., SKOLARIKOS, A., KARAYIOTIS, E. & DIMOPOULOS, M. A. 2007. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. *Oncology,* 73**,** 290-7.

BELLMUNT, J. Keynote-045: open-label, phase III study of pembrolizumab versus investigator's choice of paclitaxel, docetaxel, or vinflunine for previously treated advanced urothelial cancer. Society for Immunotherapy of Cancer, 2016.

BELLMUNT, J., BALAR, A. V., GALSKY, M. D., LORIOT, Y., THEODORE, C., GRANDE, E., CASTELLANO, D., RETZ, M., NIEGISCH, G., BRACARDA, S., NECCHI, A., VAISHAMPAYAN, U., SRIDHAR, S. S., EIGL, B. J., HUSSAIN, S. A., VAN DER HEIJEN, M. S., BOURGON, R., DING, B., MARIATHASAN, S., THÅSTRÖM, A. & ROSENBERG, J. 2016. IMvigor210: Updated Analyses of First-Line Atezolizumab in Cisplatin-Ineligible Locally Advanced/Metastatic Urothelial Carcinoma. The European Society for Medical Oncology, October 7-11, 2016 2016 Copenhagen, Denmark.

BELLMUNT, J., CHOUEIRI, T. K., FOUGERAY, R., SCHUTZ, F. A., SALHI, Y., WINQUIST, E., CULINE, S., VON DER MAASE, H., VAUGHN, D. J. & ROSENBERG, J. E. 2010. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol,* 28**,** 1850-5.

BELLMUNT, J., FOUGERAY, R., ROSENBERG, J. E., VON DER MAASE, H., SCHUTZ, F. A., SALHI, Y., CULINE, S. & CHOUEIRI, T. K. 2013. Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy†. *Annals of Oncology,* 24**,** 1466-1472.

BELLMUNT, J., ORSOLA, A., LEOW, J. J., WIEGEL, T., DE SANTIS, M. & HORWICH, A. 2014. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology,* 25**,** iii40-iii48.

BELLMUNT, J., RIBAS, A., ERES, N., ALBANELL, J., ALMANZA, C., BERMEJO, B., SOLE, L. A. & BASELGA, J. 1997. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer,* 80**,** 1966-72.

BELLMUNT, J., THEODORE, C., DEMKOV, T., KOMYAKOV, B., SENGELOV, L., DAUGAARD, G., CATY, A., CARLES, J., JAGIELLO-GRUSZFELD, A., KARYAKIN, O., DELGADO, F. M., HURTELOUP, P., WINQUIST, E., MORSLI, N., SALHI, Y., CULINE, S. & VON DER MAASE, H. 2009. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol,* 27**,** 4454-61.

BELLMUNT, J., VALDERRAMA, B. P., FONT, A., VIRIZUELA, J. A., CLIMENT, M. A., POLO, S. H., MELLADO, B., LAÍNEZ, N., DEL ALBA, A. G., ARRANZ, J. A., GUZMAN, J. C. V., DEL MAR LLORENTE, M., CASTELLANO, D. E., GALLARDO, E., DEL MURO, X. G., ANIDO, U., DOMENECH, M., PUENTE, J., PEREZ GRACIA, J. L. & GARCÍA-DONAS, J. 2015. Maintenance vinflunine post cisplatin chemotherapy (CT) in patients with advanced urothelial carcinoma (UC): Preliminary analysis of a randomized placebo controlled phase II trial (MAJA trial)-SOGUG 2011-02. *Journal of Clinical Oncology,* 33.

BELLMUNT, J., VON DER MAASE, H., MEAD, G. M., SKONECZNA, I., DE SANTIS, M., DAUGAARD, G., BOEHLE, A., CHEVREAU, C., PAZ-ARES, L., LAUFMAN, L. R., WINQUIST, E., RAGHAVAN, D., MARREAUD, S., COLLETTE, S., SYLVESTER, R. & DE WIT, R. 2012. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 30**,** 1107-13.

BOTTEMAN, M. F., PASHOS, C. L., REDAELLI, A., LASKIN, B. & HAUSER, R. 2003. The health economics of bladder cancer: a comprehensive review of the published literature. *PharmacoEconomics,* 21**,** 1315–1330.

BRISTOL MYERS SQUIBB. 2016. *YERVOY 5mgml concentrate for solution for infusion* [Online]. Available: https://www.medicines.org.uk/emc/medicine/24779 [Accessed 14th Jan 2017].

BRISTOL MYERS SQUIBB. 2017. *OPDIVO 10mg/ml concentrate for solution for infusion* [Online]. Available: https://www.medicines.org.uk/emc/medicine/30476 [Accessed 14th Jan 2017].

BURGER, M., CATTO, J. W., DALBAGNI, G., GROSSMAN, H. B., HERR, H., KARAKIEWICZ, P., KASSOUF, W., KIEMENEY, L. A., LA VECCHIA, C.,

SHARIAT, S. & LOTAN, Y. 2013. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol,* 63**,** 234-41.
BUTTE, M. J., KEIR, M. E., PHAMDUY, T. B., FREEMAN, G. J. & SHARPE, A. H. 2007. PD-L1 interacts specifically with B7-1 to inhibit T cell proliferation. *Immunity,* 27**,** 111-122.
CHEN, D. S., IRVING, B. A. & HODI, F. S. 2012. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res,* 18**,** 6580-7.
CHEN, D. S. & MELLMAN, I. 2013. Oncology meets immunology: the cancer-immunity cycle. *Immunity,* 39**,** 1-10.
CHOUEIRI, T. K., ROSS, R. W., JACOBUS, S., VAISHAMPAYAN, U., YU, E. Y., QUINN, D. I., HAHN, N. M., HUTSON, T. E., SONPAVDE, G., MORRISSEY, S. C., BUCKLE, G. C., KIM, W. Y., PETRYLAK, D. P., RYAN, C. W., EISENBERGER, M. A., MORTAZAVI, A., BUBLEY, G. J., TAPLIN, M. E., ROSENBERG, J. E. & KANTOFF, P. W. 2012. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. *J Clin Oncol,* 30**,** 507-12.
CLINICALTRIALS.GOV. 2016a. *The Effect of Atezolizumab in Combination With Gemcitabine/Carboplatin and Gemcitabine/Carboplatin Alone in Participants With Untreated Locally Advanced or Metastatic Urothelial Carcinoma Who Are Ineligible for Cisplatin-based Therapy [IMvigor130]* [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT02302807 [Accessed 17th Jan 2017].
CLINICALTRIALS.GOV. 2016b. *A Study of Atezolizumab Compared With Chemotherapy in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer [IMvigor211]* [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT02302807 [Accessed 17th Jan 2017].
COCHRANE. 2011. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [Online]. Available: http://training.cochrane.org/handbook [Accessed 17th Jan 2017].
CRUK. 2017a. *CRUK - Bladder cancer incidence statistics* [Online]. Available: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence#heading-Zero [Accessed 9th Jan 2017].
CRUK. 2017b. *CRUK - Bladder cancer mortality statistics* [Online]. Available: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/mortality [Accessed 9th Jan 2017].
CRUK. 2017c. *CRUK - Bladder cancer risks and causes* [Online]. Available: http://www.cancerresearchuk.org/about-cancer/type/bladder-cancer/about/bladder-cancer-risks-and-causes [Accessed 9th Jan 2017].
CRUK. 2017d. *CRUK - Types of bladder cancer* [Online]. Available: http://www.cancerresearchuk.org/about-cancer/type/bladder-cancer/about/types-of-bladder-cancer [Accessed 9th Jan 2017].
CULINE, S. Updated survival results of the phase III trial comparing vinflunine (V) to best supportive care (BSC) in advanced transitional cell carcinoma of the urothelium (TCCU) after failure of a prior platinum-containing regimen. European Association of Urology (EAU), 2010.
CULINE, S., FLÉCHON, A., GUILLOT, A., LE MOULEC, S., POUESSEL, D., ROLLAND, F., RAVAUD, A., HOUÉDÉ, N., MIGNOT, L., JOLY, F., OUDARD, S. & GOURGOU, S. 2011. Gemcitabine or gemcitabine plus oxaliplatin in the

first-line treatment of patients with advanced transitional cell carcinoma of the urothelium unfit for cisplatin-based chemotherapy: a randomized phase 2 study of the French Genitourinary Tumor Group (GETUG V01). *European urology,* 60**,** 1251-7.
CULINE, S., THEODORE, C., DE SANTIS, M., BUI, B., DEMKOW, T., LORENZ, J., ROLLAND, F., DELGADO, F. M., LONGEREY, B. & JAMES, N. 2006. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer,* 94**,** 1395-401.
CURTIS, L. 2016. PSSRU Unit Costs of Health & Social Care.
DANA-FARBER CANCER INSTITUTE. 2016. *Randomized Study of Docetaxel +/- Vandetanib in Metastatic TCC* [Online]. Available: https://ClinicalTrials.gov/show/NCT00880334 [Accessed 17th Jan 2017].
DE SANTIS, M. Randomized phase II/III trial comparing gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastine (M-CAVI) in patients (pts) with advanced urothelial cancer (UC) unfit for cisplatin-based chemotherapy (CHT): Phase III results of EORTC study 30986. ASCO, 2010.
DE SANTIS, M., BELLMUNT, J., MEAD, G., KERST, J. M., LEAHY, M., MAROTO, P., GIL, T., MARREAUD, S., DAUGAARD, G., SKONECZNA, I., COLLETTE, S., LORENT, J., DE WIT, R. & SYLVESTER, R. 2012. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol,* 30**,** 191-9.
DE SANTIS, M., BELLMUNT, J., MEAD, G., KERST, J. M., LEAHY, M., MAROTO, P., SKONECZNA, I., MARREAUD, S., DE WIT, R. & SYLVESTER, R. 2009. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. *J Clin Oncol,* 27**,** 5634-9.
DE VOS, F. & DE WIT, R. 2010. Choosing chemotherapy in patients with advanced urothelial cell cancer who are unfit to receive cisplatin-based chemotherapy. *Therapeutic Advances in Medical Oncology,* 2**,** 381-388.
DE WIT, M., DE GEETER, P., GALLI, L., HEGELE, A., SCHRADER, M., SCHENCK, M., VOM DORP, F., BOLTEN, M., FAHLENKAMP, D., HAMPEL, C., KRAUSE, S., RIGGI, M., FOUGERAY, R., DE ALMEIDA, C., EDLICH, B. & PICHLER, A. 2015. Vinflunine maintenance treatment following first-line therapy of advanced urothelial carcinoma-results from the JASiMA trial. *European Journal of Cancer,* 51**,** S527.
DEPARTMENT OF HEALTH. 2016a. *Drugs and pharmaceutical electronic market information (eMit)* [Online]. Available: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [Accessed 17th Jan 2017].
DEPARTMENT OF HEALTH. 2016b. *NHS reference costs* [Online]. Available: https://www.gov.uk/government/collections/nhs-reference-costs [Accessed 17th Jan 2017].
DOLAN, P. 1997. Modeling valuations for EuroQol health states. *Med Care,* 35**,** 1095-108.
ELECTRONIC MEDICINES COMPENDIUM (EMC). 2016a. *Docetaxel 20 mg/ml concentrate for solution for infusion* [Online]. Available: http://www.medicines.org.uk/emc/medicine/32013 [Accessed 17th Jan 2017].

ELECTRONIC MEDICINES COMPENDIUM (EMC). 2016b. *Paclitaxel 6mg/ml Concentrate For Solution For Infusion* [Online]. Available: http://www.medicines.org.uk/emc/medicine/24064#DOCREVISION [Accessed 17th Jan 2017].

EXCELLENCE., N. I. F. H. A. C. 2016. Atezolizumab for treating locally advanced or metastatic urothelial bladder cancer in people whose disease has progressed after platinum-based chemotherapy or for whom cisplatin-based chemotherapy is unsuitable. Draft scope (Pre-referral). .

F. HOFFMANN-LA ROCHE LTD 2014. Protocol GO29293: A phase II, multicenter, single-arm study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer.

F. HOFFMANN-LA ROCHE LTD 2015a. Clinical Study Protocol PCD4989g - A phase I, open label, dose escalation study of the safety and pharmacokinetics of atezolizumab (MPDL3280a) administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies.

F. HOFFMANN-LA ROCHE LTD 2015b. Clinical Study Report GO29293 – A phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer (Data cut-off: 14-Sep-2015).

F. HOFFMANN-LA ROCHE LTD. 2016a. *FDA approves Roche's cancer immunotherapy TECENTRIQ (atezolizumab) for people with a specific type of metastatic lung cancer* [Online]. Available: http://www.roche.com/media/store/releases/med-cor-2016-10-19.htm [Accessed 22nd Dec 2016].

F. HOFFMANN-LA ROCHE LTD 2016b. Supplemental results report for study imvigor 210 (GO29293) - Data cutoff 4th July 2016.

F. HOFFMANN-LA ROCHE LTD 2016c. Supplemental Results Report For Study PCD4989G (GO27831).

FDA. 2016. *FDA approval of atezolizuamb in pre treated PDL1 positive bladder cancer* [Online]. Available: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm501762.htm [Accessed 8th Jan 2017].

FECHNER, G., SIENER, R., REIMANN, M., KOBALZ, L., ALBERS, P. & GERMAN ASSOCIATION OF UROLOGIC ONCOLOGY BLADDER CANCER STUDY, G. 2006. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). *International journal of clinical practice,* 60**,** 27-31.

FEIFER, A. H., TAYLOR, J. M., TARIN, T. V. & HERR, H. W. 2011. Maximizing Cure for Muscle Invasive Bladder Cancer: Integration of Surgery and Chemotherapy. *European urology,* 59**,** 978-984.

FONT, A., PEREZ-VALDERRAMA, B., VIRIZUELA, J. A., HERNANDO POLO, S., CLIMENT, M. A., ARRANZ ARIJA, J. A., GUZMAN, J. C. V., LLORENTE, M. D. M., LAINEZ, N., MELLADO, B., GONZALEZ DEL ALBA, A., GALLARDO DIAZ, E., CASTELLANO, D., ANIDO HERRANZ, U., DOMENECH, M., GARCIA DEL MURO, X., PUENTE, J., MORALES, R., GARCIA-DONAS, J., BELLMUNT, J. & SOGUG 2016. Randomized, placebo-controlled phase II trial (MAJA): Efficacy results of maintenance vinflunine after cisplatin chemotherapy (CT) in patients with advanced urothelial carcinoma (UC)--SOGUG 2011-02. *J Clin Oncol, ASCO Meeting Abstracts,* 34**,** 4529.

FOUGERAY, R. Impact of first-line platinum therapy on survival in patients with platinum-refractory advanced transitional cell carcinoma of the urothelium (TCCU) treated with vinflunine. ASCO, 2012.
GALSKY, M. D., HAHN, N. M., ROSENBERG, J., SONPAVDE, G., HUTSON, T., OH, W. K., DREICER, R., VOGELZANG, N., STERNBERG, C. N., BAJORIN, D. F. & BELLMUNT, J. 2011. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. *J Clin Oncol,* 29**,** 2432-8.
GARCIA DONAS JIMÉNEZ, J., PÉREZ VALDERRAMA, B., FONT POUS, A., VIRIZUELA ECHABURU, J. A., CLIMENT DURÁN, M. A., HERNANDO POLO, S., MELLADO GONZÁLEZ, B., LÁINEZ MILAGRO, N., GONZÁLEZ DEL ALBA BAAMONDE, M. A., ARRANZ ARIJA, J. A., VILLA GUZMÁN, J. C., LLORENTE OSTIATEGUI, M. D. M., CASTELLANO GAUNA, D., GALLARDO DÍAZ, E., GARCIA DEL MURO SOLANS, X., ANIDO HERRANZ, U., DOMÈNECH SANTASUSANA, M., PUENTE VÁZQUEZ, J., PÉREZ GRACIA, J. L. & BELLMUNT MOLINS, J. 2015. MAJA trial: Maintenance vinflunine post cisplatin chemotherapy (CT) in patients with advanced urothelial carcinoma (UC). Preliminary analysis of a randomized placebo controlled phase II trial. SOGUG 2011-02. EudraCT 2011-001271-39. *European Journal of Cancer,* 51**,** S524-S525.
GELPI-HAMMERSCHMIDT, F., LEOW, J., RODRIGUEZ, D., TINAY, I., ALLARD, C., HANNA, N., KRASNOW, R., MEYER, C., ZAVASKI, M., KIBEL, A., PRESTON, M., TRINH, Q. D. & CHANG, S. 2016. Oncologic and perioperative outcomes of "cytoreductive" radical cystectomy for patients with metastatic bladder cancer in the United States. *J Urol,* 195 (4 Suppl)**,** e2.
GERHARZ, E. W., MANSSON, A., HUNT, S., SKINNER, E. C. & MANSSON, W. 2005. Quality of life after cystectomy and urinary diversion: an evidence based analysis. *J Urol,* 174**,** 1729-36.
GERULLIS, H., EIMER, C., ECKE, T. H., GEORGAS, E., FREITAS, C., KASTENHOLZ, S., ARNDT, C., HEUSCH, C. & OTTO, T. 2012. A phase II trial of temsirolimus in second-line metastatic urothelial cancer. *Med Oncol,* 29**,** 2870-6.
GEURTS, S. M. E., GRUTTERS, J. P. C., DE VEGT, F., ABEN, K. K. H., LEMMENS, V. E. E. P., WITJES, J. A., KIEMENEY, L. A., MADDUGER, L., TJAN-HEIJNEN, V. C. G., VAN DIJCK, J. & VERBEEK, A. L. M. 2014. Stratified cancer follow-up leads to a large reduction in visits and costs in the Netherlands: A simulation study. *Int J Gynecol Cancer,* 24 (8 Suppl 2).
GONTERO, P., ODERDA, M., GURIOLI, A., MARSON, F., MEHNERT, A., RINK, M., SCHMID, M., KLUTH, L., PAPPAGALLO, G., SOGNI, F., SANGUEDOLCE, F., MARTORANA, G. & CHUN, F. 2012. Is there a difference in quality of life between intravesical chemotherapy and BCG? Abstract 101. *Anticancer Research,* 32**,** 1843-1966.
GREEN, D. A., RINK, M., CHA, E. K., XYLINAS, E., CHUGHTAI, B., SCHERR, D. S., SHARIAT, S. F. & LEE, R. K. 2013. Cost-effective treatment of low-risk carcinoma not invading bladder muscle. *BJU Int,* 111**,** E78-84.
GREGORI, A., GALLI, S., GOUMAS, I., SCIERI, F., STENER, S. & GABOARDI, F. 2007. A cost comparison of laparoscopic versus open radical cystoprostatectomy and orthotopic ileal neobladder at a single Institution. *Archivio Italiano di Urologia e Andrologia,* 79**,** 127–129.
GUANCIAL, E. A., ROUSSEL, B., BERGSMA, D. P., BYLUND, K. C., SAHASRABUDHE, D., MESSING, E., MOHILE, S. G. & FUNG, C. 2015.

Bladder cancer in the elderly patient: challenges and solutions. *Clin Interv Aging,* 10**,** 939-49.
GUPTA, S., O'DONNELL, P., PLIMACK, E. R., BERGER, R., MONTGOMERY, B., HEATH, K., DOLLED-FILHART, M., PATHIRAJA, K., GAUSE, C. K., CHENG, J., PERINI, R. & BELLMUNT, J. 2015. MP68-11 A Phase 1b Study Of Pembrolizumab (PEMBRO; MK-3475) For Advanced Urothelial Cancer. *The Journal of Urology,* 193**,** e861-e862.
HAMANISHI, J., MANDAI, M., IWASAKI, M., OKAZAKI, T., TANAKA, Y., YAMAGUCHI, K., HIGUCHI, T., YAGI, H., TAKAKURA, K., MINATO, N., HONJO, T. & FUJII, S. 2007. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A,* 104**,** 3360-5.
HAN, K. S., JOUNG, J. Y., KIM, T. S., JEONG, I. G., SEO, H. K., CHUNG, J. & LEE, K. H. 2008. Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy. *Br J Cancer,* 98**,** 86-90.
HARSHMAN, L. C., DRAKE, C. G. & CHOUEIRI, T. K. 2014. PD-1 Blockade in Renal Cell Carcinoma: To Equilibrium and Beyond. *Cancer Immunology Research,* 2**,** 1132-1141.
HEALTH AND SOCIAL CARE INFORMATION CENTRE. 2016. *NHS OPCS-4 Chemotherapy Regimens List and High Cost Drugs List releases* [Online]. Available: https://isd.hscic.gov.uk/trud3/user/guest/group/0/pack/1/subpack/27/releases [Accessed 17th Jan 2017].
HERBST, R. S., SORIA, J. C., KOWANETZ, M., FINE, G. D., HAMID, O., GORDON, M. S., SOSMAN, J. A., MCDERMOTT, D. F., POWDERLY, J. D., GETTINGER, S. N., KOHRT, H. E., HORN, L., LAWRENCE, D. P., ROST, S., LEABMAN, M., XIAO, Y., MOKATRIN, A., KOEPPEN, H., HEGDE, P. S., MELLMAN, I., CHEN, D. S. & HODI, F. S. 2014. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature,* 515**,** 563-7.
HINO, R., KABASHIMA, K., KATO, Y., YAGI, H., NAKAMURA, M., HONJO, T., OKAZAKI, T. & TOKURA, Y. 2010. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. *Cancer,* 116**,** 1757-66.
HOWLADER, N., NOONE, A. M., KRAPCHO, M., NEYMAN, N., AMINOU, R., WALDRON, W., ALTEKRUSE, S. F., KOSARY, C. L., RUHL, J., TATALOVICH, Z., CHO, H., MARIOTTO, A., EISNER, M. P., LEWIS, D. R., CHEN, H. S., FEUER, E. J., CRONIN, K. A. & EDWARDS, B. K. 2011. *SEER cancer statistics review, bladder section, 1975–2008* [Online]. Available: http://seer.cancer.gov/csr/1975_2008/ [Accessed 13th Dec 2016].
HU, J. C., CHUGHTAI, B., O'MALLEY, P., HALPERN, J. A., MAO, J., SCHERR, D. S., HERSHMAN, D. L., WRIGHT, J. D. & SEDRAKYAN, A. 2016. Perioperative outcomes, health care costs, and survival after robotic-assisted versus open radical cystectomy: A national comparative effectiveness study *Eur Urol,* 70**,** 195–202.
HUILLARD 2016. Aggressiveness of care at the end of life in patients with localized and advanced bladder cancer. *J Clin Oncol,* 34.

IKEDA, M., MATSUMOTO, K., TABATA, K., MINAMIDA, S., FUJITA, T., SATOH, T., IWAMURA, M. & BABA, S. 2011. Combination of gemcitabine and paclitaxel is a favorable option for patients with advanced or metastatic urothelial carcinoma previously treated with cisplatin-based chemotherapy. *Jpn J Clin Oncol,* 41**,** 1214-20.

INMAN, B. A., LONGO, T. A., RAMALINGAM, S. & HARRISON, M. R. 2016. Atezolizumab: a PD-L1 blocking antibody for bladder cancer. *Clin Cancer Res*.

JANSEN, J. P. 2011. Network meta-analysis of survival data with fractional polynomials. *BMC Med Res Methodol,* 11**,** 61.

JOLY, F., HOUEDE, N., NOAL, S., CHEVREAU, C., PRIOU, F., CHINET-CHARROT, P., ROLLAND, F., FLECHON, A., HENRY-AMAR, M. & CULINE, S. 2009. Do patients with advanced urothelial carcinoma benefit from weekly paclitaxel chemotherapy? A GETUG phase II study. *Clin Genitourin Cancer,* 7**,** E28-33.

KAUFMAN, D. S., SHIPLEY, W. U. & FELDMAN, A. S. 2009. Bladder cancer. *Lancet,* 374**,** 239-49.

KIM, Y. S. A phase II trial of weekly docetaxel for second-line treatment of urothelial carcinoma. ASCO, 2013.

KIM, Y. S., LEE, S. I., PARK, S. H., PARK, S., HWANG, I. G., LEE, S. C., SUN, J. M., LEE, J. & LIM, H. Y. 2016. A Phase II Study of Weekly Docetaxel as Second-Line Chemotherapy in Patients With Metastatic Urothelial Carcinoma. *Clin Genitourin Cancer,* 14**,** 76-81.

KO Y, C. C., MUKHERJEE S, WINQUIST E, REAUME N, ELSER C 2010. A multi-institutional phase II study of single agent abi-007 in platinum refractory urothelial carcinoma. *Annals of Oncology,* 21.

KO, Y. J., CANIL, C. M., MUKHERJEE, S. D., WINQUIST, E., ELSER, C., EISEN, A., REAUME, M. N., ZHANG, L. & SRIDHAR, S. S. 2013. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. *Lancet Oncol,* 14**,** 769-76.

KONETY, B. R., JOYCE, G. F. & WISE, M. 2007. Bladder and upper tract urothelial cancer. *J Urol,* 177**,** 1636–45.

KOUNO, T., ANDO, M., YONEMORI, K., MATSUMOTO, K., SHIMIZU, C., KATSUMATA, N., KOMIYAMA, M., OKAJIMA, E., MATSUOKA, N., FUJIMOTO, H. & FUJIWARA, Y. 2007. Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. *Eur Urol,* 52**,** 1115-22.

KULKARNI, G. S., ALIBHAI, S. M., FINELLI, A., FLESHNER, N. E., JEWETT, M. A., LOPUSHINSKY, S. R. & BAYOUMI, A. M. 2009. Cost-effectiveness analysis of immediate radical cystectomy versus intravesical Bacillus Calmette-Guerin therapy for high-risk, high-grade (T1G3) bladder cancer. *Cancer,* 115**,** 5450-9.

KULKARNI, G. S., FINELLI, A., FLESHNER, N. E., JEWETT, M. A., LOPUSHINSKY, S. R. & ALIBHAI, S. M. 2007a. Optimal management of high-risk T1G3 bladder cancer: a decision analysis. *PLoS Med,* 4**,** e284.

KULKARNI, G. S., FINELLI, A., FLESHNER, N. E., JEWETT, M. A., LOPUSHINSKY, S. R. & ALIBHAI, S. M. 2007b. Optimal management of high-risk T1G3 bladder cancer: a decision analysis. *PLoS medicine,* 4**,** e284.

LAMB, B. W., VASDEV, N., JALIL, R. T., MCMENEMIN, R., HUGHES, S., PAYNE, H. & GREEN, J. S. A. 2014. Second-line chemotherapy for advanced bladder

cancer: A survey of current UK practice. *Urologic Oncology: Seminars and Original Investigations,* 32**,** 52.e11-52.e17.
LEE, C. T., BAROCAS, D., GLOBE, D. R., OEFELEIN, M. G., COLAYCO, D. C., BRUNO, A., O'DAY, K. & BRAMLEY, T. 2012. Economic and humanistic consequences of preventable bladder tumor recurrences in nonmuscle invasive bladder cancer cases. *J Urol,* 188**,** 2114-9.
LEE J, P. S., LIM H, KWON J, KIM G, SONG C 2011. Phase II study of a polyethoxylated castor oil-free, polymeric micelle formulation of paclitaxel for patients with advanced urothelial cancer previously treated with gemcitabine and platinum. *Journal of Clinical Oncology,* 29.
LEE, R., NG, C. K., SHARIAT, S. F., BORKINA, A., GUIMENTO, R., BRUMIT, K. F. & SCHERR, D. S. 2011. The economics of robotic cystectomy: Cost comparison of open versus robotic cystectomy. *BJU Int,* 108**,** 1886–1892.
LENCIONI, R. & LLOVET, J. M. 2010. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis,* 30**,** 52-60.
LIDA, K., NAGAI, T., ETANI, T., NAIKI, T., ANDO, R., KAWAI, N., TOZAWA, K. & YASUI, T. 2016a. 1151 Gemcitabine plus paclitaxel as third-line chemotherapy: A feasible option for metastatic urothelial carcinoma patients. *European Urology Supplements,* 15**,** e1151.
LIDA, K., NAGAI, T., ETANI, T., NAIKI, T., ANDO, R., KAWAI, N., TOZAWA, K. & YASUI, T. 2016b. Gemcitabine plus paclitaxel as third-line chemotherapy: A feasible option for metastatic urothelial carcinoma patients. *European Urology Supplements,* 15.
LLOVET, J. M., DI BISCEGLIE, A. M., BRUIX, J., KRAMER, B. S., LENCIONI, R., ZHU, A. X., SHERMAN, M., SCHWARTZ, M., LOTZE, M., TALWALKAR, J., GORES, G. J. & PANEL OF EXPERTS IN, H. C. C. D. C. T. 2008. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst,* 100**,** 698-711.
LOEHRER, P. J., SR., EINHORN, L. H., ELSON, P. J., CRAWFORD, E. D., KUEBLER, P., TANNOCK, I., RAGHAVAN, D., STUART-HARRIS, R., SAROSDY, M. F., LOWE, B. A. & ET AL. 1992. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol,* 10**,** 1066-73.
LONDON CANCER ALLIANCE. 2013. *Bladder cancer / Transitional cell carcinoma* [Online]. Available: http://www.londoncanceralliance.nhs.uk/media/62149/Bladder%20Cancer-TCC%20Regimens%20v7.01%20Approved%20NWLCN%2015Oct13.pdf [Accessed 17th Jan 2017].
LORIOT, Y., ROSENBERG, J., POWLES, T., NECCHI, A., HUSSAIN, S. A., MORALES, R., RETZ, M., NIEGISCH, G., DURÁN, I., THEODORE, C., PEREZ-GRACIA, J. L., GRANDE, E., THÅSTRÖM, A., BOURGON, R., LI, S., MARIATHASAN, S., ABIDOYE, O. & VAN DER HEIJDEN, M. S. Atezolizumab in Platinum-Treated Locally Advanced or Metastatic Urothelial Carcinoma (mUC): Updated OS, Safety and Biomarkers From the Phase II IMvigor210 Study. The European Society for Medical Oncology, October 7-11, 2016 2016 Copenhagen, Denmark.
M.D. ANDERSON CANCER CENTER. 2015. Iressa and Taxotere Study in Patients With Metastatic Urothelial Cancer. *ClinicalTrials.gov* [Online]. Available: https://clinicaltrials.gov/ct2/show/study/NCT00479089 [Accessed 05.07.2016].

MAK, R. H., HUNT, D., SHIPLEY, W. U., EFSTATHIOU, J. A., TESTER, W. J., HAGAN, M. P., KAUFMAN, D. S., HENEY, N. M. & ZIETMAN, A. L. 2014. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol,* 32**,** 3801-9.

MATSUMOTO, K., IRIE, A., SATOH, T., OKAZAKI, M., IWAMURA, M. & BABA, S. 2007. Gemcitabine and paclitaxel chemotherapy as a second-line treatment for advanced or metastatic urothelial carcinoma. *Int J Urol,* 14**,** 1000-4; discussion 1004.

MCCAFFREY, J. A., HILTON, S., MAZUMDAR, M., SADAN, S., KELLY, W. K., SCHER, H. I. & BAJORIN, D. F. 1997. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol,* 15**,** 1853-7.

MELUCH, A. A., GRECO, F. A., BURRIS, H. A., 3RD, O'ROURKE, T., ORTEGA, G., STEIS, R. G., MORRISSEY, L. H., JOHNSON, V. & HAINSWORTH, J. D. 2001. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 19**,** 3018-24.

MENG, X., HUANG, Z., TENG, F., XING, L. & YU, J. 2015. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. *Cancer Treat Rev,* 41**,** 868-76.

MERCK SHARP AND DOHME. 2016. *KEYTRUDA 50mg powder for concntrate for solution for infusion* [Online]. Available: https://www.medicines.org.uk/emc/medicine/30602 [Accessed 16th Jan 2017].

MILLIKAN, R., DINNEY, C., SWANSON, D., SWEENEY, P., RO, J. Y., SMITH, T. L., WILLIAMS, D. & LOGOTHETIS, C. 2001. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. *J Clin Oncol,* 19**,** 4005-13.

MIYATA, Y., ASAI, A., MITSUNARI, K., MATSUO, T., OHBA, K. & SAKAI, H. 2015. Safety and efficacy of combination therapy with low-dose gemcitabine, paclitaxel, and sorafenib in patients with cisplatin-resistant urothelial cancer. *Med Oncol,* 32**,** 235.

MU, C. Y., HUANG, J. A., CHEN, Y., CHEN, C. & ZHANG, X. G. 2011. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. *Med Oncol,* 28**,** 682-8.

MULLASSERY, V. M. 2010. Carcinoma of the bladder. *GM2,* November**,** 22-27.

NADEEM, H., JAYAKRISHNAN, T. T., GAMBLIN, T. C. & TURAGA, K. 2014. Cost differential among systemic therapies for breast, bladder, lung, and colon cancer. *J Clin Oncol,* 32 (15 Suppl 1)**,** e17541.

NADEEM, H., JAYAKRISHNAN, T. T., RAJEEV, R., JOHNSTON, F. M., GAMBLIN, T. C. & TURAGA, K. K. 2016. Cost differential of chemotherapy for solid tumors. *J Oncol Pract,* 12**,** e299–307, 251.

NAIKI, T., IIDA, K., ANDO, R., ETANI, T., KAWAI, N., NAGAI, T., SUGIYAMA, Y., KONDO, M., OKAMURA, T. & YASUI, T. 2016. MP06-17 Gemcitabine Plus Paclitaxel As Third Line Chemotherapy: A Feasible Option For Metastatic Urothelial Carcinoma Patients. *The Journal of Urology,* 195**,** e74.

NAKANISHI, J., WADA, Y., MATSUMOTO, K., AZUMA, M., KIKUCHI, K. & UEDA, S. 2007. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother,* 56**,** 1173-82.

NATIONAL COLLABORATING CENTRE FOR CANCER. 2015. *Bladder cancer: diagnosis and management* [Online]. Available: https://www.guideline.gov/summaries/summary/49119 [Accessed 13th Jan 2016].

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE. 2002. *Improving Outcomes in Urological Cancers* [Online]. Available: https://www.nice.org.uk/guidance/csg2/resources/improving-outcomes-in-urological-cancers-773372413 [Accessed 13th Jan 2017].

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE. 2012. *Appendix F Quality appraisal checklist – quantitative intervention studies* [Online]. Available: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies [Accessed 17th Jan 2012].

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE. 2015. *Pembrolizumab for advanced melanoma not previously treated with ipilimumab* [Online]. Available: https://www.nice.org.uk/guidance/ta366 [Accessed 17th Jan 2017].

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE. 2016. *Nivolumab for treating advanced (unresectable or metastatic) melanoma* [Online]. Available: https://www.nice.org.uk/guidance/ta384 [Accessed 17th Jan 2017].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2007. *Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer* [Online]. Available: https://www.nice.org.uk/guidance/ipg235 [Accessed 13th Dec 2016].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2008. *Electrically-stimulated intravesical chemotherapy for superficial bladder cancer* [Online]. Available: https://www.nice.org.uk/guidance/ipg277 [Accessed 13th Dec 2016].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2009. *Laparoscopic cystectomy* [Online]. Available: https://www.nice.org.uk/guidance/ipg287 [Accessed 13th Dec 2016].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2013. *Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract* [Online]. Available: https://www.nice.org.uk/guidance/ta272 [Accessed 13th Dec 2016].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2015a. *Bladder Cancer* [Online]. Available: https://www.nice.org.uk/guidance/qs106/resources/bladder-cancer-75545241003205 [Accessed 13th Dec 2016].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2015b. *Bladder cancer: diagnosis and management* [Online]. Available: https://www.nice.org.uk/guidance/ng2/resources/bladder-cancer-diagnosis-and-management-of-bladder-cancer-51036766405 [Accessed 13th Dec 2016].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2016a. *Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma* [Online]. Available: https://www.nice.org.uk/guidance/ta414 [Accessed 17th Jan 2017].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2016b. *Suspected cancer* [Online]. Available: https://www.nice.org.uk/guidance/qs124 [Accessed 13th Dec 2016].
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2017a. *Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900]* [Online]. Available: https://www.nice.org.uk/guidance/indevelopment/gid-tag524 [Accessed 17th Jan 2017].
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2017b. *Lung cancer (non-small-cell, squamous, metastatic) - nivolumab (after chemotherapy) [ID811]* [Online]. Available: https://www.nice.org.uk/guidance/indevelopment/gid-tag506 [Accessed 17th Jan 2017].
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2017c. *Pembrolizumab for treating PDL1-positive non-small-cell lung cancer after chemotherapy* [Online]. Available: https://www.nice.org.uk/guidance/ta428 [Accessed 17th Jan 2017].
NATIONAL INSTITUTES OF HEALTH. 2014. *Quality Assessment Tool for Case Series Studies* [Online]. Available: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series [Accessed 17th Jan 2017].
NIEGISCH, G., RETZ, M., SIENER, R. & ALBERS, P. 2016. Quality of life in patients with cisplatin-resistant urothelial cancer: Typical ailments and effect of paclitaxel-based salvage therapy. *Urol Oncol,* 34**,** 256 e15-21.
NOGUCHI, M., MATSUMOTO, K., UEMURA, H., ARAI, G., ETO, M., NAITO, S., OHYAMA, C., NASU, Y., TANAKA, M., MORIYA, F., SUEKANE, S., MATSUEDA, S., KOMATSU, N., SASADA, T., YAMADA, A., KAKUMA, T. & ITOH, K. 2016. An Open-Label, Randomized Phase II Trial of Personalized Peptide Vaccination in Patients with Bladder Cancer that Progressed after Platinum-Based Chemotherapy. *Clin Cancer Res,* 22**,** 54-60.
NOGUCHI M, M. K., UEMURA H, ARAI G, ETO M, NAITO S 2014. Randomized phase II study of personalized peptide vaccination in patients with advanced bladder cancer progressing after chemotherapy. *Journal of Clinical Oncology,* 32.
O'DONNELL, P. H., PLIMACK, E. R., BELLMUNT, J., BERGER, R., MONTGOMERY, R. B., HEATH, K., DOLLED-FILHART, M., PATHIRAJA, K., GAUSE, C. K., CHENG, J. D., PERINI, R. F. & GUPTA, S. 2015. Pembrolizumab (Pembro; MK-3475) for advanced urothelial cancer: Results of a phase IB study. *J Clin Oncol, ASCO Meeting Abstracts,* 33**,** 296.
O'LEARY, J. F., FAIRCLOUGH, D. L., JANKOWSKI, M. K. & WEEKS, J. C. 1995. Comparison of time-tradeoff utilities and rating scale values of cancer patients and their relatives: evidence for a possible plateau relationship. *Med Decis Making,* 15**,** 132-7.
OHAEGBULAM, K. C., ASSAL, A., LAZAR-MOLNAR, E., YAO, Y. & ZANG, X. 2015. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. *Trends in molecular medicine,* 21**,** 24-33.
ONCOGENEX TECHNOLOGIES, INC. 2011. A Randomized, Double-blind Phase 2 Study Comparing Gemcitabine and Cisplatin in Combination with OGX-427 or Placebo in Patients With Advanced Transitional Cell Carcinoma. EudraCT Number: 2011-002424-41. *EU Clinical Trials Register* [Online]. Available:

https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-002424-41.
PETRYLAK DP, T. S., KOHL M, EISEN A, CANIL C, SRIDHAR SS 2015. Three-arm phase II randomized trial of docetaxel monotherapy or combined with ramucirumab or icrucumab in second-line locally advanced or metastatic urothelial carcinoma European journal of cancer. *European journal of cancer,* 51**,** S476.
PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE. 2015. *VINFLUNINE Public Summary Document – November 2015 PBAC Meeting* [Online]. Available: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-11/files/vinflunine-psd-november-2015.pdf [Accessed 17th Jan 2017].
PIERRE FABRE LTD 2015. Javlor 25mg/ml concentrate for solution for infusion.
PIMLACK, E. R. PDL1 Pathway Inhibitors Herald a New Era for Urothelial Cancer. ASCO, 2016 2016 Chicago, USA.
PLOEG, M., ABEN, K. K. H. & KIEMENEY, L. A. 2009. The present and future burden of urinary bladder cancer in the world. *World Journal of Urology,* 27**,** 289-293.
POND, G. R., AGARWAL, N., BELLMUNT, J., CHOUEIRI, T. K., QU, A., FOUGERAY, R., VAUGHN, D., JAMES, N. D., SALHI, Y., ALBERS, P., NIEGISCH, G., GALSKY, M. D., WONG, Y. N., KO, Y. J., STADLER, W. M., O'DONNELL, P. H., SRIDHAR, S. S., VOGELZANG, N. J., NECCHI, A., DI LORENZO, G., STERNBERG, C. N., MEHTA, A. & SONPAVDE, G. 2014. A nomogram including baseline prognostic factors to estimate the activity of second-line therapy for advanced urothelial carcinoma. *BJU Int,* 113**,** E137-43.
POWLES, T., EDER, J. P., FINE, G. D., BRAITEH, F. S., LORIOT, Y., CRUZ, C., BELLMUNT, J., BURRIS, H. A., PETRYLAK, D. P., TENG, S.-L., SHEN, X., BOYD, Z., HEGDE, P. S., CHEN, D. S. & VOGELZANG, N. J. 2014. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature,* 515**,** 558-562.
POWLES, T., HUSSAIN, S. A., PROTHEROE, A., BLRTLE, A., CHAKRABORTL, P. R., HUDDART, R., JAGDEV, S., BAHL, A., STOCKDALE, A., SUNDAR, S., CRABB, S. J., DIXON-HUGHES, J., ALEXANDER, L., BRAY, C. A., STOBO, J., WIMALASINGHAM, A. G., ACKERMAN, C., PAUL, J. & JONES, R. 2016. PLUTO: A randomised phase II study of pazopanib versus paclitaxel in relapsed urothelial tumours. *Journal of Clinical Oncology,* 34.
RISPOLI, A., PAVONE, I., BONGINI, A., DI LORO, F., PONCHIETTI, R. & RIZZO, M. 2005. Genitourinary Cancer: Psychological Assessment and Gender Differences. *Urologia Internationalis,* 74**,** 246-249.
RITTMEYER, A., BARLESI, F., WATERKAMP, D., PARK, K., CIARDIELLO, F., VON PAWEL, J., GADGEEL, S. M., HIDA, T., KOWALSKI, D. M., DOLS, M. C., CORTINOVIS, D. L., LEACH, J., POLIKOFF, J., BARRIOS, C., KABBINAVAR, F., FRONTERA, O. A., DE MARINIS, F., TURNA, H., LEE, J. S., BALLINGER, M., KOWANETZ, M., HE, P., CHEN, D. S., SANDLER, A. & GANDARA, D. R. 2016. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*.
ROBINSON, P., MAASE, H., BHALLA, S., KIELHORN, A., ARISTIDES, M., BROWN, A. & TILDEN, D. 2004. Cost-utility analysis of the GC versus MVAC

regimens for the treatment of locally advanced or metastatic bladder cancer. *Expert Rev Pharmacoecon Outcomes Res,* 4**,** 27-38.
ROSENBERG, J., PETRYLAK, D., ABIDOYE, O., VAN DER HEIJDEN, M. S., HOFMAN-CENSITS, J., NECCHI, A., O'DONNELL, P. H., BALMANOUKIAN, A., LORIOT, Y., RETZ, M., PEREZ-GRACIA, J. L., DAWSON, N. A., BALAR, A., GALSKY, M. D., FLEMING, M. T., POWLES, T., CUI, N. & MARIATHASAN, S. 2015. Atezolizumab in patients (pts) with locally-advanced or metastatic urothelial carcinoma (mUC): Results from a pivotal multicenter phase II study (IMvigor 210). *European journal of cancer,* 51**,** S720, Abstract No. 21LBA.
ROSENBERG, J. E., HOFFMAN-CENSITS, J., POWLES, T., VAN DER HEIJDEN, M. S., BALAR, A. V., NECCHI, A., DAWSON, N., O'DONNELL, P. H., BALMANOUKIAN, A., LORIOT, Y., SRINIVAS, S., RETZ, M. M., GRIVAS, P., JOSEPH, R. W., GALSKY, M. D., FLEMING, M. T., PETRYLAK, D. P., PEREZ-GRACIA, J. L., BURRIS, H. A., CASTELLANO, D., CANIL, C., BELLMUNT, J., BAJORIN, D., NICKLES, D., BOURGON, R., FRAMPTON, G. M., CUI, N., MARIATHASAN, S., ABIDOYE, O., FINE, G. D. & DREICER, R. 2016a. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *The Lancet,* 387**,** 1909-1920.
ROSENBERG, J. E., HOFFMAN-CENSITS, J., POWLES, T., VAN DER HEIJDEN, M. S., BALAR, A. V., NECCHI, A., DAWSON, N., O'DONNELL, P. H., BALMANOUKIAN, A., LORIOT, Y., SRINIVAS, S., RETZ, M. M., GRIVAS, P., JOSEPH, R. W., GALSKY, M. D., FLEMING, M. T., PETRYLAK, D. P., PEREZ-GRACIA, J. L., BURRIS, H. A., CASTELLANO, D., CANIL, C., BELLMUNT, J., BAJORIN, D., NICKLES, D., BOURGON, R., FRAMPTON, G. M., CUI, N., MARIATHASAN, S., ABIDOYE, O., FINE, G. D. & DREICER, R. 2016b. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet (London, England),* 387**,** 1909-20.
SCHADENDORF, D., HODI, F. S., ROBERT, C., WEBER, J. S., MARGOLIN, K., HAMID, O., PATT, D., CHEN, T.-T., BERMAN, D. M. & WOLCHOK, J. D. 2015. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *Journal of Clinical Oncology,* 33**,** 1889-1894.
SCHMID P, KOWANETZ M, KOEPPEN H, ZOU W, WISTUBA I, KOCKX M, KADEL III EE, CHAFT J, RIZVI NA, HIRSCH FR, SMITH D, MILEY N, LEVEQUE V, SHAMES DS, SANDLER A, MELLMAN I, CHEN DS, HEGDE PS & GETTINGER S. NSCLC with high PD-L1 expression on tumor cells or tumor-infiltrating immune cells represents distinct cancer subtypes. European Society For Medical Oncology, September 25–29 2015 Vienna, Austria.
SEAL 2015. Evaluating the Cost of Treating Bladder Cancer With and Without Metastases. *Value in Health,* 18.
SHARMA P, B. P., KIM JW, SPILIOPOULOU P, CALVO E, PILLAI RN. Efficacy and safety of nivolumab monotherapy in metastatic urothelial cancer (mUC): Results from the phase I/II CheckMate 032 study. ASCO, 2016. 4501.
SHARMA, S., KSHEERSAGAR, P. & SHARMA, P. 2009. Diagnosis and treatment of bladder cancer. *Am Fam Physician,* 80**,** 717-23.

SONPAVDE, G., STERNBERG, C. N., ROSENBERG, J. E., HAHN, N. M., GALSKY, M. D. & VOGELZANG, N. J. 2010. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. *Lancet Oncol,* 11**,** 861-70.
SRIDHAR SS, C. C., EISEN A, TANNOCK IF, KNOX JJ, REAUME N 2009. A phase II study of single agent abraxane as second-line therapy in patients with advanced urothelial carcinoma. *Journal of Clinical Oncology,* 15.
SRIDHAR SS, C. C., MUKHERJEE SD, WINQUIST E, ELSER C, EISEN A 2010. A phase II study of single-agent nab-paclitaxel as second-line therapy in patients with metastatic urothelial carcinoma. *Journal of Clinical Oncology,* 28.
SRIDHAR SS, C. C., MUKHERJEE SD, WINQUIST E, ELSER C, EISEN A, 2011. Results of a phase II study of single-agent nab-paclitaxel in platinum-refractory second-line metastatic urothelial carcinoma (UC). *29,* 7.
SRINIVAS, S. & GUARDINO, A. E. 2005. A nonplatinum combination in metastatic transitional cell carcinoma. *Am J Clin Oncol,* 28**,** 114-8.
STENZL, A., COWAN, N. C., DE SANTIS, M., KUCZYK, M. A., MERSEBURGER, A. S., RIBAL, M. J., SHERIF, A. & WITJES, J. A. 2011. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. *Eur Urol,* 59**,** 1009-18.
STERNBERG, C. N., CALABRO, F., PIZZOCARO, G., MARINI, L., SCHNETZER, S. & SELLA, A. 2001. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer,* 92**,** 2993-8.
STEVENSON, S. M., DANZIG, M. R., GHANDOUR, R. A., DEIBERT, C. M., DECASTRO, G. J., BENSON, M. C. & MCKIERNAN, J. M. 2014. Cost-effectiveness of neoadjuvant chemotherapy before radical cystectomy for muscle-invasive bladder cancer. *Urol Oncol,* 32**,** 1172-7.
STITZENBERG, K. B., CHANG, Y., SMITH, A. B. & NIELSEN, M. E. 2015. Exploring the burden of inpatient readmissions after major cancer surgery. *J Clin Oncol,* 33**,** 455–464.
SUN PHARMA 2016. Gemcitabine 10mg/ml, solution for infusion.
SUTTON, A. J. 2012. *Evidence synthesis for decision making in healthcare*, John Wiley & Sons.
SUYAMA, T., UEDA, T., FUKASAWA, S., IMAMURA, Y., NAKAMURA, K., MIYASAKA, K., SAZUKA, T., EGOSHI, K., NIHEI, N., HAMANO, M., ICHIKAWA, T. & MARUOKA, M. 2009. Combination of gemcitabine and paclitaxel as second-line chemotherapy for advanced urothelial carcinoma. *Jpn J Clin Oncol,* 39**,** 244-50.
SYLVESTER, R. J., VAN DER MEIJDEN, A. P., OOSTERLINCK, W., WITJES, J. A., BOUFFIOUX, C., DENIS, L., NEWLING, D. W. & KURTH, K. 2006. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol,* 49**,** 466-5; discussion 475-7.
TAKAHASHI, T., HIGASHI, S., NISHIYAMA, H., SEGAWA, T., NAKAMURA, E., KINOSHITA, H., ITOH, N., YAMAMOTO, S., KAMOTO, T., HABUCHI, T. & OGAWA, O. 2006. Biweekly paclitaxel and gemcitabine for patients with advanced urothelial cancer ineligible for cisplatin-based regimen. *Jpn J Clin Oncol,* 36**,** 104-8.
THERASSE, P., ARBUCK, S. G., EISENHAUER, E. A., WANDERS, J., KAPLAN, R. S., RUBINSTEIN, L., VERWEIJ, J., VAN GLABBEKE, M., VAN OOSTEROM,

A. T., CHRISTIAN, M. C. & GWYTHER, S. G. 2000. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst,* 92**,** 205-16.

THOMPSON, R. H., KUNTZ, S. M., LEIBOVICH, B. C., DONG, H., LOHSE, C. M., WEBSTER, W. S., SENGUPTA, S., FRANK, I., PARKER, A. S., ZINCKE, H., BLUTE, M. L., SEBO, T. J., CHEVILLE, J. C. & KWON, E. D. 2006. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res,* 66**,** 3381-5.

TUMA, R. S. 2011. Immunotherapies in clinical trials: do they demand different evaluation tools? *J Natl Cancer Inst,* 103**,** 780-1.

TURNER, R. M., DAVEY, J., CLARKE, M. J., THOMPSON, S. G. & HIGGINS, J. P. 2012. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol,* 41**,** 818-27.

TURNER, R. M., JACKSON, D., WEI, Y., THOMPSON, S. G. & HIGGINS, J. P. 2015. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat Med,* 34**,** 984–98.

U.S. FOOD & DRUG ADMINISTRATION. 2016. *FDA approves new, targeted treatment for bladder cancer* [Online]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm501762.htm [Accessed 16th Dec 2016].

VAISHAMPAYAN, U. N., FAULKNER, J. R., SMALL, E. J., REDMAN, B. G., KEISER, W. L., PETRYLAK, D. P. & CRAWFORD, E. D. 2005. Phase II trial of carboplatin and paclitaxel in cisplatin-pretreated advanced transitional cell carcinoma: a Southwest Oncology Group study. *Cancer,* 104**,** 1627-32.

VAN DEN HOUT, W. B. 2006. EuroQol data in terminally-ill cancer patients. *Poster presented at the 10th Biennial European Meeting of the Society for Medical Decision Making, 11-13 June 2006, Birmingham, United Kingdom.*

VAUGHN, D. J., MANOLA, J., DREICER, R., SEE, W., LEVITT, R. & WILDING, G. 2002. Phase II study of paclitaxel plus carboplatin in patients with advanced carcinoma of the urothelium and renal dysfunction (E2896): a trial of the Eastern Cooperative Oncology Group. *Cancer,* 95**,** 1022-7.

VAUGHN, D. J., SRINIVAS, S., STADLER, W. M., PILI, R., PETRYLAK, D., STERNBERG, C. N., SMITH, D. C., RINGUETTE, S., DE WIT, E., PAUTRET, V. & GEORGE, C. 2009. Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase 2 study. *Cancer,* 115**,** 4110-7.

VON DER MAASE, H. Multicentre phase III trial comparing vinflunine (V) plus best supportive care (BSC) vs BSC alone as 2nd line therapy after a platinum-containing regimen, in advanced transitional cell carcinoma of the urothelium (TCCU). ESMO, 2008.

VON DER MAASE, H., SENGELOV, L., ROBERTS, J. T., RICCI, S., DOGLIOTTI, L., OLIVER, T., MOORE, M. J., ZIMMERMANN, A. & ARNING, M. 2005. Long-Term Survival Results of a Randomized Trial Comparing Gemcitabine Plus Cisplatin, With Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin in Patients With Bladder Cancer. *Journal of Clinical Oncology,* 23**,** 4602-4608.

WEI, L., LI, Q., LIANG, H. & JIANBO, L. 2014. The quality of life in patients during intravesical treatment and correlation with local symptoms. *J Chemother,* 26**,** 165-8.
WINQUIST, E., WILSON, J. J., DORREEN, M., WONG, R., JONKER, D. & ISCOE, N. 2004. A 3-week gemcitabine-cisplatin regimen for metastatic urothelial cancer. *The Canadian journal of urology,* 11**,** 2445-9.
WITJES, J. A., COMPERAT, E., COWAN, N. C., DE SANTIS, M., GAKIS, G., LEBRET, T., RIBAL, M. J., VAN DER HEIJDEN, A. G. & SHERIF, A. 2014. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. *Eur Urol,* 65**,** 778-92.
WITTIG, K., RUEL, N., BARLOG, J., CROCITTO, L., CHAN, K., LAU, C., WILSON, T. & YUH, B. 2016. Critical Analysis of Hospital Readmission and Cost Burden After Robot-Assisted Radical Cystectomy. *J Endourol,* 30**,** 83–91.
XU, N., ZHANG, X. C., XIONG, J. P., FANG, W. J., YU, L. F., QIAN, J. & ZHANG, L. 2007. A phase II trial of gemcitabine plus carboplatin in advanced transitional cell carcinoma of the urothelium. *BMC cancer,* 7**,** 98.
ZACHARIAH, F., GALLO, M., LOSCALZO, M. & CROCITTO, L. E. 2014. Embedding palliative care into care coordination. *J Clin Oncol,* 32.

8 Appendices

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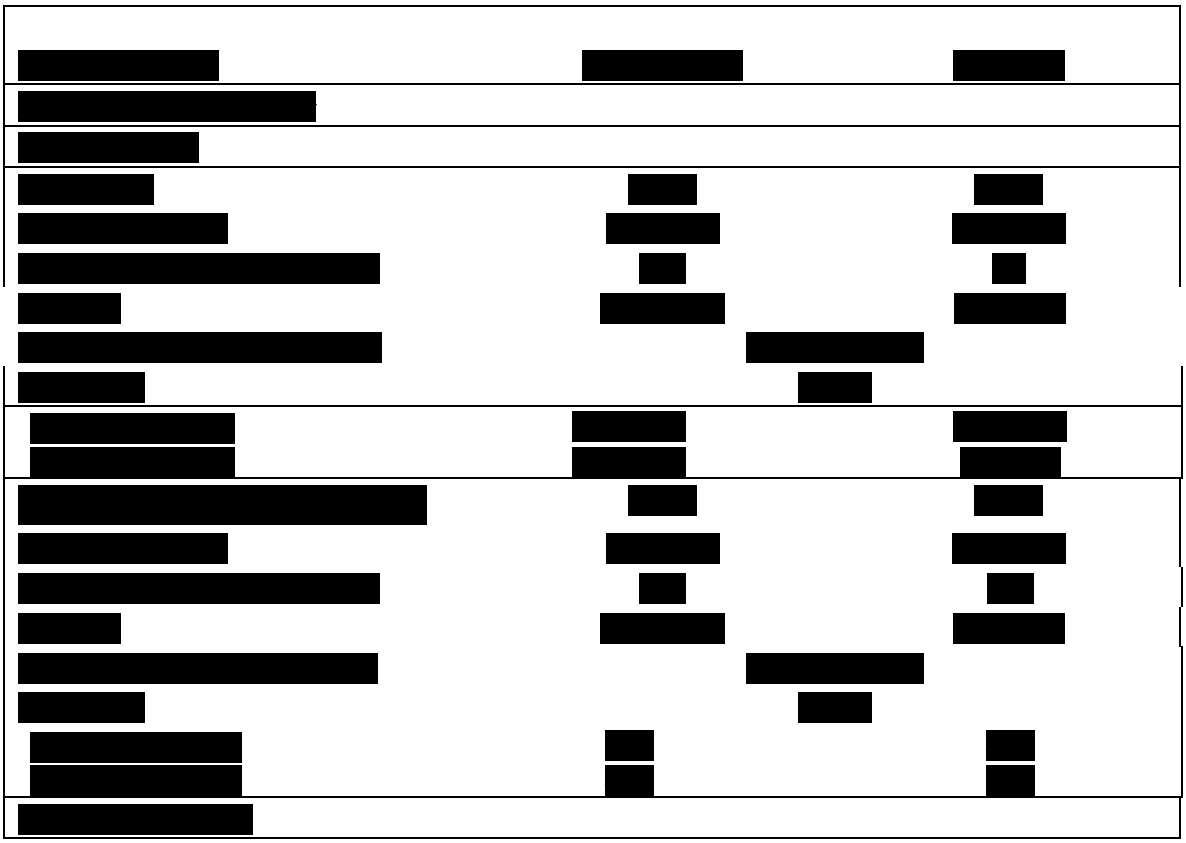

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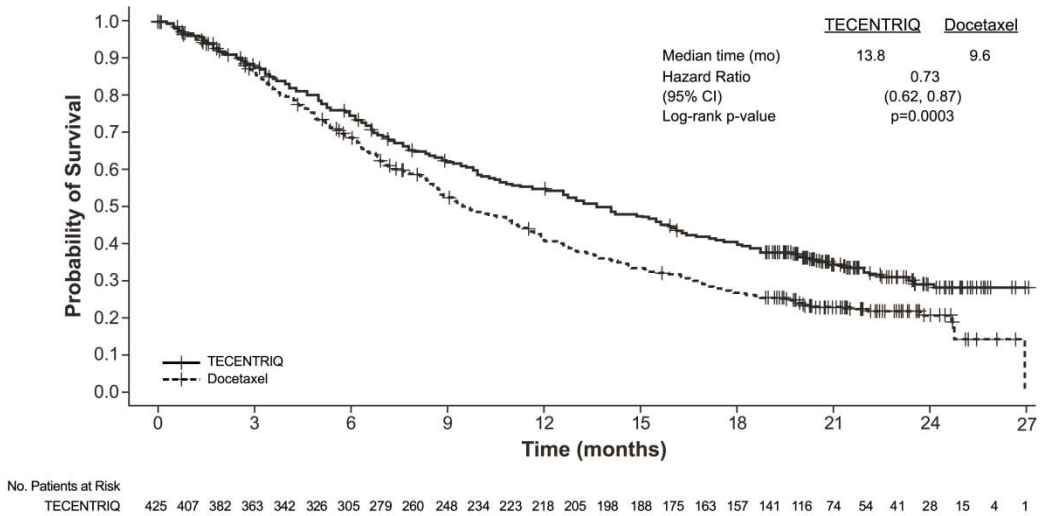

Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

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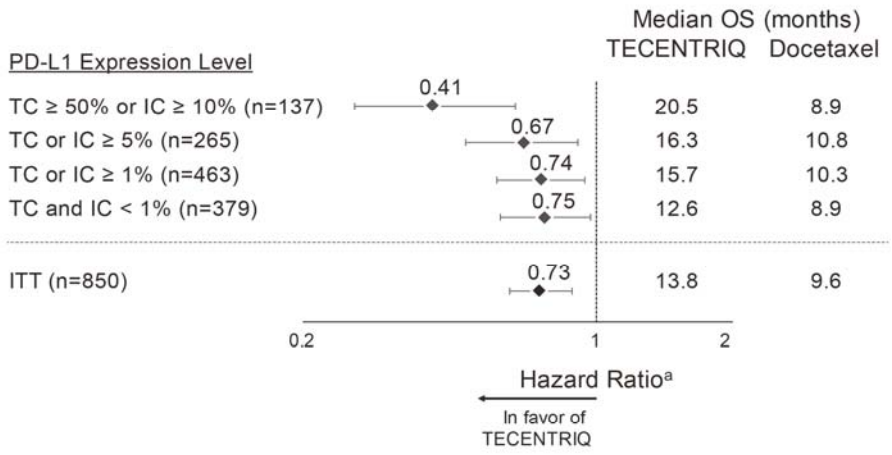

[a]Stratified HR for ITT and TC or IC ≥ 1%. Unstratified HR for other subgroups

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8.2 NMA excluded studies

1st line

Trial name	Treatment arms	Primary data source(s)	Reason
Adamo, 2005	Cisplatin + Gemcitabine	Adamo et al. (2005)	Population not cisplatin ineligible; study not usable as bridging study
Bellmunt, 1997	M-VAC (Cisplatin + Doxorubicin+ Methotrexate + Vinblastine) vs. M-CAVI	Bellmunt et al. (1997)	Population not cisplatin ineligible; study not usable as bridging study
Culine, 2011	Gemcitabine + Oxaliplatin vs. Gemcitabine	Culine et al. (2011)	Conector not of interest
ISRCTN88259320	Carboplatin + Gemcitabine	Xu et al. (2007)	Population not cisplatin ineligible; study not usable as bridging study
NCT00022191	Cisplatin + Gemcitabine + Paclitaxel vs. Cisplatin + Gemcitabine	Bellmunt et al. (2012)	Population not cisplatin ineligible; study not usable as bridging study
Winquist, 2004	Cisplatin + Gemcitabine	Winquist et al. (2004)	Population not cisplatin ineligible; study not usable as bridging study
NCT02108652 (IMvigor210)	Atezolizumab	Balar et al. (2016a)	Atezolizumab study

2nd line

Trial name	Treatment arms	Primary data source(s)	Reason
AUO trial AB 20/99 (Phase 2)	Gemcitabine + Paclitaxel (Three Weekly) vs. Gemcitabine + Paclitaxel (Two Weekly)	Albers et al. (2002b) Fechner et al. (2006)	No KM curve, no predictors. Phase 3 is included
JASiMA	Vinflunine (Maintenance)	De Wit et al. (2015)	No KM curve, no predictors
Meluch, 2001	Gemcitabine + Paclitaxel	Meluch et al. (2001)	Poor data (no predictors)
Naiki, 2016	Gemcitabine + Paclitaxel	Naiki et al. (2016) lida et al. (2016a)	poor reporting and data inconsistency
NCT00479089	Docetaxel + Gefitinib vs. Docetaxel	M.D. Anderson Cancer Center (2015)	No KM curve
NCT00949455	Paclitaxel Vs. Pazopanib	Powles et al. (2016)	No KM curve
NCT01529411	Vinflunine (Maintenance) + BSC Vs. BSC	Bellmunt et al. (2015) Font et al. (2016) Garcia Donas Jiménez et al. (2015)	No KM curve
NCT01848834	Pembrolizumab	Gupta et al. (2015) O'Donnell et al. (2015)	Subpopulation pdl-1
NCT02108652 (Cohort 2)	Atezolizumab	NCT02108652 (Cohort 2) Rosenberg et al. (2015), Rosenberg et al. (2016b) Rosenberg, Petrylak, 2015 [59], Rosenberg, Hoffman-Censits, 2016 [60]	Atezolizumab study

8.3 Quality assessment of identified trials

1st line

Ref ID	Author and year [author_year]	Study acronym or NCT number	Was randomisation carried out appropriately?		Was the concealment of treatment allocation adequate?		Were the groups similar at the outset of the study in terms of prognostic factors?		Were the care providers, participants and outcome assessors blind to treatment allocation?		Were there any unexpected imbalances in drop-outs between groups?		Is there any evidence to suggest that the authors measured more outcomes than they reported?		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
			Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification
3939	Bamias, 2007	NR	N/A	This was a single arm study	N/A	This was a single arm study	N/A	This was a single arm study	high risk	This was a single arm study	No	drop-outs were accounted for	No	There is no evidence that would suggest that authors measured more outcomes than they reported.	No	There is no evidence that would suggest that authors measured more outcomes than they reported.
8728, 451, 631	De Santis 2009, De Santis 2010, De Santis, 2012	EORTC Study 30986; NCT00014274	Not clear	Patients were centrally randomly assigned by the EORTC Headquarters to receive either gemcitabine/carboplatin (GC) or M-CAVI, using the minimization technique with stratification for PS, renal function (GFR), and institution. Generation of randomization sequence not described.	No	This was an open-label trial.	Yes	Patient characteristics were generally well balanced between the arms. There was a slight imbalance in the distribution of liver and visceral metastases.	No	Care providers, participants and outcome assessors were not blinded.	no	There were not unexpected imbalances in drop-outs.	No	There is no evidence that would suggest that authors measured more outcomes than they reported.	Yes	Analysis were carried out according to intent-to-treat.

2nd line

Ref ID	Author and year [author_year]	Study acronym or NCT number	Was randomisation carried out appropriately?		Was the concealment of treatment allocation adequate?		Were the groups similar at the outset of the study in terms of prognostic factors?		Were the care providers, participants and outcome assessors blind to treatment allocation?		Were there any unexpected imbalances in drop-outs between groups?		Is there any evidence to suggest that the authors measured more outcomes than they reported?		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
			Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification
18009, 18006, 331, 14735, 13984, 15093, 18	Bellmunt: 2008, 2009,2013; Culine, 2010; Fougeray, 2012; von der Masse, 2008; EMA, 2009	NCT00315237	Not clear	2:1 allocation; Random assignment was stratified by study site and by refractoriness to previous platinum treatment.	No	This was an open-label trial.	Yes	Baseline characteristics and dempgraphics were generally balanced between groups, except for the ECOG status (10% more status 1 patients were assigned to the VFL + BSC arm)	No	Care providers, participants and outcome assessors were not blinded to treatment allocation.	No	There were not unexpected imbalances in drop-outs between groups.	No	There is no evidence that would suggest that authors measured more outcomes than they reported.	Yes	All randomized patients were included in the intent-to-treat population for efficacy analysis. Safety analysis was conducted using a safety set (all patients receiving at least study drug once).
446, 8564, CT281	Choueiri, 2012, Choueri, 2011; Dana-Farber Cancer Institute	NCT00880334	Yes	Patients were randomly assigned 1:1 to vandetanib plus docetaxel or placebo plus docetaxel. Randomized treatment codes were generated by the Dana-Farber Cancer Institute's Quality Assurance Office for Clinical Trials QACT) office.	Yes	Randomized treatment codes were generated by the Dana-Farber Cancer Institute's Quality Assurance Office for Clinical Trials (QACT) office. A computerized random number generator was used to produce permuted locks of treatment codes	No	Differences in population groups stratified according to Hb level was observed	Yes	Masking: Double Blind (Subject, Investigator)	No	all reported	No	There is no evidence that would suggest that authors measured more outcomes than they reported.	not clear	There is no information on ITT anylsis.
7249; 13556	Kim, 2016; Kim, 2013	NCT01711112	N/A	This was a single arm study.	N/A	This was a single arm study.	N/A	This was a single arm study.	high risk	This was a single arm study.	N/A	This was a single arm study.	No	There is no evidence that would suggest that authors measured more outcomes than they reported.	Yes	Analyses were carried out according to intent-to-treat.
462; 14445	Lee, 2012; Lee, 2011	NCT012426126	N/A	This was a single arm study.	N/A	This was a single arm study.	N/A	This was a single arm study.	high risk	This was a single arm study.	N/A	This was a single arm study.	No	There is no evidence that would suggest that authors measured more outcomes than they reported.	Yes	Analyses were carried out according to intent-to-treat.

Ref ID	Author and year [author_year]	Study acronym or NCT number	Was randomisation carried out appropriately?		Was the concealment of treatment allocation adequate?		Were the groups similar at the outset of the study in terms of prognostic factors?		Were the care providers, participants and outcome assessors blind to treatment allocation?		Were there any unexpected imbalances in drop-outs between groups?		Is there any evidence to suggest that the authors measured more outcomes than they reported?		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
			Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification	Yes/no/not clear/N/A	Justification
37; 8107	Noguchi, 2016; Noguchi, 2014	UMIN000003157	Not clear	1:1 random assignment; no further details about the randomization process and generation of the randomization frequence.	Yes	Randomization was performed centrally at the clinical research unit of Kurume University in Kurume, Japan.	No	Patient characteristics were well balanced between the arms.	No	This was an open-label study.	No	There were not unexpected imbalances in drop-outs between groups.	No	There is no evidence that would suggest that authors measured more outcomes than they reported.	Yes	Analyses were carried out according to intent-to-treat.

1st line

Author and year	Study acronym or NCT number	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Bamias, 2007	NR					🟢	🟢	🔴
De Santis 2009, De Santis	EORTC Study 30986; NCT00014274	🟡	🔴	🟢	🔴	🟢	🟢	🟢

Table 98: Quality assessment summary (Critical appraisal NICE)

2nd line

Author and year	Study acronym or NCT number	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
OncoGenex Technologies	2011-002424-41							
Akaza, 2007	NR							
Albers 2002	NR							
Albers, 2008, Albers 2011	AUO trial AB 20/99 (phase 3)							
Bellmunt: 2008, 2009,2013	NCT00315237							
Culine, 2006	NR							
Choueiri, 2012, Choueri, 2	NCT00880334							
Han, 2008	NR							
Ikeda, 2011	NR							
Joly, 2009	GETUG							
Kim, 2016; Kim, 2013	NCT01711112							
Ko, 2010; Ko, 2013; Sridha	NCT00683059							
Kouno, 2007	NR							
Lee, 2012; Lee, 2011	NCT012426126							
Matsumoto, 2007	NR							
McCaffrey, 1997	NR							
Naiki, 2016; Iida, 2016	NR							
Noguchi, 2016; Noguchi, 2	UMIN000003157							
Petrylak, 2015	NCT01282463							
Srinivas, 2005	NR							
Sternberg, 2001	NR							
Suyama, 2009	NR							
Takahashi, 2006	NR							
Vaishampayan, 2005	NR							
Vaughn, 2002	NR							
Vaughn, 2009	NR							
Sharma, 2016	NCT01928394							

Table 99:: Quality assessment summary (Cochrane)

1st line

Ref ID	Author and year	Study acronym or NCT number	Compared interventions [name]	Random sequence generation		Allocation concealment		Blinding of participants and personnel		Blinding of outcome assessment		Incomplete outcome data		Selective reporting		Any other sources of bias	
				Y / N /?	Justification	Y / N /?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification
3939	Bamias, 2007	NR	GEMCITABINE + CARBOPLATIN	N/A	This was a single arm study.	N/A	This was a single arm study.	N/A	This was a single arm study.	Unclear risk of bias	This was a single arm study.	Low risk of bias	There is no evidence that would suggest that authors measured	Low risk of bias	No evidence of selective reporting.	Low risk of bias	There appears to be no other source of bias.

													more outcomes than they reported.				
8728, 451, 631	De Santis 2009, De Santis 2010, De Santis, 2012	EORTC Study 30986	GEMCITABINE + CARBOPLATIN vs METHOTREXATE + CARBOPLATIN + VINBLASTINE	Unclear risk of bias	Patients were centrally randomly assigned by the EORTC Headquarters to receive either gemcitabine/carboplatin (GC) or M-CAVI, using the minimization technique with stratification for PS, renal function (GFR), and institution. Generation of randomization sequence not described	High risk of bias	This was an open label trial.	N/A	This was an open label trial.	High risk of bias	This was an open label trial.	Low risk of bias	There is no evidence that would suggest that authors measured more outcomes than they reported.	Low risk of bias	No evidence of selective reporting.	Low risk of bias	There appears to be no other source of bias.

Table 100: Quality assessment summary (Cochrane)

2nd line

Ref ID	Author and year [author_year]	Study acronym or NCT number	Compared interventions [name]	Random sequence generation		Allocation concealment		Blinding of participants and personnel		Blinding of outcome assessment		Incomplete outcome data		Selective reporting		Any other sources of bias	
				Y / N /?	Justification	Y / N /?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification
18009, 18006, 331, 14735, 13984, 15093	Bellmunt: 2008, 2009, 2013; Culine, 2010; Fougeray, 2012; von der Masse, 2008; EMA, 2009	NCT00315237	VINFLUNINE + BEST SUPPORTIVE CARE	Unclear risk of bias	2:1 allocation; Random assignment was stratified by study site and by refractoriness to previous platinum treatment.	Unclear risk of bias	Method of concealment of treatment allocation was not addressed.	High risk of bias	Care providers and participants were not blinded to treatment allocation.	High risk of bias	Outcome assessors were not blinded.	Low risk of bias	There is no evidence that would suggest that authors measured more outcomes than they reported.	Low risk of bias	No evidence of selective reporting.	Low risk of bias	There appears to be no other source of bias.
446, 8564, CT281	Choueiri, 2012, Choueri, 2011; Dana-Farber Cancer Institute	NCT00880334	VANDETANIB + DOCETAXEL vs DOCETAXEL + PLACEBO	Low risk of bias	Patients were randomly assigned 1:1 to vandetanib plus docetaxel or placebo plus docetaxel. Randomized treatment codes were generated by the Dana-Farber Cancer Institute's Quality Assurance Office for Clinical Trials (QACT) office.	Low risk of bias	computerized random number generator was used to produce permuted blocks of treatment codes. The number of possible permutations depended on the block size and number of individual treatments and was undisclosed to investigators.	Unclear risk of bias	Blinding not described	Unclear risk of bias	Blinding not described	Low risk of bias	All outcomes are well described	Unclear risk of bias	No evidence of selective reporting.	Unclear risk of bias	There appears to be no other source of bias.

Ref ID	Author and year [author_year]	Study acronym or NCT number	Compared interventions [name]	Random sequence generation		Allocation concealment		Blinding of participants and personnel		Blinding of outcome assessment		Incomplete outcome data		Selective reporting		Any other sources of bias	
				Y / N /?	Justification	Y / N /?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification	Y / N / ?	Justification
							A string of permuted blocks was generated for each stratification factor combination, and treatment assignments were consumed sequentially										
7249; 13556	Kim, 2016; Kim, 2013	NCT01711112	DOCETAXEL	N/A	This was a single arm study.	N/A	This was a single arm study.	N/A	This was a single arm study. Participants and personnel were not blinded.	High risk of bias	Outcome assessors were not blinded.	Low risk of bias	There is no evidence that would suggest that authors measured more outcomes than they reported.	Low risk of bias	No evidence of selective reporting.	Low risk of bias	There appears to be no other source of bias.
462; 14445	Lee, 2012; Lee, 2011	NCT012426126	PACLITAXEL (POLYMERIC MICELLE FORMULATION)	N/A	This was a single arm study.	N/A	This was a single arm study.	N/A	This was a single arm study. Participants and personnel were not blinded.	High risk of bias	Outcome assessors were not blinded.	Low risk of bias	There is no evidence that would suggest that authors measured more outcomes than they reported.	Low risk of bias	No evidence of selective reporting.	Low risk of bias	There appears to be no other source of bias.
37; 8107	Noguchi, 2016; Noguchi, 2014	UMIN000003157	PERSONALIZED PEPTIDE VACCINATION + BEST SUPPORTIVE CARE	Unclear risk of bias	1:1 random assignment; no further details about the randomization process and generation of the randomization frequence.	Low risk of bias	Randomization was performed centrally at the clinical research unit of Kurume University in Kurume, Japan.	N/A	This was a single arm study. Participants and personnel were not blinded.	High risk of bias	Outcome assessors were not blinded.	Low risk of bias	There is no evidence that would suggest that authors measured more outcomes than they reported.	Low risk of bias	No evidence of selective reporting.	Low risk of bias	There appears to be no other source of bias.

Table 101: Quality assessment summary (Cochrane)

1st line

Author and year	Study acronym or NCT number	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Any other sources of bias
Bamias, 2007	NR							
De Santis 2009, De Santis 2010, De Santis, 2012	EORTC Study 30986							

Table 102: Quality assessment summary (Cochrane)2nd line

Author and year	Study acronym or NCT number	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Any other sources of bias
OncoGenex Technologies, Inc. 2011	2011-002424-41							
Akaza, 2007	NR							
Albers 2002	NR							
Albers, 2008, Albers 2011	AUO trial AB 20/99, phase 3							
Bellmunt. 2008, 2009, 2013; Culine, 2010; Fougeray, 2012; Gnoudin, 2012; Gnoudin, 2011; Dana-Farber Cancer Institute	NCT00315237							
	NCT00880334							
Culine, 2006	NR							
Han, 2008	NR							
Ikeda, 2011	NR							
Joly, 2009	GETUG							
Kim, 2016; Kim, 2013	NCT01711112							
Ko, 2010; Ko, 2013; Sridhar, 2009, 2010, 2011	NCT00683059							
Kouno, 2007	NR							
Lee, 2012; Lee, 2011	NCT012426126							
Matsumoto, 2007	NR							

Author and year	Study acronym or NCT number	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Any other sources of bias
McCaffrey, 1997	NR							
Naiki, 2016	NR							
Noguchi, 2016; Noguchi, 2014	UMIN000003157							
Petrylak, 2015	NCT01282463							
Srinivas, 2005	NR							
Sternberg, 2001	NR							
Suyama, 2009	NR							
Takahashi, 2006	NR							
Vaishampayan, 2005	NR							
Vaughn, 2002	NR							
Vaughn, 2009	NR							
Sharma, 2016	NCT01928394							

Table 103: Quality assessment summary (Single arm studies)

Source	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the length of follow-up adequate?	Were the statistical methods well-described?	Were the results well-described?	Count (x from 8 possible)
Bamias, 2007	yes	yes	no	yes	yes	yes	yes	yes	7
Akaza, 2007	yes	yes	no	yes	yes	yes	no	yes	6
Albers, 2002	yes	no	NR	yes	yes	yes	yes	yes	6
Culine, 2006	yes	yes	no	yes	yes	yes	yes	yes	7
Han, 2008	yes	yes	no	yes	yes	yes	yes	yes	7
Ikeda, 2011	yes	yes	no	yes	yes	yes	yes	yes	7
Joly, 2009	yes	yes	no	yes	yes	yes	yes	yes	7
NCT01711112 (Kim, 2013; Kim, 2016)	yes	yes	no	yes	yes	yes	yes	yes	7
NCT00683059 Ko, 2010	yes	yes	no	yes	yes	yes	yes	yes	7
Kouno, 2007	yes	yes	no	yes	yes	yes	yes	yes	7
NCT01426126 Lee, 2011 Lee, 2012	yes	yes	no	yes	yes	yes	yes	yes	7
Matsumoto, 2007	yes	yes	yes	yes	yes	yes	yes	yes	8
McCaffrey, 1997	yes	yes	no	yes	yes	yes	yes	yes	7
Suyama, 2009	yes	yes	no	yes	yes	yes	yes	yes	7
NCT01928394 Sharma, 2016	yes	no	CD	yes	yes	yes	no	yes	5
Srinivas, 2005	yes	yes	no	yes	yes	yes	no	yes	6
Sternberg, 2001	yes	yes	no	yes	yes	yes	yes	yes	7
Takahashi, 2006	yes	yes	no	yes	yes	yes	yes	yes	7
Vaishampayan, 2005	yes	yes	no	yes	yes	yes	yes	yes	7
Vaughn, 2002	yes	yes	no	yes	yes	yes	yes	yes	7
Vaughn, 2009	yes	yes	no	yes	yes	yes	yes	yes	7
Atezo study									
IMvigor210 study Balar, 2016	yes	no	CD	yes	yes	yes	no	yes	5
Rosenberg, 2016	yes	yes	no	yes	yes	yes	yes	yes	7
IMvigor210, cohort 1 and 2 CSR STUDY IMVIGOR 210 (GO29293)	yes	yes	no	yes	yes	yes	yes	yes	7

8.4 Binary outcomes: Prediction model and NMA methodology

Prediction model methodology: Binary outcomes

For binary endpoints, predictions from each of the estimated models for each OOB patient were produced. Model selection was based on the best predictive performance (largest concordance-index) for the prediction of the outcome of atezolizumab, in the single arm trials of interest. (Royston, 2009)

From the bootstrap estimates generated, there were 1,000 predicted outcomes for each trial. An average of these was used to obtain the predicted outcomes along with a variance and 95%CI for each trial to be used in the NMA. For the binary endpoints, this led to a mean and variance for the predicted response probability. These were transformed into a predicted sample size n, and predicted number of events r by approximating a beta density. The resulting pairs (n, r) – one for each competitor trial of interest – were then used in the NMA.

NMA methodology: Binary outcomes

For objective response rate and 12-months milestone OS data, standard RE and FE NMA models were fit. We used a binomial likelihood for the outcomes in each trial, $r_{jk} \sim binomial \quad (p_{jk}, n_{jk})$ where *r* is the observed number of cases, *n* is the sample size, and *p* is the underlying probability in study *j* for treatment *k*. A logit link function, $logit \ (p_{jk})$, was used to transform it to the log odds scale to use with the NMA models.

The RE model was selected, with the base case informative prior specified in the table below:

Table 104: Priors for between study heterogeneity

Endpoint	Base case: Informative prior derived from Turner (2015)	Weakly informative prior	Vague prior
ORR	τ2 ~ Log-normal (-2.94, 1.792) Source in Turner (2015) Table IV: Internal/external structure related outcomes,	τ2 ~ Log-normal (-2.94, 2.22) Log-normal with same median as base case but 2x larger upper 95% quantile.	τ ~uniform (0,2)

	pharmacological vs pharmacological		
OS: 12-months milestone survival	τ2 ~ Log-normal (-4.18, 1.412) Source in Turner (2015) Table IV: All-cause mortality, pharmacological vs pharmacological	τ2 ~ Log-normal (-4.18, 1.82) Log-normal with same median as base case but 2x larger upper 95% quantile	τ ~uniform (0,2)

Rationale for this are:

- FE models assume total absence of between-trial heterogeneity, which is not supported by the available data.
- Evidence base is limited to a star shaped network, with few studies for each comparison (often only a single trial). Therefore, between-trial heterogeneity could not be estimated from the available studies alone. The informative priors described above are based on empirical evidence and are therefore appropriate for application in the analysis.

8.5 PFS NMA Results

Progression-free survival: Base-case results (1L)

First line PFS data for the comparator of interest were only available from one trial, Bamias (2007). The trial reported baseline prognostic factors age, sex, and ECOG, but not liver metastases. Therefore, only a smaller number of prediction models could be investigated. Including interaction terms did not improve the predictive performance. Therefore, model m1, which contained the three main prognostic factors (proportion above 65, male, proportion with ECOG>=1), was selected.

Overall, predictive performance was poor in this case with a concordance index of 0.56. According to Royston et al. the c-index for a prognostic model is typically between 0.6 and 0.85. Additionally, the trial reported in Bamias (2007) was relatively small with n=34 patients enrolled.

Table 105 Parameter estimates and performance of competing models

Model	m0a	m0b	m1	m2	m3
Parameter					
p65	-0.06 (-0.63, 0.51)		-0.06 (-0.65, 0.51)	-0.29 (-1.42, 0.58)	-0.05 (-0.64, 0.51)
male	0.21 (-0.4, 0.83)		0.23 (-0.4, 0.91)	0.24 (-0.39, 0.94)	-0.17 (-1.18, 0.72)
ecog1		0.11 (-0.33, 0.51)	0.14 (-0.31, 0.57)	-0.18 (-1.36, 0.96)	-0.36 (-1.65, 0.87)
ecog1.p65				0.38 (-0.83, 1.65)	
ecog1.male					0.59 (-0.82, 1.9)
errorsum[1]	2.31 (0.96, 4.91)	2.3 (0.98, 5.01)	2.33 (0.98, 5.19)	2.35 (1.04, 5.23)	2.34 (0.97, 4.96)
RSS[2]	0.26 (0.05, 0.91)	0.26 (0.05, 0.95)	0.27 (0.05, 0.95)	0.27 (0.05, 0.96)	0.27 (0.04, 0.95)
c.index[3]	0.53 (0.49, 0.58)	0.53 (0.46, 0.6)	0.56 (0.49, 0.62)	0.58 (0.5, 0.64)	0.57 (0.5, 0.63)

[1]Sum of absolute differences between observed and predicted.

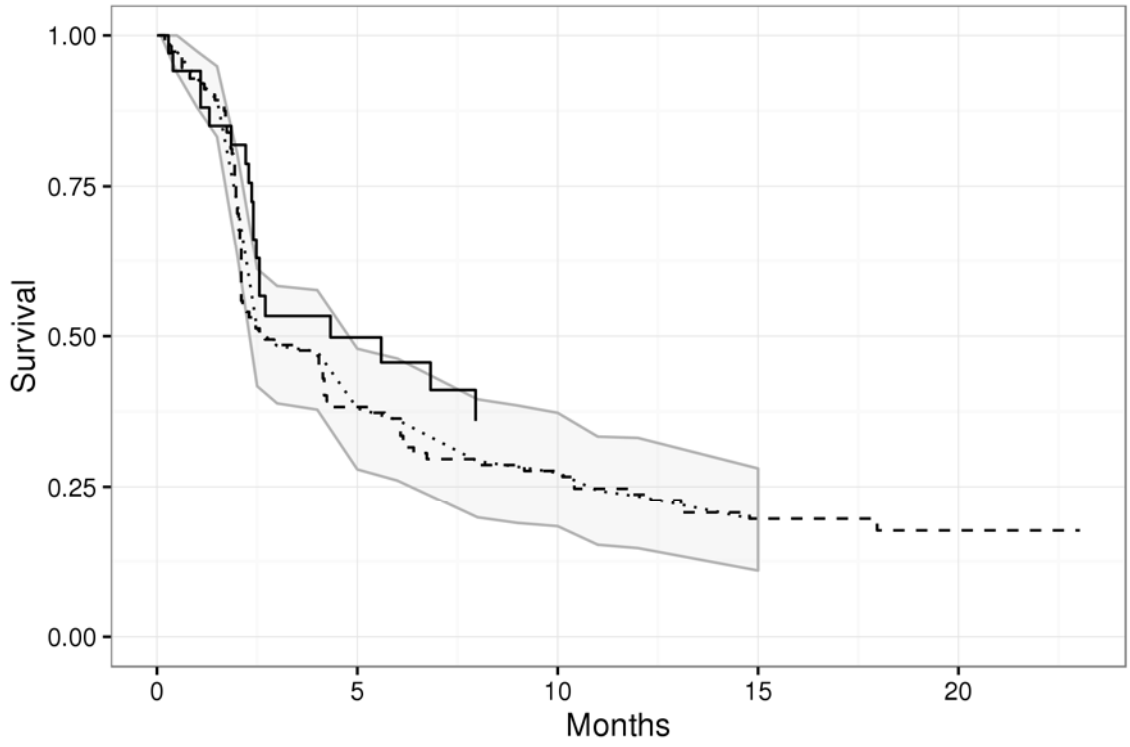
[2]Sum of squared differences between observed and predicted.

[3]Concordance index.

Using this model, atezolizumab PFS KMs were predicted for the Bamias study (Figure 50 below). The observed atezolizumab curve taken from cohort 1 of the IMvigor 210 study is included for comparison.

Incorporation into the NMA was not necessary, as only one study was available with PFS data.

Figure 50 : Observed gemcitabine + carboplatin (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Bamias(2007)



Progression-free survival: Base-case results (2L)

Including interaction terms or the number of prior chemotherapies did not improve the predictive performance. Therefore, model m1 which contained the four main prognostic factors (proportion above 65, male, proportion with ECOG ≥1, liver metastasis) was selected (see Table 106 below).

Table 106: Parameter estimates and performance of competing models– PFS 2L

Model	m0a	m0b	m1	m2	m3	m4	m5	m6
Parameter								
p65	0.01 (-0.24, 0.26)		0 (-0.25, 0.25)	0.03 (-0.22, 0.27)	0.06 (-0.25, 0.38)	0.02 (-0.24, 0.27)	-0.07 (-0.47, 0.34)	0.01 (-0.23, 0.27)
male	-0.15 (-0.44, 0.14)		-0.14 (-0.43, 0.16)	-0.14 (-0.44, 0.17)	-0.14 (-0.44, 0.18)	-0.04 (-0.4, 0.29)	-0.14 (-0.45, 0.16)	-0.41 (-0.95, 0.14)
ecog1		0.47 (0.23, 0.75)	0.47 (0.22, 0.75)	0.48 (0.24, 0.76)	0.49 (0.23, 0.76)	0.5 (0.25, 0.78)	0.4 (0.02, 0.82)	0.18 (-0.38, 0.8)
liverMet		0.39 (0.15, 0.64)	0.4 (0.15, 0.67)	0.42 (0.16, 0.68)	0.49 (0.12, 0.87)	0.66 (0.07, 1.3)	0.42 (0.16, 0.69)	0.41 (0.15, 0.67)
priorChem2				-0.23 (-0.48, 0.02)	-0.23 (-0.48, 0.02)	-0.21 (-0.47, 0.04)	-0.23 (-0.48, 0.02)	-0.24 (-0.5, 0.01)
liverMet.p65					-0.11 (-0.62, 0.39)			
liverMet.male						-0.31 (-0.99, 0.36)		
ecog1.p65							0.15 (-0.37, 0.64)	
ecog1.male								0.4 (-0.29, 1.06)
errorsum1	2.62 (1.19, 5.42)	2.56 (1.13, 5.18)	2.57 (1.12, 5.19)	2.57 (1.14, 5.24)	2.58 (1.16, 5.25)	2.58 (1.14, 5.22)	2.57 (1.14, 5.19)	2.57 (1.16, 5.35)
RSS2	0.16 (0.03, 0.54)	0.15 (0.03, 0.51)	0.15 (0.03, 0.51)	0.16 (0.03, 0.52)	0.16 (0.03, 0.53)	0.16 (0.03, 0.51)	0.16 (0.03, 0.52)	0.16 (0.03, 0.53)
c.index3	0.52 (0.5, 0.55)	0.59 (0.55, 0.62)	0.6 (0.56, 0.63)	0.6 (0.57, 0.64)	0.6 (0.57, 0.64)	0.61 (0.57, 0.64)	0.6 (0.56, 0.64)	0.61 (0.57, 0.64)

1Sum of absolute differences between observed and predicted.
2Sum of squared differences between observed and predicted.
3Concordance index.

Using this model, atezolizumab PFS KMs were predicted for each comparator study. These curves are presented below in Figure 51, Figure 52, Figure 53, Figure 54, Figure 55, Figure 56, Figure 57, Figure 58, and Figure 59 with observed atezolizumab curve taken from cohort 2 of the IMvigor 210 study included for comparison.

Figure 51: Observed bsc (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Noguchi(2016) – PF

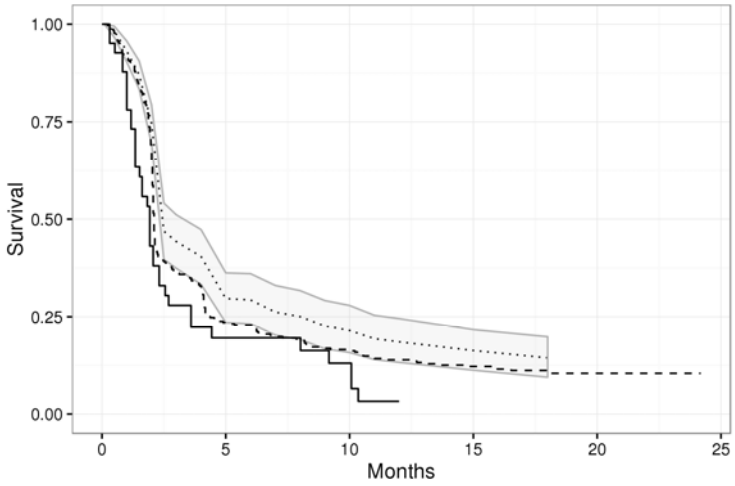


Figure 52 Observed nab-paclitaxel (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Ko(2013) - PFS

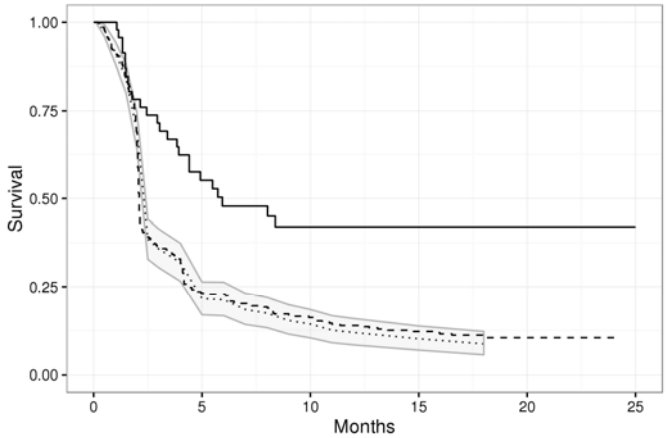


Figure 53 Observed bsc (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Bellmunt(2013/2009) - PFS

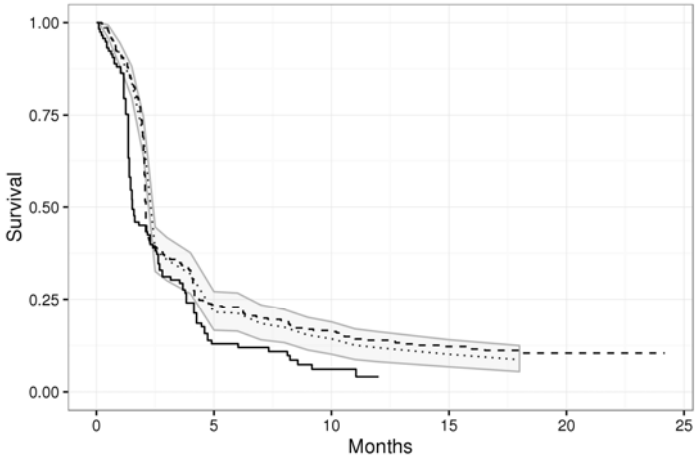


Figure 54 Observed vinflunine (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Bellmunt(2013/2009) - PFS

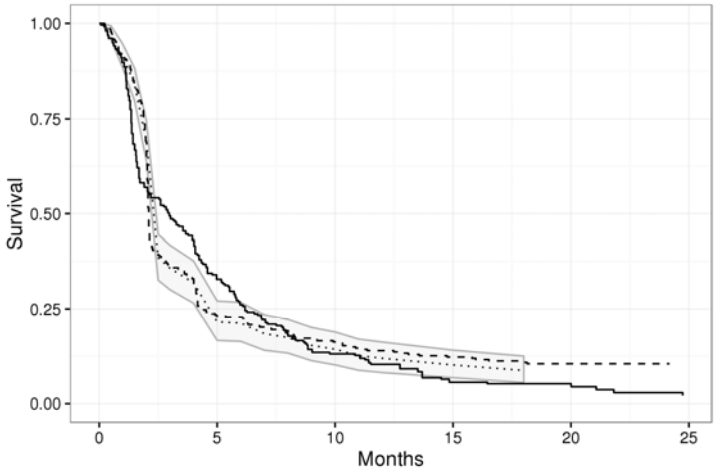


Figure 55 Observed docetaxel (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Choueiri(2012) - PFS

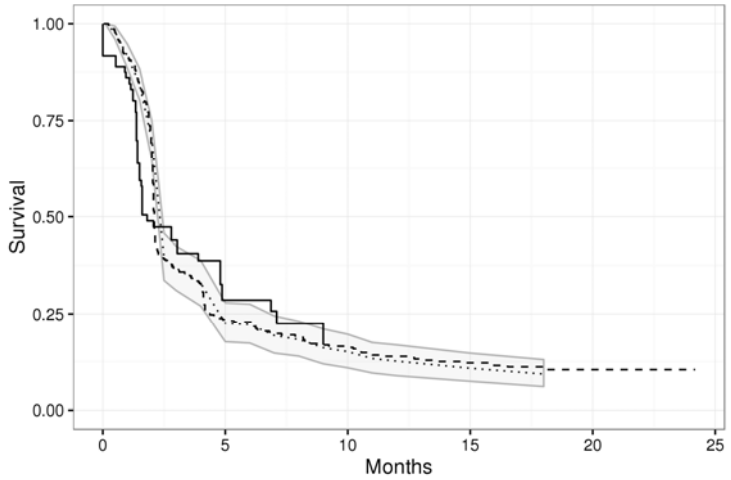


Figure 56 Observed paclitaxel (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Lee(2012) - PFS

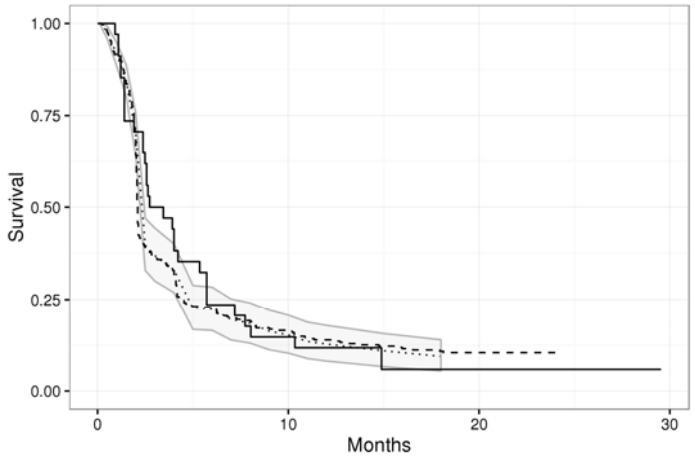


Figure 57 Observed paclitaxel+carboplatin (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Kouno(2007) - PFS

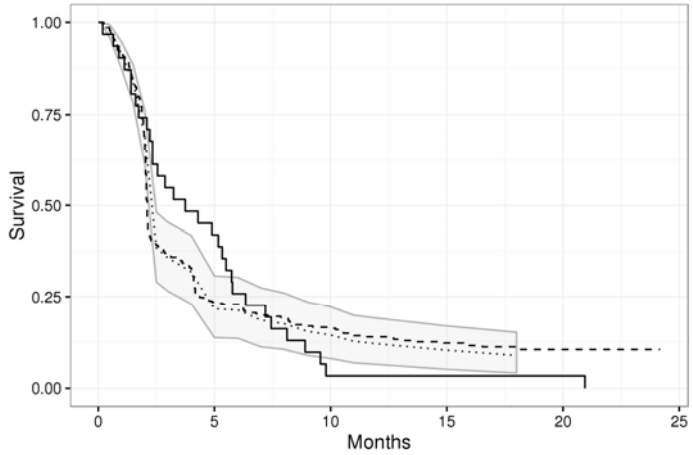


Figure 58 Observed docetaxel (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Kim(2016) - PFS

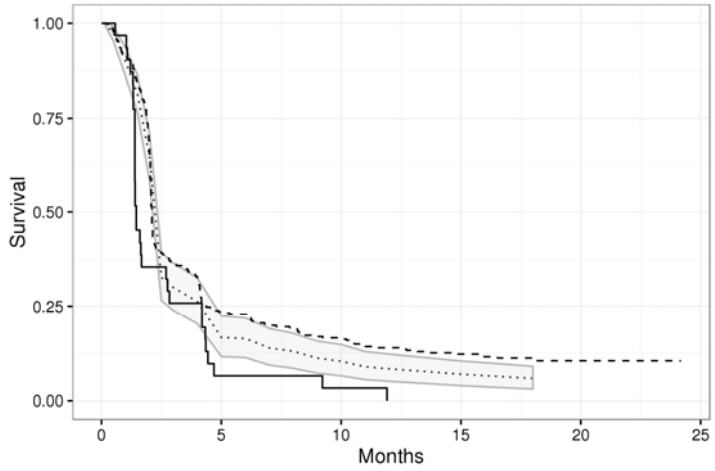
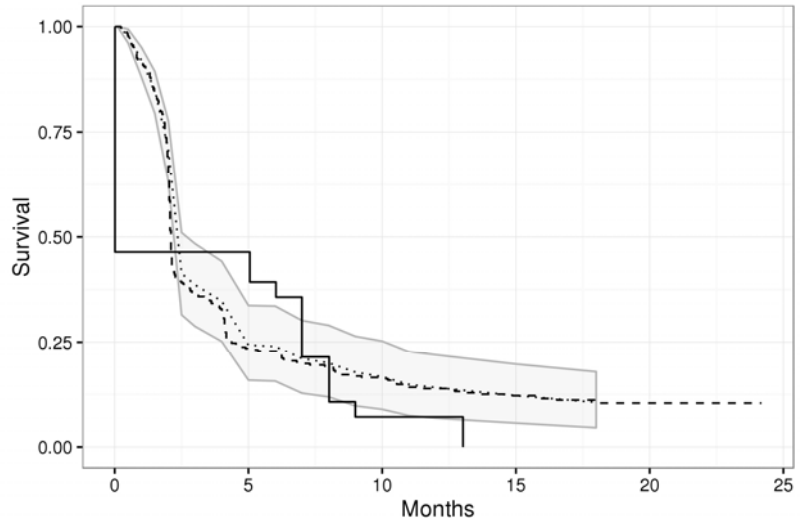


Figure 59 Observed gemcitabine (solid line), predicted Atezolizumab (dotted) and observed Atezolizumab (dashed) survival curves from Albers(2002) - PFS



For incorporation of these results into the NMA, the FE model was first fit for the fractional polynomial (as described above)

Table 107: Overview and model comparison under FE fractional polynomial model for PFS (2L)

Model	P	Comment	DIC	pD	mean Dev	Absolute posterior correlations between effect estimates in the fractional polynomial	
						Min.	Max.
Zero order fractional polynomial	NULL	Exponential model, proportional hazards	2723.8	15	2708.7	--	--
First order fractional polynomial	P1=0	Weibull model	2540.3	29.8	2510.6	0.60	0.95
First order fractional polynomial	P1=1	Gompertz model	2164.8	29.8	2135	0.70	0.85
Second order fractional polynomial	P1=0, P2=0	NULL	NaN	NaN	1622.4	0.24	0.99
Second order fractional polynomial	P1=0, P2=1	NULL	NaN	NaN	1600	0.03	0.99
Second order fractional polynomial	P1=1, P2=1	NULL	NaN	NaN	1874.4	0.88	0.99

NaN not a number

Table 107 presents the model fit statistics (DIC) for the FE model. Considering the lowest DIC, the Second order fractional polynomial model with P1=0 and P2=0 provided the best data fit. However, following similar rationales as for OS and given convergence limitations observed for second order fractional polynomial models, the Gompertz model was determined most appropriate for the primary analysis and base case. The results of other models are considered as a sensitivity analysis.

Hazard ratio estimates for the comparators of interest are presented in Figure 60

Figure 60 Hazard ratio estimates for atezolizumab vs other treatments for PFS under FE fractional polynomial model.

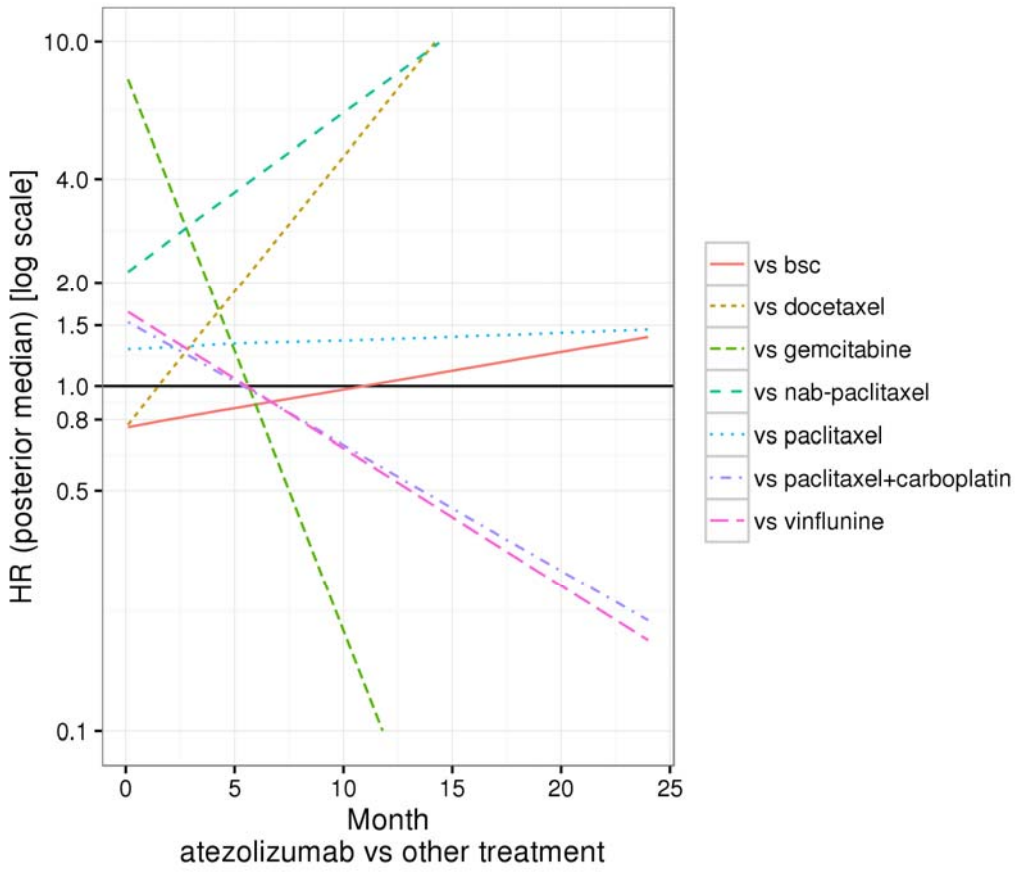


Table 108 provides contrast estimates of the intercept and slope parameters of the log HR function, with respect to comparators of interest vs atezolizumab (the network reference), as well as the posterior correlation between the intercept and slope parameters.

Table 108: Contrast estimates and posterior correlations for PFS under FE fractional polynomial model for comparators of interest (2L)

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation between intercept and slope
BSC	0.276	-0.032	0.580	-0.025	-0.116	0.056	-0.743
paclitaxel	-0.245	-0.803	0.285	-0.005	-0.127	0.094	-0.705
docetaxel	0.277	-0.161	0.706	-0.181	-0.363	-0.025	-0.796

8.6 NMA programming language

Fractional polynomial models

FIXED EFFECTS, ZERO ORDER MODEL

```
# Fractional polynomial, 0-order, fixed effect model
# Index treatment in network: response derived via predictive modeling approach
#                             therefore data from this arm as log-hazard (and SE)
#                             modeled with normal likelihood
# ------------------------------------------------------------------------------
# Code adapted from Redwood (from NMA of trts in 2L UBC project)
# May 2016

model{

## Sampling model
for (i in 1:Npred){
  # likelihood: data points from prediction model (log-hazards)
  PREC_LOGH[i] <- 1/(SE_logh[i]*SE_logh[i])
  logh[i] ~ dnorm(LOGH[i], PREC_LOGH[i])

  # fractional polynomial
  LOGH[i] <- Beta[s[i], a[i]]
  }


for (i in (Npred+1):N){
  # likelihood: digitized KM curves
  r[i] ~ dbin(p[i], z[i])
  p[i] <- 1 - exp(-h[i] * dt[i])  # cumulative hazard over interval [t,t+dt] expressed as
deaths per person-month

  # fractional polynomial
  log(h[i]) <- Beta[s[i], a[i]]
  }


## Arm level parameters = study effect + trt effect (consistency eq)
for (l in 1:Ns){
  for (ll in 1:na[l]){
    Beta[l, ll] <- mu[l] + d[t[l, ll]] - d[t[l, 1]]
    }
  }

## Priors
for (j in 1:Ns){
  mu[j] ~ dnorm(mean, prec)
  }

d[1] <- 0
for (k in 2:Ntx){
  d[k] ~ dnorm(mean, prec)
  }


} # end of model
```

FIXED EFFECTS, FIRST ORDER MODEL

```
# Fractional polynomial, 1st order, fixed effect model
# Index treatment in network: response derived via predictive modeling approach
#                             therefore data from this arm as log-hazard (and SE)
#                             modeled with normal likelihood
# ------------------------------------------------------------------------------
# Code adapted from Redwood (from NMA of trts in 2L UBC project)
# May 2016

model{

## Sampling model
for (i in 1:N){
  timen[i] <- (time[i])    # time is expressed in months
  timen1[i] <- (equals(P1,0) * log(timen[i]) + (1-equals(P1,0)) * pow(timen[i],P1)   )
```

```
  }

for (i in 1:Npred){
  # likelihood: data points from prediction model (log-hazards)
  PREC_LOGH[i] <- 1/(SE_logh[i]*SE_logh[i])
  logh[i] ~ dnorm(LOGH[i], PREC_LOGH[i])

  # fractional polynomial
  LOGH[i] <- Beta[s[i], a[i], 1] + Beta[s[i], a[i], 2] * timen1[i]
  }


for (i in (Npred+1):N){
  # likelihood: digitized KM curves
  r[i] ~ dbin(p[i], z[i])
  p[i] <- 1 - exp(-h[i] * dt[i])  # cumulative hazard over interval [t,t+dt] expressed as
deaths per person-month

  # fractional polynomial
  log(h[i]) <- Beta[s[i], a[i], 1] + Beta[s[i], a[i], 2] * timen1[i]
  }


## Arm level parameters = study effect + trt effect (consistency eq)
for (l in 1:Ns){
  for (ll in 1:na[l]){
    Beta[l, ll, 1] <- mu[l, 1] + d[t[l, ll], 1] - d[t[l, 1], 1]
    Beta[l, ll, 2] <- mu[l, 2] + d[t[l, ll], 2] - d[t[l, 1], 2]
    }
  }

## Priors
for (j in 1:Ns){
  mu[j, 1:2] ~ dmnorm(mean[1:2], prec2[,])
  }

d[1, 1] <- 0
d[1, 2] <- 0
for (k in 2:Ntx){
  d[k, 1:2] ~ dmnorm(mean[1:2], prec2[,])
  }

       } # end of model
```

FIXED EFFECTS, SECOND ORDER MODEL

```
# Fractional polynomial, 2nd order, fixed effect model
# Index treatment in network: response derived via predictive modeling approach
#                             therefore data from this arm as log-hazard (and SE)
#                             modeled with normal likelihood
# ------------------------------------------------------------------------------
# Code adapted from Redwood (from NMA of trts in 2L UBC project)
# May 2016

model{

## Sampling model
for (i in 1:N){
  timen[i] <- (time[i])    # time is expressed in months
  timen1[i] <- (equals(P1,0) * log(timen[i]) + (1-equals(P1,0)) * pow(timen[i],P1)   )
  timen2[i] <- (  (1-equals(P2,P1)) * (   equals(P2,0) * log(timen[i]) + (1-equals(P2,0)) *
pow(timen[i],P2)  ) +
                equals(P2,P1) * (   equals(P2,0) * log(timen[i])*log(timen[i])   +   (1-
equals(P2,0)) * pow(timen[i],P2) * log(timen[i]) ) )
  }

for (i in 1:Npred){
  # likelihood: data points from prediction model (log-hazards)
  PREC_LOGH[i] <- 1/(SE_logh[i]*SE_logh[i])
  logh[i] ~ dnorm(LOGH[i], PREC_LOGH[i])

  # fractional polynomial
```

```
  LOGH[i] <- Beta[s[i], a[i], 1] + Beta[s[i], a[i], 2] * timen1[i] + Beta[s[i], a[i], 3] *
timen2[i]
  }


for (i in (Npred+1):N){
  # likelihood: digitized KM curves
  r[i] ~ dbin(p[i], z[i])
  p[i] <- 1 - exp(-h[i] * dt[i])  # cumulative hazard over interval [t,t+dt] expressed as
deaths per person-month

  # fractional polynomial
  log(h[i]) <- Beta[s[i], a[i], 1] + Beta[s[i], a[i], 2] * timen1[i] + Beta[s[i], a[i], 3] *
timen2[i]
  }


## Arm level parameters = study effect + trt effect (consistency eq)
for (l in 1:Ns){
  for (ll in 1:na[l]){
    Beta[l, ll, 1] <- mu[l, 1] + d[t[l, ll], 1] - d[t[l, 1], 1]
    Beta[l, ll, 2] <- mu[l, 2] + d[t[l, ll], 2] - d[t[l, 1], 2]
    Beta[l, ll, 3] <- mu[l, 3] + d[t[l, ll], 3] - d[t[l, 1], 3]
    }
  }

## Priors
for (j in 1:Ns){
  mu[j, 1:3] ~ dmnorm(mean[1:3], prec2[,])
  }

d[1, 1] <- 0
d[1, 2] <- 0
d[1, 3] <- 0
for (k in 2:Ntx){
  d[k, 1:3] ~ dmnorm(mean[1:3], prec2[,])
  }


} # end of model
```

RANDOM EFFECTS, FIRST ORDER MODEL (RANDOM INTERCEPT)

```
# Fractional polynomial, 1st order, RE model: a RE is put only on the scale parameter
#                                             i.e. on the intercept in the frac poly
# Index treatment in network: response derived via predictive modeling approach
#                             therefore data from this arm as log-hazard (and SE)
#                             modeled with normal likelihood
# ------------------------------------------------------------------------------
# Code adapted from Redwood (from NMA of trts in 2L UBC project)
# May 2016

model{

## Sampling model
for (i in 1:N){
  timen[i] <- (time[i])    # time is expressed in months
  timen1[i] <- (equals(P1,0) * log(timen[i]) + (1-equals(P1,0)) * pow(timen[i],P1)   )
  }

for (i in 1:Npred){
  # likelihood: data points from prediction model (log-hazards)
  PREC_LOGH[i] <- 1/(SE_logh[i]*SE_logh[i])
  logh[i] ~ dnorm(LOGH[i], PREC_LOGH[i])

  # fractional polynomial
  LOGH[i] <- Beta[s[i], a[i], 1] + Beta[s[i], a[i], 2] * timen1[i]
  }


for (i in (Npred+1):N){
  # likelihood: digitized KM curves
  r[i] ~ dbin(p[i], z[i])
```

```
  p[i] <- 1 - exp(-h[i] * dt[i])  # cumulative hazard over interval [t,t+dt] expressed as
deaths per person-month

  # fractional polynomial
  log(h[i]) <- Beta[s[i], a[i], 1] + Beta[s[i], a[i], 2] * timen1[i]
  }


## Arm level parameters = study effect + trt effect (RE model, consistency eq for pop pars)
for (l in 1:Ns){
  w[l, 1] <- 0
  delta[l, 1] <- 0

  for (ll in 1:na[l]){
    Beta[l, ll, 1] <- mu[l, 1] + delta[l, ll]
    Beta[l, ll, 2] <- mu[l, 2] + d[t[l, ll], 2] - d[t[l, 1], 2]
    }

  for (ll in 2:na[l]){
    delta[l, ll] ~ dnorm(md[l, ll], re.prec.d[l, ll])
    md[l, ll] <- d[t[l, ll], 1] - d[t[l, 1], 1] + sw[l, ll]
    w[l, ll] <- (delta[l, ll] - d[t[l, ll], 1] + d[t[l, 1], 1])
    sw[l, ll] <- sum(w[l, 1:(ll - 1)]) / (ll - 1)
    re.prec.d[l, ll] <- re.prec * 2 * (ll - 1) / ll
    }

  }


## Priors
for (j in 1:Ns){
  mu[j, 1:2] ~ dmnorm(mean[1:2], prec2[,])
  }

d[1, 1] <- 0
d[1, 2] <- 0
for (k in 2:Ntx){
  d[k, 1:2] ~ dmnorm(mean[1:2], prec2[,])
  }

#sd ~ dunif(0, 2)
#re.prec <- 1 / (sd * sd)
sd2 ~ dlnorm(ln.prior.mn, ln.prior.prec)
re.prec <- 1/sd2
sd <- sqrt(sd2)


} # end of model
```

8.7 Systematic literature searches for economic analyses

Databases searched and service provider

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R): 1946 to present
- Embase (Ovid): 1980 to present
- The Cochrane Library, incorporating:
  - the NHS Economic Evaluation Database (NHS EED)
  - the Cochrane Database of Systematic Reviews
  - the Health Technology Assessment database
- EconLit (Ovid): 1886 to present

Date of search
The searches were conducted on the 16th September 2016.
Search strategy

All the following searches were combined and inclusion/exclusion criteria combined.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present; searched on September 16th 2016

	Search	Results
1	Carcinoma, Transitional Cell/ or Urinary Bladder Neoplasms/ or Ureteral Neoplasms/ or Urologic Neoplasms/	57370
2	((urothelial or transitional cell or ureter* or renal pelvi* or urachus or urethra* or bladder) adj (cancer or neoplasm* or tumo?r* or carcinoma*)).mp.	65893
3	1 or 2	68754
4	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	585
5	exp Cost-Benefit Analysis/	67840
6	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	69450
7	(cost utility analys* or (cost-utility adj1 analys*)).mp.	2161
8	(cost consequence analys* or (cost-conseq* adj1 analys*)).mp.	166
9	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	9108
10	or/4-9	72906
11	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	13784
12	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	54439
13	exp decision theory/ or exp decision trees/	10569
14	decision tree.mp.	4527

15	models, economic/	7812
16	(markov or deterministic).mp.	28967
17	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	166140
18	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	523
19	(incremental-cost or incremental cost).mp.	7697
20	(ICER or QALY or DALY or WTP or TTO).mp.	9596
21	11 and (or/12-20)	4898
22	10 or 21	74327
23	3 and 22	126

Embase 1980 to 2016 Week 37; Searched on September 16th 2016

	Search	Results
1	transitional cell carcinoma/ or bladder tumor/ or ureter tumor/ or urinary tract tumor/	38747
2	((urothelial or transitional cell or ureter* or renal pelvi* or urachus or urethra* or bladder) adj (cancer or neoplasm* or tumo?r* or carcinoma*)).mp.	89298
3	1 or 2	89610
4	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	3169
5	exp "cost benefit analysis"/	72485
6	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	74251
7	(cost utility analys* or (cost-utility adj1 analys*)).mp.	7870
8	"cost utility analysis"/ or economic evaluation/	17777
9	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	119424
10	"cost effectiveness analysis"/	116685
11	or/4-10	193131
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	26023
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	54242
14	exp decision theory/ or "decision tree"/	9371
15	decision tree.mp.	10868
16	economic model.mp.	2300
17	(markov or deterministic).mp.	31068

18	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	238589
19	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	886
20	(incremental-cost or incremental cost).mp.	12157
21	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	16516
22	or/13-21	337067
23	12 and 22	8178
24	11 or 23	194037
25	3 and 24	545

The Cochrane Library, incorporating: the Cochrane Database of Systematic Reviews 2005 to September 15, 2016, Database Info Icon EBM Reviews - Health Technology Assessment 3rd Quarter 2016, Database Info Icon EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2015; searched on September 16th 2016

	Search	Results
1	Carcinoma, Transitional Cell/ or Urinary Bladder Neoplasms/ or Ureteral Neoplasms/ or Urologic Neoplasms/	80
2	((urothelial or transitional cell or ureter* or renal pelvi* or urachus or urethra* or bladder) adj (cancer or neoplasm* or tumo?r* or carcinoma*)).mp.	158
3	1 or 2	160

Econlit 1886 to August 2016; searched on September 16th 2016

	Search	Results
1	((urothelial or transitional cell or ureter* or renal pelvi* or urachus or urethra* or bladder) adj (cancer or neoplasm* or tumo?r* or carcinoma*)).mp.	13

Additional searches

Additional studies were identified via hand searching the following sources:

- Reference lists of included studies
- The following conference proceedings (last 3 years, depending on availability):

- American Society of Clinical Oncology (ASCO) (2014, 2015 and 2016)
- European Society for Medical Oncology (ESMO) (2013, 2014 and 2015)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (International and European congresses) (2014, 2015 and 2016)
- HTAi Annual Meeting (2014)
- Society for Medical Decision Making (SMDM) (2012, 2014 and 2016)

- Submission documents from the following HTA agencies:
  - National Institute for Health and Care Excellence (NICE)
  - Scottish Medicines Consortium (SMC)
  - Canadian Agency for Drugs and Technologies in Health (CADTH) and the pan-Canadian Oncology Drugs Review (pCODR)
  - Pharmaceutical Benefits Advisory Committee (PBAC)
- The following additional sources, as recommended by NICE:
  - Cost Effectiveness Analysis Registry (https://research.tufts-nemc.org/cear4/Default.aspx)
  - EconPapers within Research Papers in Economics (RePEc) (http://repec.org/)
  - EQ-5D website: http://www.euroqol.org/
  - INAHTA website: http://www.inahta.org/
  - NIHR HTA website: http://www.nihr.ac.uk/
- University of Sheffield ScHARRHUD utility database: http://www.scharrhud.org/

Eligibility criteria

The eligibility criteria in accordance with the NICE draft scope (Excellence., 2016) is applied throughout the review is summarised in Table 109.

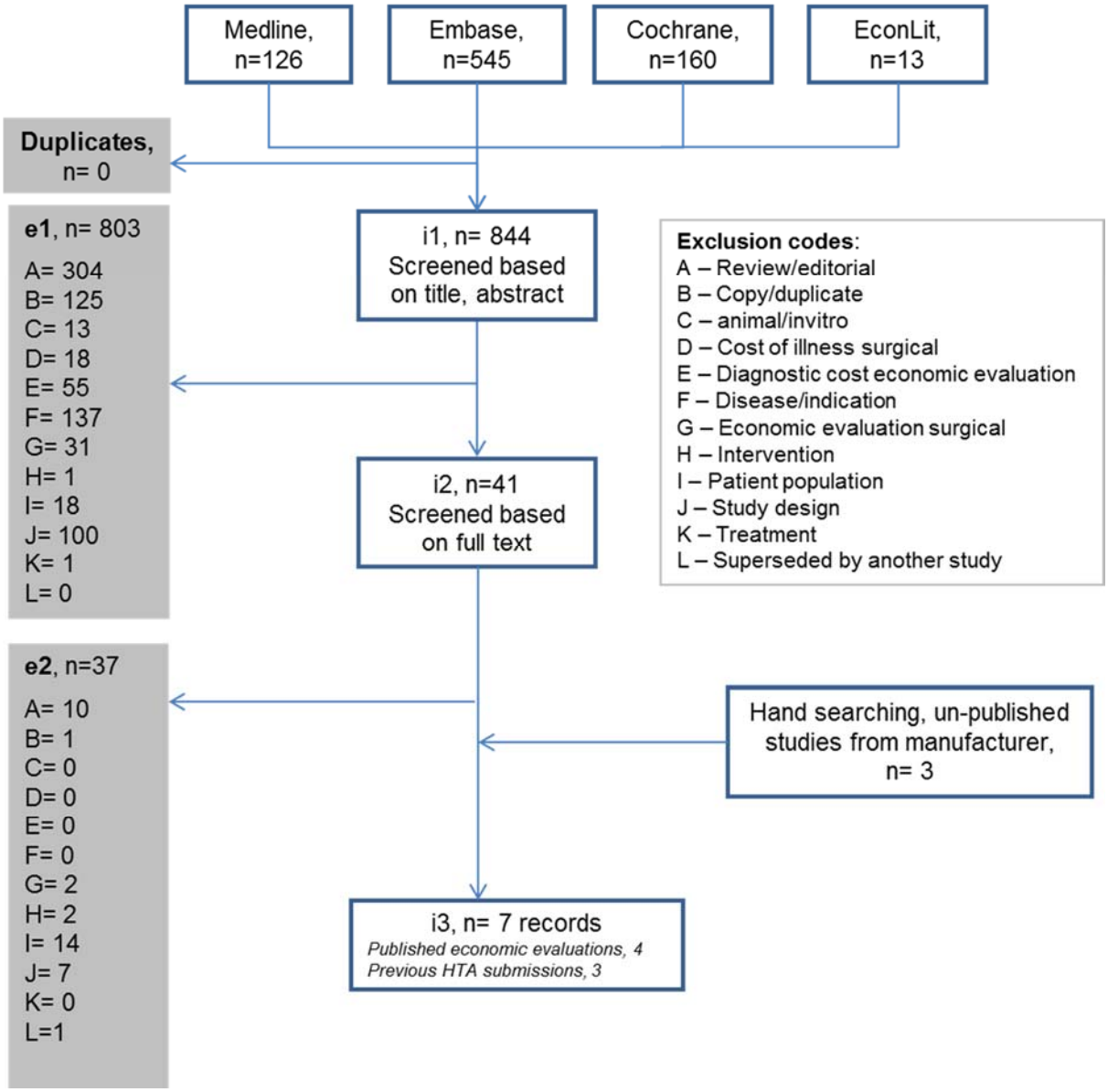
Table 109. Eligibility criteria for the economic evaluation systematic review

Criteria	Include
Population	• Patients with advanced/metastatic urinary bladder cancer who have progressed after at least one prior chemotherapy regimen (or who are intolerant of cisplatin-based chemotherapy).
Treatments	• Chemotherapy treatment regimens such as gemcitabine, docetaxel, paclitaxel • BSC

Criteria	Include
Outcomes	Main outcomes: • ICER: Cost/QALY, cost/DALY, cost per event avoided Additional outcomes: • Range of ICERs as per sensitivity analyses • Assumptions underpinning model structures • Key costs drivers • Sources of clinical, cost and quality of life inputs • Discounting of costs and health outcomes • Model summary and structure
Setting/study design	• Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses
Language of publication	English abstracts of foreign publications were considered. Studies printed in a foreign language were flagged, and their inclusion was decided on in conjunction with Roche.
Date of publication	No restriction
Countries/global reach	No restriction

Abbreviations: BSC, best supportive care; DALY, Disability Adjusted Life Year; ICER, Incremental Cost-Effectiveness Ratio; QALY, Quality Adjusted Life Year

PRISMA flow diagram for the systematic review of cost-effectiveness evidence



8.8 Alternative PFS extrapolation curves

First Line

Figure 61: Alternative PFS extrapolation: Log logistic (1L)

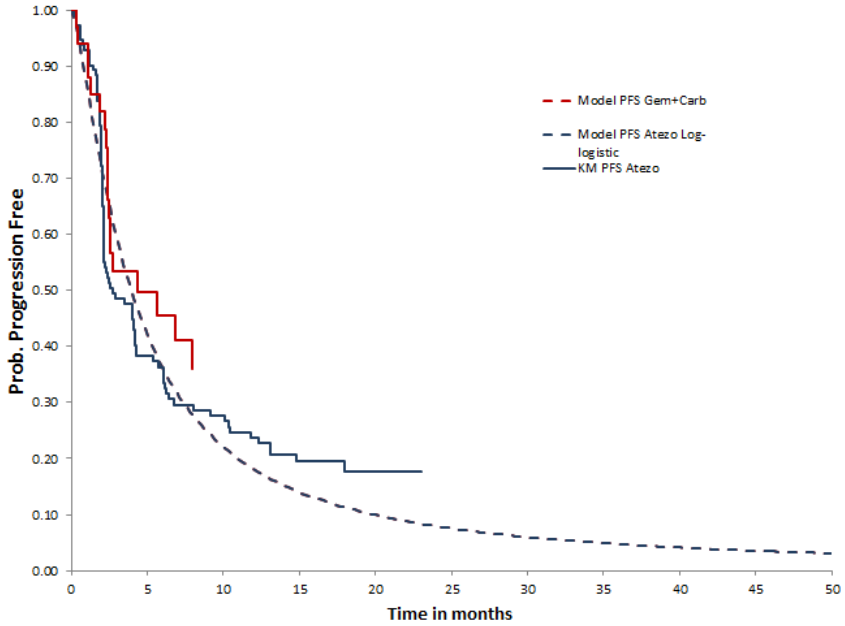


Figure 62: Alternative PFS extrapolation: Gompertz (1L)

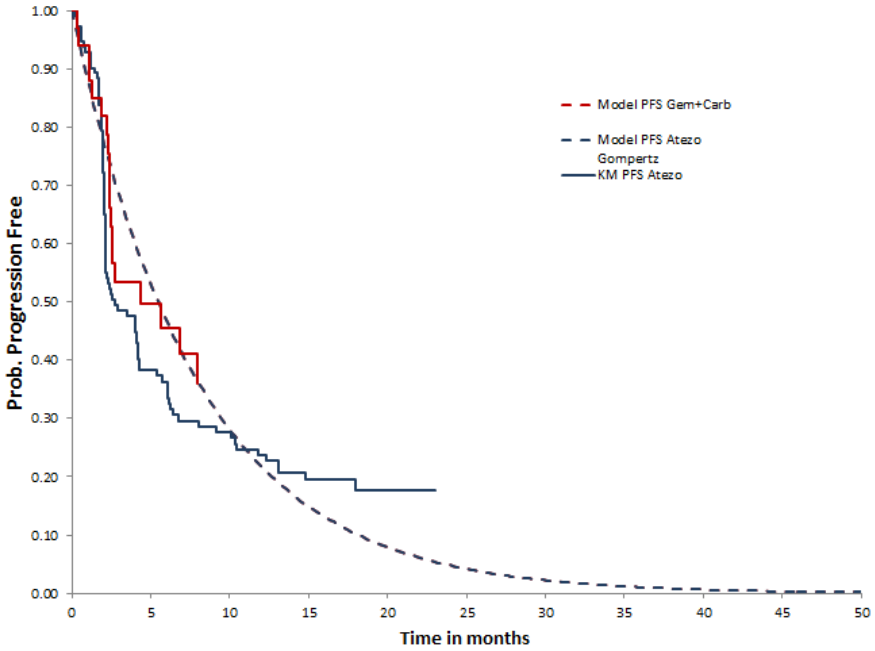


Figure 63: Alternative PFS extrapolation: Exponential (1L)

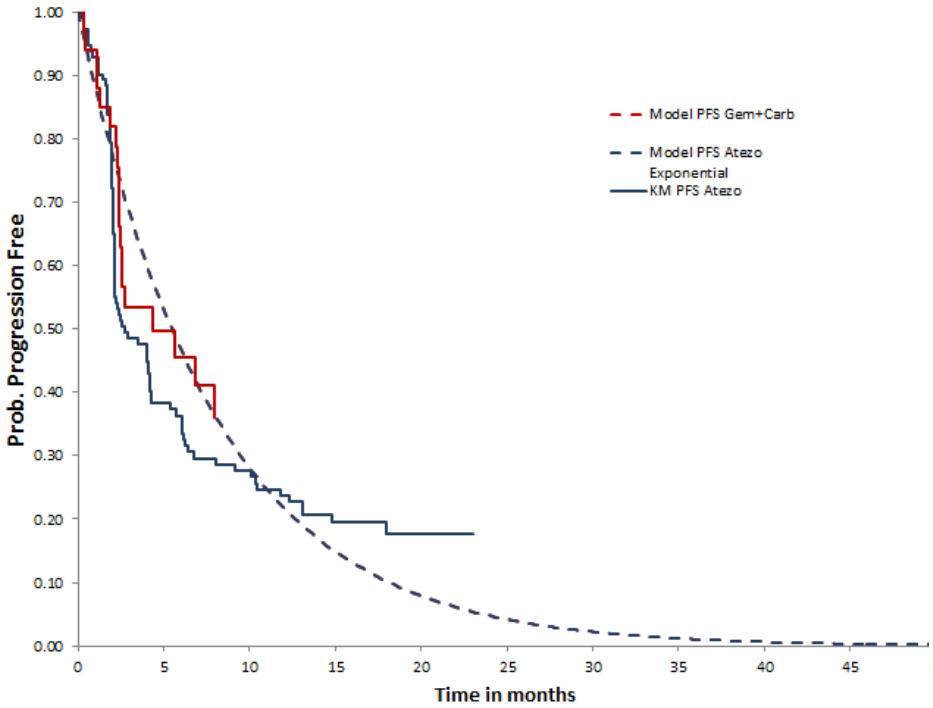


Figure 64: Alternative PFS extrapolation: Weibull (1L)

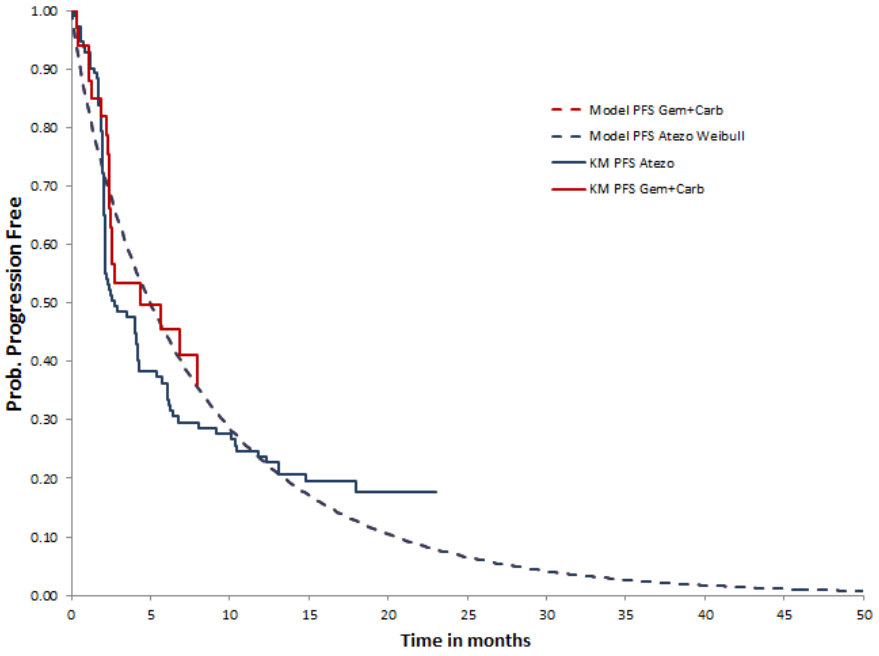
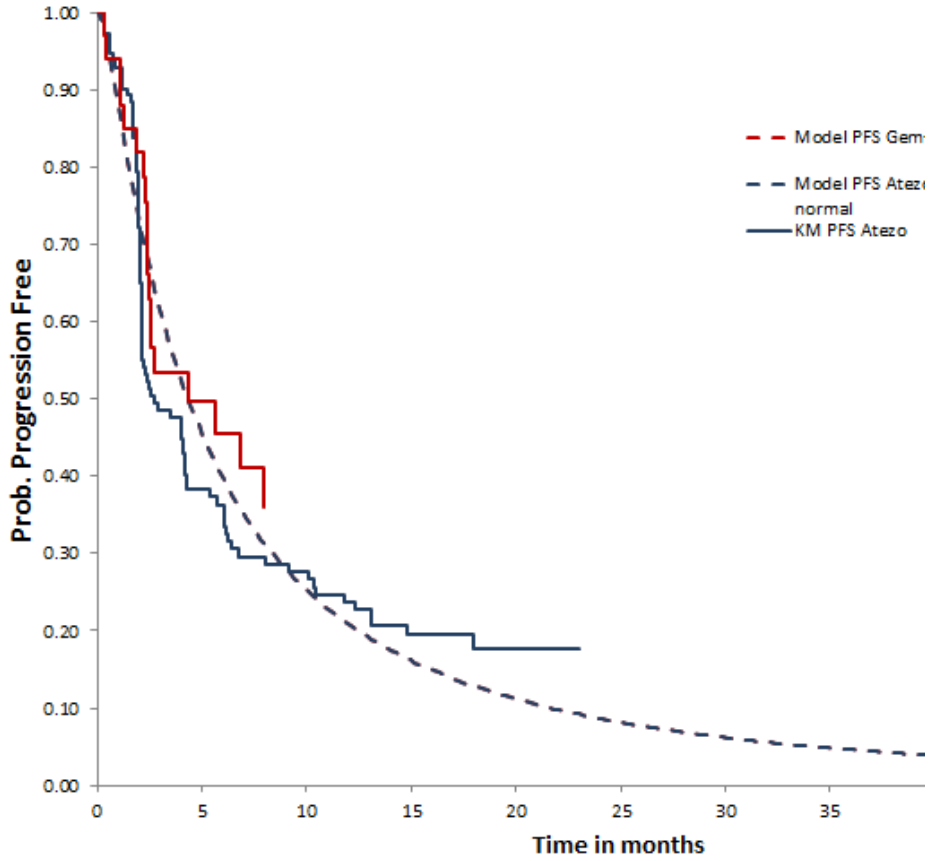


Figure 65: Alternative PFS extrapolation: Lognormal (1L)



Second Line

Figure 66: Alternative PFS extrapolation: Log logistic (2L)

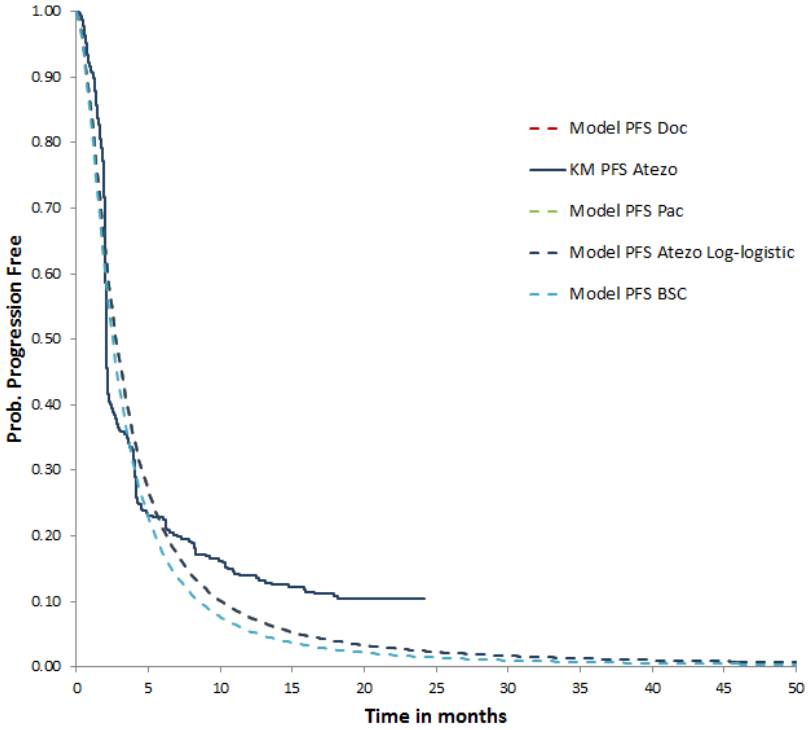


Figure 67: Alternative PFS extrapolation: Gompertz (2L)

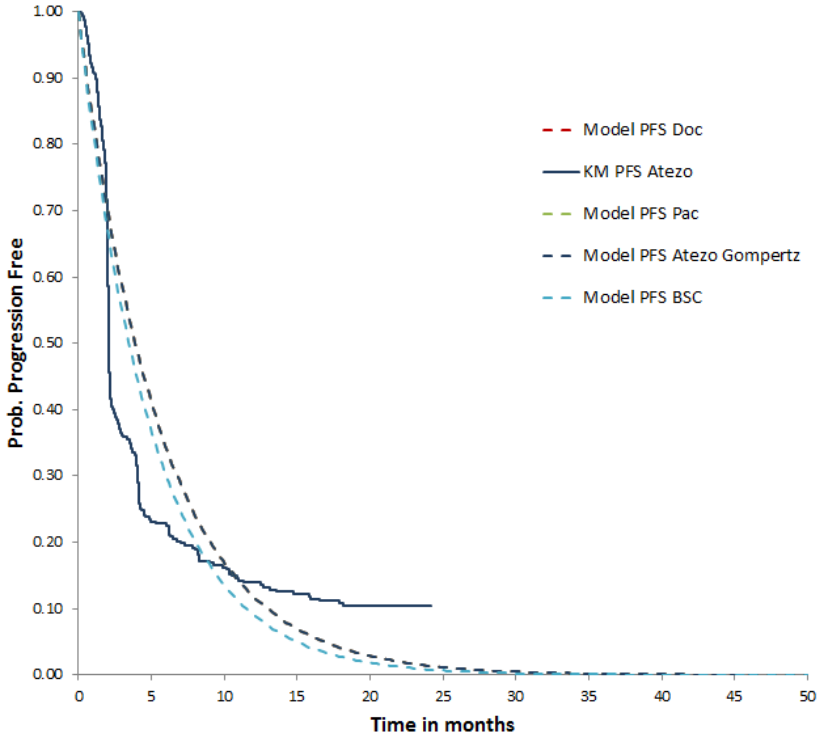


Figure 68: Alternative PFS extrapolation: Exponential (2L)

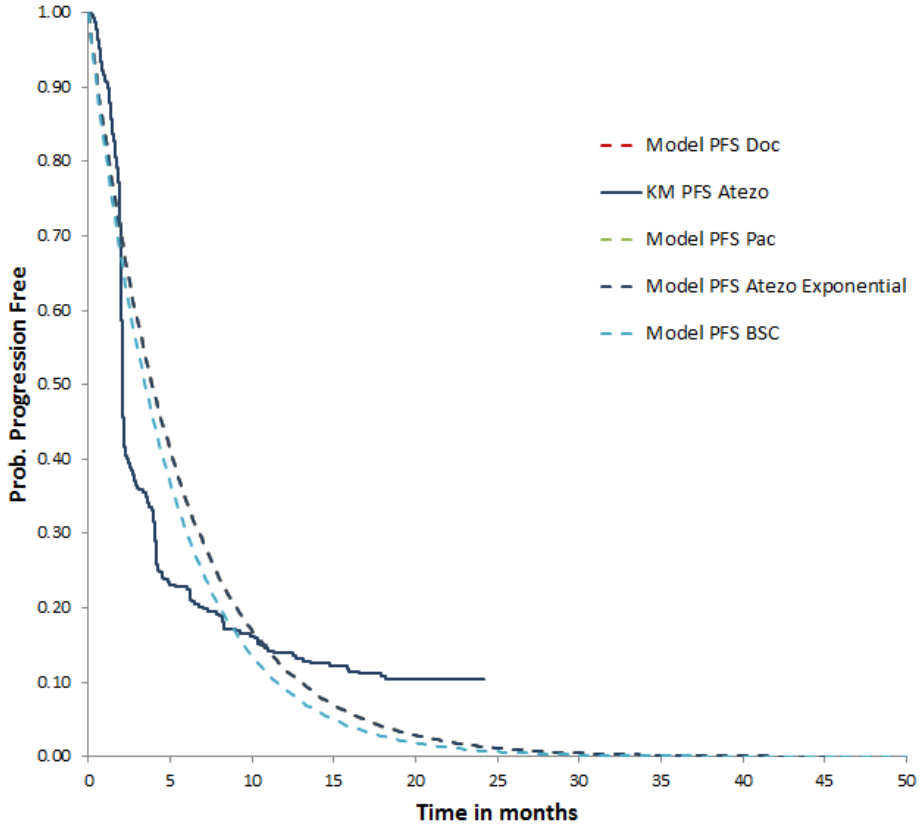


Figure 69: Alternative PFS extrapolation: Weibull(2L)

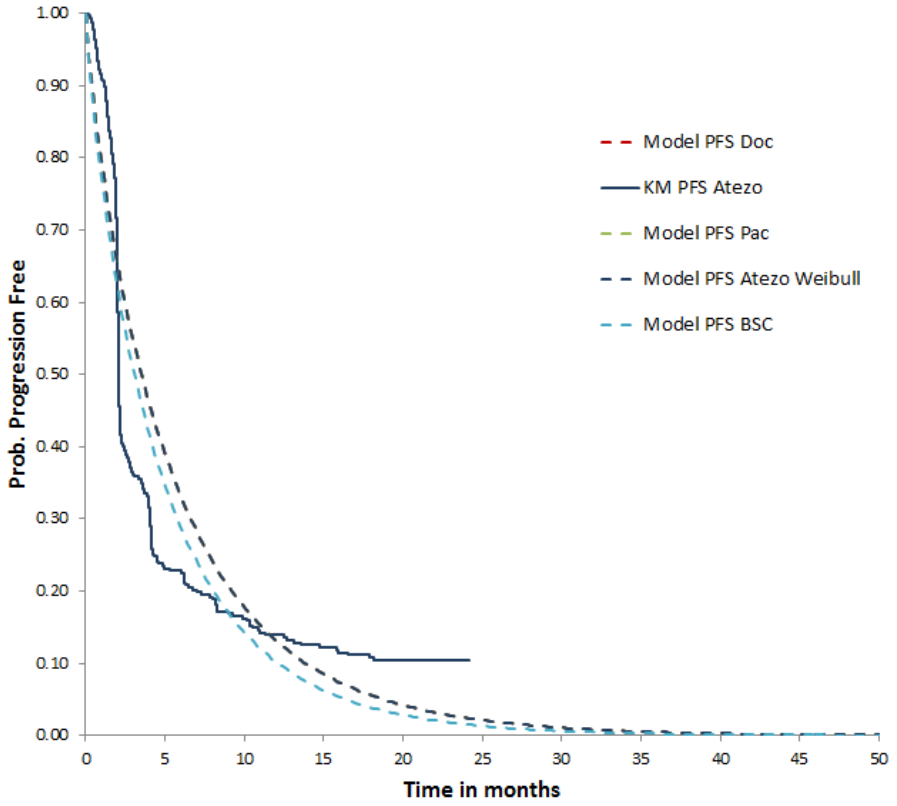
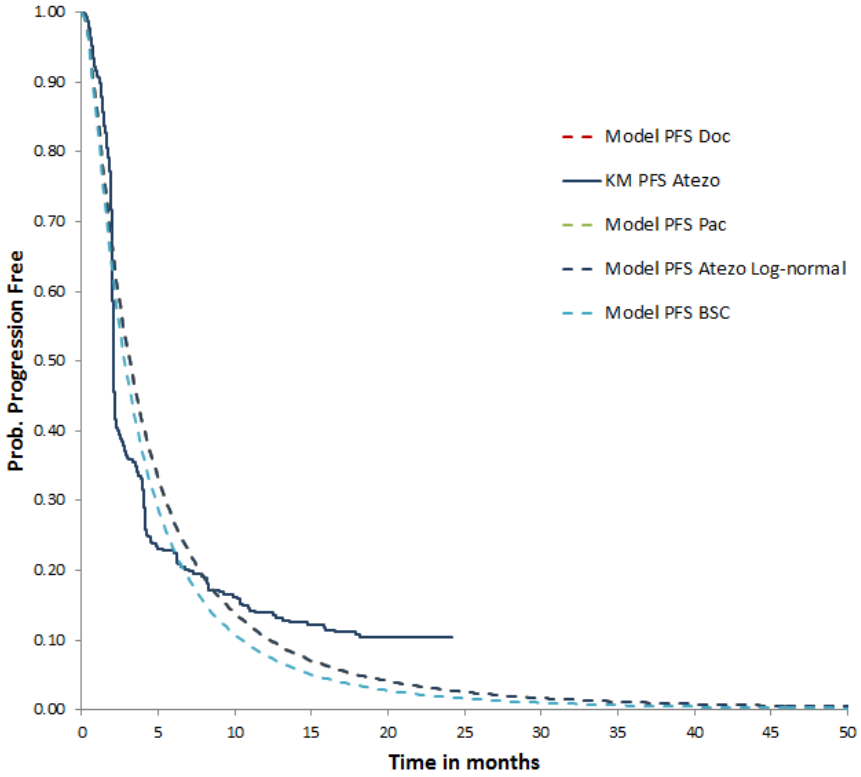


Figure 70: Alternative PFS extrapolation: Log normal (2L)



8.9 Systematic literature searches for utility data

Databases searched and service provider

The following electronic databases were searched via the Ovid platform:

- Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE®: 1946 to present
- Embase: 1980 to 2016 Week 37
- The Cochrane Library, incorporating:
  - the Cochrane Central Register of Controlled Trials: August 2016
  - the Cochrane Database of Systematic Reviews: 2005 to September 15, 2016
  - DARE: 1st Quarter 2015
  - the HTA database: 3rd Quarter 2016
  - NHS EED: 1st Quarter 2015

Date of search

The searches were conducted on the 16th September 2016.

Search strategy

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
1946 to present; Searched on 16th September 2016

	Searches	Results
1	Carcinoma, Transitional Cell/ or Urinary Bladder Neoplasms/ or Ureteral Neoplasms/	54845
2	((urothelial or transitional cell or ureter* or renal pelvi* or urachus or urethra* or bladder) adj (cancer or neoplasm* or tumo?r* or carcinoma*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	65925
3	Urologic Neoplasms/	3910
4	1 or 2 or 3	68786
5	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6196
6	(Health utilities index or HUI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare	1269

	Searches	Results
	disease supplementary concept word, unique identifier]	
7	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	938
8	(short form 6D or short-form 6D).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	107
9	(standard gamble or ("SG" adj2 "standard gamble")).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	743
10	(15D or 16D or 17D).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2344
11	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	20021
12	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	3931
13	(medical outcomes survey or MOS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6283
14	(Quality of wellbeing index or QWB).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	194
15	or/5-14	38614
16	(QoL or HRQoL or HRQL).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	37988
17	quality of life.mp. or exp "Quality of Life"/	245774
18	(health related quality of life or health-related quality of life).mp. [mp=title, abstract, original title,	29907

	Searches	Results
	name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
19	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	32515
20	or/16-19	246775
21	health state$.mp.	4727
22	utilit$.mp.	151996
23	Patient Preference/ or preference.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	84437
24	(map$ or regression).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1131517
25	health status.mp. or *Health Status/	124491
26	health status indicators.mp. or *Health Status Indicators/	22067
27	*"Activities of Daily Living"/	17118
28	*Health Surveys/ or health survey*.mp.	73971
29	*Psychometrics/ or psychometric*.mp.	76234
30	(health* year* equivalent* or HYE*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	820
31	or/21-30	1575523
32	20 and 31	60244
33	15 or 32	84284
34	4 and 33	180

Embase 1980 to 2016 Week 37; Searched on 16th September 2016

	Searches	Results
1	transitional cell carcinoma/ or bladder tumor/ or ureter tumor/ or urinary tract tumor/	39779
2	((urothelial or transitional cell or ureter* or renal pelvi* or urachus or urethra* or bladder) adj (cancer or neoplasm* or tumo?r* or carcinoma*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	90081
3	1 or 2	90423
4	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	11384
5	(Health utilities index or HUI).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	2589
6	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	1310
7	(short form 6D or short-form 6D).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	244
8	(standard gamble or ("SG" adj2 "standard gamble")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	927
9	(15D or 16D or 17D).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	3186
10	exp short form 12/ or exp short form 20/ or exp short form 36/	22492
11	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	22
12	(medical outcome adj1 (survey or stud*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	941
13	or/4-12	39995
14	(QoL or HRQoL or HRQL).mp. [mp=title, abstract, heading word, drug trade name, original title,	66489

	Searches	Results
	device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	
15	exp "quality of life"/	382003
16	(health related quality of life or health-related quality of life).mp.	42393
17	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	73859
18	or/14-17	389213
19	health state$.mp.	7652
20	utilit*.mp.	206341
21	Patient Preference/ or preference.mp.	115479
22	(map$ or regression).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	1291028
23	exp health status/	206161
24	health survey/	174056
25	exp daily life activity/	70530
26	("Activities of Daily Living" or "IADL").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	28172
27	Psychometrics.mp. or exp psychometry/	76935
28	("health year equivalent" or "HYE").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	86
29	or/19-28	2017302
30	18 and 29	96838
31	13 or 30	119207
32	3 and 31	320

The Cochrane Library, incorporating: the Cochrane Central Register of Controlled Trials August 2016; **the Cochrane Database of Systematic Reviews** 2005 to September

15, 2016; **the Database of Abstracts of Reviews of Effects** 1st Quarter 2015**; the Health Technology Assessment database** 3rd Quarter 2016; **the NHS Economic Evaluation Database** 1st Quarter 2015; Searched on 16th September 2016

	Searches	Results
1	Carcinoma, Transitional Cell/ or Urinary Bladder Neoplasms/ or Ureteral Neoplasms/	1079
2	((urothelial or transitional cell or ureter* or renal pelvi* or urachus or urethra* or bladder) adj (cancer or neoplasm* or tumo?r* or carcinoma*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	2249
3	Urologic Neoplasms/	53
4	1 or 2 or 3	2267
5	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	3172
6	(Health utilities index or HUI).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	383
7	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	463
8	(short form 6D or short-form 6D).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	38
9	(standard gamble or ("SG" adj2 "standard gamble")).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	273
10	(15D or 16D or 17D).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	150
11	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	6820
12	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	1064
13	(medical outcomes survey or MOS).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	969
14	(Quality of wellbeing index or QWB).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	57
15	or/5-14	11746
16	(QoL or HRQoL or HRQL).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	9547
17	quality of life.mp. or exp "Quality of Life"/	52558
18	(health related quality of life or health-related quality of life).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	7890
19	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	11146
20	or/16-19	53124
21	health state$.mp.	1896

	Searches	Results
22	utilit$.mp.	12593
23	Patient Preference/ or preference.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	8031
24	(map$ or regression).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	44368
25	health status.mp. or *Health Status/	8924
26	health status indicators.mp. or *Health Status Indicators/	1062
27	*"Activities of Daily Living"/	1
28	*Health Surveys/ or health survey*.mp.	3954
29	*Psychometrics/ or psychometric*.mp.	4840
30	(health* year* equivalent* or HYE*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	45
31	or/21-30	76535
32	20 and 31	14159
33	15 or 32	21053
34	4 and 33	54

Additional searches
Additional studies were identified via hand searching the following sources:

- Reference lists of included studies
- The following conference proceedings (last 3 years availability):
  - American Society of Clinical Oncology (ASCO)
  - European Society for Medical Oncology (ESMO)
  - International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (International and European congresses)
  - HTAi Annual Meeting
  - Society for Medical Decision Making (SMDM)
- Submission documents from the following HTA agencies:
  - National Institute for Health and Care Excellence (NICE)
  - Scottish Medicines Consortium (SMC)

  - Canadian Agency for Drugs and Technologies in Health (CADTH) and the pan-Canadian Oncology Drugs Review (pCODR)
  - Pharmaceutical Benefits Advisory Committee (PBAC)
- The following additional sources, as recommended by NICE:
  - EQ-5D website: http://www.euroqol.org/
  - INAHTA website: http://www.inahta.org/
  - NIHR HTA website: http://www.nihr.ac.uk/
- University of Sheffield ScHARRHUD utility database: http://www.scharrhud.org/

8.10 Systematic literature searches for resource use and cost data

Data sources

The following electronic data sources were searched for articles published between 1 January 2001 and 1 December 2016:

1. MEDLINE® In-Process & Other Non-indexed Citations and OVID MEDLINE1946–present
2. Embase® 1974–present
3. Cochrane Library, comprising:
    a. Cochrane Database of Systematic Reviews (CDSR)
    b. Database of Abstracts of Reviews of Effects (DARE)
    c. Cochrane Central Register of Controlled Trials (CENTRAL)
    d. NHS Economic Evaluations Database (NHS EED)
    e. The Health technology Assessment Database (HTA)
    f. American College of Physicians (ACP) journal club
4. EconLit 1886–present

Proceedings from the following congresses over the past 2 years (2014–2016) were interrogated for relevant abstracts:

1. International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (US and European): http://www.ispor.org
2. American Society of Clinical Oncology (ASCO): http://www.asco.org/meetings
3. European Society for Medical Oncology (ESMO): http://www.esmo.org/
4. Genitourinary Cancers Symposium (ASCO GU): http://gucasym.org/
5. European Association of Urology (EAU): http://uroweb.org/
6. European Meeting on Urologic Cancers (EMUC): http://emuc2014.uroweb.org/

Manufacturer submissions and evidence review group/assessment reports from NICE were reviewed for additional cost data:

1. NICE: https://www.nice.org.uk

The additional sources were also hand searched:

1. Cost Effectiveness Analysis (CEA) Registry: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx
2. Scottish Medicines Consortium (SMC) https://www.scottishmedicines.org.uk
3. Research Papers in Economics (RePEc): http://repec.org/docs/RePEcIntro.html

Search strings
Embase®, ran 1 December 2016

#	Searches	Results
1	exp transitional cell carcinoma/	21943
2	exp bladder cancer/ or bladder tumo?r/	73322
3	('kidney pelvis carcinoma' or 'kidney pelvis cancer' or 'kidney pelvis tumo?r').mp.	1817
4	('kidney cancer' and ('kidney pelvis' or 'kidney pelvis tumo?r' or 'kidney pelvis' or 'renal pelvis')).mp.	301
5	exp ureter cancer/ or ureter tumo?r/	3994
6	exp urethra cancer/ or urethra tumo?r'/	2135
7	'urinary tract cancer'.mp. or 'urinary tract tumo?r'/	5640
8	('urothelial cancer' or 'urothelial carcinoma' or 'metastatic urothelial cancer' or 'advanced urothelial cancer' or 'metastatic urothelial carcinoma' or 'advanced urothelial carcinoma').mp.	11100
9	(transitional adj3 cell adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	12215
10	(bladder adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	60355
11	(urothelial adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	14747
12	(urothelium adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	867
13	(ureter* adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	3907
14	(urethra* adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	1739
15	('renal pelvis' adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	1895
16	('kidney pelvis' adj4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	79
17	('urinary tract' adj (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)).ti,ab.	1427
18	or/1-17	101741
19	(metasta* or advanced or stage 3 or stage III or stage 4 or stage IV or transitional).mp.	1163421
20	18 and 19	41059
21	Cost$.mp.	825922
22	(Resource adj2 (utili$ation or use$)).mp.	12340
23	Cost of illness/	16900
24	Cost control/	62208
25	Financial management/	111732
26	Health care cost/	161487
27	Health care utilization/	55414
28	Health care utilisation/	55414

29	Health care financing/	12748
30	Health economics/	37217
31	Hospital cost/	18182
32	(fiscal or financial or finance or funding).tw.	136435
33	(cost adj estimate$).mp.	2580
34	(cost adj variable$).mp.	187
35	(unit adj cost$).mp.	3340
36	or/21-35	1056256
37	20 and 36	798
38	(animals not (humans and animals)).mp.	658714
39	37 not 38	793
40	limit 39 to yr="2001 -Current"	689

MEDLINE® and MEDLINE® In-Process, ran 1 December 2016

#	Searches	Results
1	Carcinoma, Transitional Cell/	17804
2	Urinary Bladder Neoplasms/	50551
3	Ureteral Neoplasms/	4466
4	Urethral Neoplasms/	2429
5	kidney neoplasms/ and (kidney pelvis/ or kidney pelvis.ti,ab. or renal pelvis.ti,ab.)	2917
6	Urologic Neoplasms/	4120
7	Urogenital Neoplasms/	3695
8	(transitional adj2 cell adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	10567
9	(bladder and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	62802
10	(urothelial and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	11810
11	(urothelium and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	2507
12	(ureter* and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	9213
13	(urethra* and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	5247
14	(renal pelvis and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	2577
15	(kidney pelvis and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	137
16	(urinary tract adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	1690
17	or/1-16	95836
18	(metasta* or advanced or stage 3 or stage III or stage 4 or stage IV or transitional).mp.	854659

19	Cost$.mp.	584404
20	(Resource adj2 (utili$ation or use$)).mp.	9581
21	Cost of illness/	23421
22	Cost control/	22150
23	Financial management/	16766
24	Health care costs/	34849
25	"Patient Acceptance of Health Care"/	40174
26	Health care financing.mp.	2483
27	Economics, Medical/	9389
28	Hospital costs/	9735
29	(fiscal or financial or finance or funding).tw.	117943
30	(cost adj estimate$).mp.	1940
31	(cost adj variable$).mp.	137
32	(unit adj cost$).mp.	2124
33	or/19-32	732163
34	17 and 18 and 33	428
35	(animals not (humans and animals)).mp.	4611590
36	34 not 35	427
37	limit 36 to yr="2001 -Current"	290

Cochrane, ran 1 December 2016

#	Searches	Results
1	Carcinoma, Transitional Cell/	424
2	Urinary Bladder Neoplasms/	1040
3	Ureteral Neoplasms/	6
4	Urethral Neoplasms/	2
5	kidney neoplasms/ and (kidney pelvis/ or kidney pelvis.ti,ab. or renal pelvis.ti,ab.)	0
6	Urologic Neoplasms/	54
7	Urogenital Neoplasms/	35
8	(transitional adj2 cell adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	316
9	(bladder and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	2308
10	(urothelial and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	318
11	(urothelium and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	42
12	(ureter* and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	82
13	(urethra* and (carcinoma* or cancer* or neoplasm* or tumo?r* or	157

	malignanc*)).ti,ab.	
14	(renal pelvis and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	12
15	(kidney pelvis and (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	0
16	(urinary tract adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or malignanc*)).ti,ab.	56
17	or/1-16	2750
18	(metasta* or advanced or stage 3 or stage III or stage 4 or stage IV or transitional).mp.	49056
19	Cost$.mp.	67586
20	(Resource adj2 (utili$ation or use$)).mp.	5993
21	Cost of illness/	1250
22	Cost control/	276
23	Financial management/	17
24	Health care costs/	4450
25	"Patient Acceptance of Health Care"/	2285
26	Health care financing.mp.	133
27	Economics, Medical/	37
28	Hospital costs/	1456
29	(fiscal or financial or finance or funding).tw.	34200
30	(cost adj estimate$).mp.	2419
31	(cost adj variable$).mp.	90
32	(unit adj cost$).mp.	5200
33	or/19-32	80710
34	17 and 18 and 33	72
35	(animals not (humans and animals)).mp.	1641
36	34 not 35	70
37	limit 36 to yr="2001 -Current" [Limit not valid in DARE; records were retained]	60

Econlit, ran 1 December 2016

#	Searches	Results
1	(urothellial cancer or bladder cancer).mp.	12

8.11 Resource use and cost data excluded studies

List of publications that met the inclusion criteria of the cost and resource use SR, but were not considered relevant to current HTA submission

Author	Year	Title	Reason for omission from HTA document
Gelpi-Hammerschmidt *et al.* (congress abstract)(Gelpi-Hammerschmidt et al., 2016)	2016	Oncologic and perioperative outcomes of "cytoreductive" radical cystectomy for patients with metastatic bladder cancer in the United States	This study assessed the cost associated with cytoreductive surgery in patients with metastatic bladder cancer, which was not considered relevant to this submission. Additionally, findings were reported in the congress abstract and only a 90-day direct hospital cost was reported, with no further breakdown of cost or resource use provided
Nadeem *et al.* (congress abstract)(Nadeem et al., 2014)	2014	Cost differential among systemic therapies for breast, bladder, lung, and colon cancer	This study assessed the cost differentials between 70 chemotherapeutic regimens for 4 different common cancers, including bladder cancer. Costs reported included the mean 6-month cost associated with chemotherapeutic regimens including those for bladder cancer. As the costs related to the cost of chemotherapy in the US, the study was not considered relevant to this submission
Nadeem *et al.* (full publication)(Nadeem et al., 2016)	2016	Cost differential of chemotherapy for solid tumors	This study assessed the cost differentials between 62 chemotherapeutic regimens for 4 different common cancers, including bladder cancer. Costs reported included the mean 6-month cost associated with three chemotherapeutic regimens (DDMVAC, CMV, gemcitabine and cisplatin). As the costs related to the cost of chemotherapy in the US, the study was not considered relevant to this submission

CMV, methotrexate, vinblastine, cisplatin, and folinic acid, DDMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EC, epirubicin and cyclophosphamide; US, United States

Publications excluded following full paper review

Konety *et al.*, 2007(Konety et al., 2007)	Population: most patients had stage 1 disease
Geurts *et al.*, 2014(Geurts et al., 2014)	Population: the stage of cancer not reported and costs were not reported separately for bladder cancer in the abstract
Botteman *et al.*, 2003(Botteman et al., 2003)	Study design: systematic review

Hu *et al*., 2016(Hu et al., 2016)	Population: patients with metastatic disease were excluded from the study
Wittig *et al*., 2016(Wittig et al., 2016)	Population: the stage of the disease was not clearly reported (the study focused on costs after readmission after robot-assisted radical cystectomy)
Gregori *et al*., 2007(Gregori et al., 2007)	Population: the stage of the disease was not clearly reported (patients were candidates for radical surgery)
Stitzenberg *et al*., 2015(Stitzenberg et al., 2015)	Population: most patients had localized early stage cancer
Lee *et al*., 2011(Lee et al., 2011)	Population: the study focused on patients with recurrent high-grade superficial urothelial carcinoma or carcinoma in situ or urothelial carcinoma invading muscle
Zachariah *et al*., 2014(Zachariah et al., 2014)	Outcome: this article discussed the development of a pilot program for palliative care for patients with bladder cancer, however, no results were reported. The potentially relevant findings were discussed as part of the methods section only (e.g. length of stay)

8.12 Commercial in Confidence Checklist

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2016

Atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma after prior chemotherapy and patients who are considered cisplatin-ineligible (ID939)

1 Introduction

The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2104) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company/ of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

Atezolizumab (brand name: Tecentriq) for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible (ID939)

The Marketing Authorisation Application also seeks approval for use of atezolizumab in the following indication:

Atezolizumab for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy (ID970).

3.2 Please outline the rationale for developing the Patient Access Scheme.

In light of the clinical promise of atezolizumab in metastatic urothelial carcinoma (mUC), and the desire for effective treatment options in clinical practice, Roche proposes atezolizumab be made available for patients via the Cancer Drugs Fund (CDF). This interim funding solution will provide patients access to this important new medicine until availability of phase III clinical trial data, which will resolve the most significant uncertainties.

Due to the joint regulatory filing of atezolizumab in both mUC and NSCLC indications, both NICE submission appraisals are ongoing in parallel. A simple patient access scheme (PAS) has been submitted to the Patient Access Schemes Liaison Until (PASLU), and included within the submission to NICE for the NSCLC indication (ID970). Due to the timeline for submission of the mUC dossier (ID939) results with this scheme were not incorporated.

Roche is engaging with NHS England (NHSE) for further discussion regarding the Commercial Access Agreement for the mUC indication. At this time the access agreement available for atezolizumab is in the form of the simple PAS, awaiting endorsement from PASLU.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

A confidential simple PAS of [redacted] discount from the proposed list price (not yet confirmed with the Department of Health). Proposed list price is [redacted] per 1200mg vial, with resulting net price following PAS application of [redacted] per 1200mg vial

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

As the proposed PAS is a simple PAS, the discount applies to all populations within the anticipated marketing authorisation

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The simple PAS will be a condition of positive NICE guidance; as such will apply from the point of NICE guidance

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patient populations as per the anticipated marketing authorisation

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

A simple discount, which will be applied at the point of sale to the NHS and appear on the original invoice.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

A simple discount which will be applied at the point of sale to the NHS and appear on the original invoice.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable – simple discount applied at the point of sale to the NHS and appearing on the original invoice.

3.10 Please provide details of the duration of the scheme.

The commercial access agreement will operate in the form of a simple PAS, and will be a condition of any positive NICE guidance.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No identified equity or equality issues.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company/sponsor submission of evidence'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

Not applicable – the populations are consistent with the company submission

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable – NICE Appraisal Committee Meeting not yet occurred.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

A reduction in the net price of atezolizumab for the first, and all subsequent administrations by [redacted] to [redacted] per 1200mg vial.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

Clinical effectiveness data for atezolizumab in mUC is taken from the single arm, phase II registration study, IMvigor 210 (NCT02108652). Details of the

clinical effectiveness and evidence synthesis are available in section 4 of the company submission, and are unchanged with application of this simple PAS.

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 5.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

Simple PAS at invoice applied to all populations of atezolizumab. As such, no additional PAS administration -related costs incurred.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Simple PAS at invoice applied to all populations of atezolizumab. As such, no additional treatment-related costs incurred. Please see section 5.5 of company submission for details.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

The mUC indication for atezolizumab includes two populations – those after prior chemotherapy, and those who are considered cisplatin ineligible. These populations include different comparators, as such results are presented for each population separately. For ease, patients treated with atezolizumab

after prior chemotherapy are herein referred to as second line plus (2L+), and those considered cisplatin ineligible are herein referred to as first line (1L).

Table 1: Base-case cost-effectiveness results (1L)

	Atezolizumab	Gemcitabine + carboplatin
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	n/a	[redacted]
LYG	3.74	1.84
LYG difference	n/a	1.91
QALYs	2.69	1.35
QALY difference	n/a	1.34
ICER (£)	n/a	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.
*difference in cost/QALY stated compared to calculated, due to rounding

Table 2: Base-case cost-effectiveness results (2L+)

	Atezolizumab	Docetaxel	Paclitaxel	Best Supportive Care (BSC)
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)		[redacted]	[redacted]	[redacted]
LYG	1.69	1.04	0.96	0.75
LYG difference	n/a	0.65	0.73	0.94
QALYs	1.23	0.76	0.71	0.55
QALY difference	n/a	0.47	0.53	0.68
ICER (£)	n/a	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.
*difference in cost/QALY stated compared to calculated, due to rounding

4.8 Please present in separate tables the incremental results as follows. [1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 3: Base-case incremental results without PAS (1L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	3.74	2.69				
Gemcitabine + carboplatin	[redacted]	1.84	1.35	[redacted]	1.91	1.34	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 4: Base-case incremental results with PAS (1L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	3.74	2.69				
Gemcitabine + carboplatin	[redacted]	1.84	1.35	[redacted]	1.91	1.34	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

[1] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 5: Base-case incremental results without PAS (2L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.69	1.23				
Docetaxel	[redacted]	1.04	0.76	[redacted]	0.65	0.47	[redacted]
Paclitaxel	[redacted]	0.96	0.71	[redacted]	0.73	0.53	[redacted]
BSC	[redacted]	0.75	0.55	[redacted]	0.94	0.68	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 6: Base-case incremental results with PAS (2L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.69	1.23				
Docetaxel	[redacted]	1.04	0.76	[redacted]	0.65	0.47	[redacted]
Paclitaxel	[redacted]	0.96	0.71	[redacted]	0.73	0.53	[redacted]
BSC	[redacted]	0.75	0.55	[redacted]	0.94	0.68	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1: Comparison to gemcitabine + carboplatin univariate sensitivity analysis with PAS (dark blue = lower value; light blue = higher value) (1L)

Figure 2: Comparison to docetaxel univariate sensitivity analysis with PAS (dark blue = lower value; light blue = higher value) (2L+)

Figure 3: Comparison to paclitaxel univariate sensitivity analysis with PAS (dark blue = lower value; light blue = higher value) (2L+)

Figure 4: Comparison to best supportive care univariate sensitivity analysis with PAS (dark blue = lower value; light blue = higher value) (2L+)

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis (PSA) was conducted using 1000 samples, to assess uncertainty surrounding variables. The distributions and sources to estimate parameters can be found in section 5.6 of the company submission. Analyses are based on the proposed PAS price of atezolizumab, and the eMIT drug prices for comparators.

Results of the PSA should be interpreted with caution, as they are unlikely to be reliable. The high level of uncertainty in the fractional polynomial model and prediction model provides a skewed output for OS. This subsequently impacts other model outputs.

Results of the PSA compared to deterministic results at PAS price, for 1L and 2L are presented in Table 7and Table 8below.

Scatterplots in Figure 5 and Figure 6 show iterations for 1L and 2L respectively. Cost effectiveness acceptability curves for 1L and 2L are shown in Figure 7and Figure 8

Table 7: PSA results compared to base-case with PAS (1L)

	Costs		**QALYs**		**ICER**	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Atezolizumab	[redacted]	[redacted]	2.69	2.718		
Gemcitabine + carboplatin	[redacted]	[redacted]	1.35	1.450	[redacted]	[redacted]

Table 8: PSA results compared to base-case with PAS (2L+)

	Costs		QALYs		ICER	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Atezolizumab	[redacted]	[redacted]	1.23	1.247		
Docetaxel	[redacted]	[redacted]	0.76	0.803	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	0.71	0.8821	[redacted]	[redacted]
BSC	[redacted]	[redacted]	0.55	0.581	[redacted]	[redacted]

Figure 5: Scatterplot of PSA results for cost effectiveness plane with PAS (1L)

Figure 6: Scatterplot of PSA results for cost effectiveness plane with PAS (2L+)

Figure 7: Cost-effectiveness acceptability curve with PAS (1L)

Figure 8: Cost-effectiveness acceptability curve with PAS (2L+)

4.11 Please present scenario analysis results as described for the main company/sponsor submission of evidence for the technology appraisal.

Table 9: Resulting ICER vs gemcitabine + carboplatin from scenario analyses with PAS (1L)

Scenario	Parameter	Value	ICER vs. gemcitabine + carboplatin
Base-case	Intervention price	List price for atezolizumab	[redacted]
PAS price for atezolizumab applies to all subsequent ICERs			
Base case	Comparator price	eMIT drug prices	[redacted]
		List prices	[redacted]
Base case	Cure rate	0%	[redacted]
		1%	[redacted]
		2%	[redacted]
		3%	[redacted]
Base case	Distribution PFS	Generalized gamma	[redacted]
		Log-normal	[redacted]
		Log-logistic	[redacted]
Base case	Treatment duration assumption	Actual treatment duration	[redacted]
		Until progression	[redacted]
Base case	Time horizon	20	[redacted]
		10	[redacted]
		15	[redacted]
Base case	On treatment utility (all products)	0.750	[redacted]
	Atezo on treatment utility	0.800	[redacted]
	G+C on treatment utility	0.653	[redacted]
Base case	Off treatment utility	0.710	[redacted]
		0.500	[redacted]
		0.750	[redacted]
Base case	Discount rate – effects and costs	3.5% for both	[redacted]
	Discount rate - costs	1.5% (3.5% for effects)	[redacted]
	Discount rate – effects	1.5% (3.5% for costs)	[redacted]
	Discount rate – effects and costs	1.5% for both	[redacted]

Table 10: Resulting ICERs vs docetaxel, paclitaxel or BSC from scenario analyses with PAS (2L)

Scenario	Parameter	Value	ICER vs. docetaxel	ICER vs. paclitaxel	ICER vs. BSC
Base case	Intervention price	List price for atezolizumab	[redacted]	[redacted]	[redacted]
PAS price for atezolizumab applies to all subsequent ICERs					
Base case	Comparator price	eMIT drug prices	[redacted]	[redacted]	[redacted]
		List prices	[redacted]	[redacted]	[redacted]
Base case	Cure rate	0%	[redacted]	[redacted]	[redacted]
		1%	[redacted]	[redacted]	[redacted]
		2%	[redacted]	[redacted]	[redacted]
		3%	[redacted]	[redacted]	[redacted]
Base case	Distribution PFS	Generalized gamma	[redacted]	[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]	[redacted]
Base case	Comparator relative effect PFS	Equal to atezolizumab	[redacted]	[redacted]	[redacted]
		FP	[redacted]	[redacted]	[redacted]
Base case	Treatment duration assumption	Actual treatment duration	[redacted]	[redacted]	[redacted]
		Until progression	[redacted]	[redacted]	[redacted]
Base case	Time horizon	20	[redacted]	[redacted]	[redacted]
		10	[redacted]	[redacted]	[redacted]
		15	[redacted]	[redacted]	[redacted]
Base case	On treatment utility (all products)	0.750	[redacted]	[redacted]	[redacted]
	Atezo on treatment utility	0.800	[redacted]	[redacted]	[redacted]
	Comparator on	0.653	[redacted]	[redacted]	[redacted]

	treatment utility				
Base case	Off treatment utility	0.710	[redacted]	[redacted]	[redacted]
		0.500	[redacted]	[redacted]	[redacted]
		0.750	[redacted]	[redacted]	[redacted]
Base case	Discount rate – effects and costs	3.5% for both	[redacted]	[redacted]	[redacted]
	Discount rate - costs	1.5% (3.5% for effects)	[redacted]	[redacted]	[redacted]
	Discount rate – effects	1.5% (3.5% for costs)	[redacted]	[redacted]	[redacted]
	Discount rate – effects and costs	1.5% for both	[redacted]	[redacted]	[redacted]

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable – simple PAS on invoice.

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Please see Table 9 and Table 10 above for scenario analyses of 1L and 2L respectively. These are reflections of Tables 93 and 94 of the company submission, with the PAS price applied to all scenarios.

5 Appendix A: Details for outcome-based schemes only

Not applicable

Given the limited evidence base, the zero-order and the two first order fractional polynomial models were fit, but the second order fractional polynomial models were not utilised.

Table 1: Overview and model comparison for the FE fractional polynomial model for OS (1L)

Model	P parameter	Comment	DIC	pD	meanDev
Zero order fractional polynomial	NULL	Exponential model, proportional hazards	236.2	3	233.2
First order fractional polynomial	P1=0	Weibull model	240	6	234
First order fractional polynomial	P1=1	Gompertz model	236.9	6	230.9

The zero-order model had the lowest DIC, though DIC differences were not large enough to differentiate between models (differences of less than 5 points; Table 21). The more complex first order fractional polynomials did not perform better than the proportional hazards model with exponential distribution. However, as the proportional hazard assumption is unlikely to hold true, the first-order gompertz model was selected as base case.

For the first-order gompertz model the contract estimates of the intercept and slope parameters of the logHR function, with respect to comparators of interest vs atezolizumab (the network reference), as well as the posterior correlation between the intercept and slope parameters can be found below:

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation between intercept and slope
gemcitabine +carboplatin	0.21	-0.242	0.647	0.051	-0.009	0.112	-0.749

1.1.1.1 Overall survival: Base-case results (2L+)

Including interaction terms or the number of prior chemotherapies did not improve the predictive performance, as seen in Table 22 below. Therefore, model m1 which contained the four main prognostic factors (proportion above 65, male, proportion with ECOG ≥1, liver metastasis) was selected.

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Single technology appraisal

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Dear Catherine,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 18 January 2017 from Roche. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **24 February 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (Ross.Dent@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

Executive summary (page 20)

A1. Please clarify the role of the expert clinical advisory panel and explain if there were disagreements about any of the issues covered in the company submission.

Statement of the decision problem

A2. Please define best supportive care for the second-line population (people whose disease has progressed after platinum-based chemotherapy or people for whom cisplatin-based chemotherapy is unsuitable and whose disease has progressed after platinum-based therapy).

A3. Please clarify what the numbers in the following sentence refer to: "Taxane choice for patients recruited from the UK is heavily weighted towards paclitaxel [redacted] vs. docetaxel [redacted]" (page 22 of company submission).

Clinical pathway of care

A4. Please provide an explanation for the statement in the company submission that the European Society of Medical Oncology Guidelines are not relevant to UK clinical practice.

Literature searching

A5. Please provide the search strategy used to identify relevant sources of clinical effectiveness evidence, indicating the number of records identified for each search line.

Review strategy

A6. Please clarify the following relating to the eligibility screening process for selecting studies to include in the systematic literature review:

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- Were all of the eligibility criteria that are reported in the company submission specified *a priori*?
- The number of reviewers that assessed titles/abstracts and full texts
- The parts of Figure 3 in the company submission that correspond to the title/abstract and full-text screening steps

A7. Figure 3 in the company submission states that 631 publications were excluded from the systematic literature review but reasons for exclusion are only given for 373 of these. Please explain why the remaining publications were excluded.

A8. Figure 3 in the company submission suggests that 233 publications were included in a qualitative synthesis, but no qualitative synthesis with the corresponding number of publications is reported. Please give details of the qualitative synthesis, and if possible provide the results.

A9. The reasons for exclusion of studies from the network meta-analysis, listed in Appendix 8.2, are not clear, as the following explanations are ambiguous: connector "not of interest", "poor reporting", "poor data" and "poor reporting and data inconsistency". Please provide a more detailed description of the above reasons.

A10. Table 16 in the company submission lists the studies providing evidence for the comparators for the second-line population that are eligible for inclusion in a network meta-analysis of overall survival and progression-free survival. However, when compared with Table 14 it appears that Table 16 has omitted seven studies that reported either overall survival or progression-free survival but not both (Joly 2009, McCaffery 1997, Srinivas 2005, Suyama 2009, Sternberg 2002, Takahashi 2006, Vaughn 2002). Please explain the reasons for this.

A11. **Priority question.** The ERG has identified the following studies that appear to meet the eligibility criteria for inclusion in the network meta-analysis using the criteria given in the company submission which are not listed in the company submission or appendices. Please explain whether these studies were identified and checked for eligibility and, if so, please explain why they were excluded:

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Bamias A, Dafni U, Karadimou A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol 2013; 24:1011.
Calabrò F, Lorusso V, Rosati G, et al. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 2009; 115:2652.
Gebbia, V et al. Single agent 2',2'-difluorodeoxycytidine in the treatment of metastatic urothelial carcinoma: a phase II study. La Clinica terapeutica. 1999; 150(1): 11-15.
Gondo, T et al. The efficacy and safety of gemcitabine plus cisplatin regimen for patients with advanced urothelial carcinoma after failure of M-VAC regimen. International Journal of Clinical Oncology 2011; 16(4): 345-351.
Halim, A. Methotrexate-paclitaxel-epirubicin-carboplatin as second-line chemotherapy in patients with metastatic transitional cell carcinoma of the bladder pretreated with cisplatin-gemcitabine: A phase II study. Asia-Pacific Journal of Clinical Oncology 2013; 9(1): 60-65.
Kanai, K et al. Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. International Journal of Clinical Oncology 2008; 13(6): 510-514.
Kaufman, DS et al. A multi-institutional phase II trial of gemcitabine plus paclitaxel in patients with locally advanced or metastatic urothelial cancer. Urologic Oncology 2004; 22(5): 393-397.
Krege S, Rembrink V, Börgermann C, et al. Docetaxel and ifosfamide as second line treatment for patients with advanced or metastatic urothelial cancer after failure of platinum chemotherapy: a phase 2 study. J Urol 2001; 165:67.
Li J, Juliar B, Yiannoutsos C, et al. Weekly paclitaxel and gemcitabine in advanced transitional-cell carcinoma of the urothelium: a phase II Hoosier Oncology Group study. J Clin Oncol 2005; 23:1185.
Lin CC, Hsu CH, Huang CY, et al. Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study. Anticancer Drugs 2007; 18:487.
Plimack ER, Bellmunt J, Gupta S, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol 2017.
Pronzato P, Vigani A, Pensa F, et al. Second line chemotherapy with ifosfamide as outpatient treatment for advanced bladder cancer. Am J Clin Oncol 1997; 20:519.
Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016; 17:1590.
Soga, N et al. Paclitaxel Carboplatin chemotherapy as a second-line chemotherapy for advanced platinum resistant urothelial cancer in Japanese cases. International Journal of Urology 2007; 14(9): 828-832.

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Sweeney CJ, Roth BJ, Kabbinavar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol 2006; 24:3451.
Tsuruta, H et al. Combination therapy consisting of gemcitabine, carboplatin, and docetaxel as an active treatment for advanced urothelial carcinoma. International Journal of Clinical Oncology 2011; 16(5): 533-538.
Uhm, JE et al. Paclitaxel with cisplatin as salvage treatment for patients with previously treated advanced transitional cell carcinoma of the urothelial tract. Neoplasia 2007; 9(1): 18-22.
Witte RS, Elson P, Bono B, et al. Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol 1997; 15:589.

Meta-analysis

A12. Please explain the rationale for conducting a network meta-analysis of the binary outcomes objective response rate and 12-month overall survival, given that these outcomes do not inform the economic model.

A13. The rationale given in the company submission for conducting the fractional polynomial analysis was that the proportional hazards assumption was likely to be violated. However, zero-order fractional polynomial analysis was conducted for all comparisons, which also assumes proportional hazards. Please explain the rationale for conducting this analysis given the apparent contradiction.

A14. **Priority question.** The fractional polynomial network meta-analysis consists largely of direct comparisons. Please explain why this approach to network meta-analysis was chosen instead of direct comparison meta-analyses between the simulated atezolizumab arm and each comparator.

A15. **Priority question.** Please provide the following analyses for each cohort:

(a) An unadjusted direct comparison of overall survival and progression-free survival from the IMvigor210 trial and each of the relevant comparator studies.

(b) An adjusted direct meta-analysis comparison between the simulated atezolizumab arm and comparator arm for each of the relevant comparator studies.

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Alternatively, provide justification why these analyses are not considered appropriate.

Please consider clarification questions A30 and A31 below before providing these analyses, as these raise issues related to the analysis approach.

A16. **Priority question.** The rationale given in sections 3.5.3 and 4.10.4 of the company submission for identifying the prognostic factors used to match patients in the atezolizumab trials to those in comparator trials, is based on two publications. Please provide evidence that no known prognostic factors or effect modifiers have been missed from the prediction model.

A17. **Priority question.** Please provide evidence to justify the cut-off used in section 4.10.4 of the company submission for the age covariate of the prediction model (65 years or older).

A18. **Priority question.** Please provide evidence to justify the cut-off used for the prior chemotherapies covariate of the prediction model (2 or more).

A19. Please clarify why liver metastasis was selected as a prognostic factor rather than visceral metastasis (i.e. bone, liver or lung) which is mentioned as a prognostic factor in section 3.5.3 of the company submission. Would specification of liver rather than visceral metastasis be unnecessarily restrictive given the already poor evidence base and could this have led to exclusion of any otherwise relevant studies?

A20. Please explain why in section 4.10.5 overall survival at 12 months was selected as an outcome instead of also including overall survival measured at other time points? Could this have led to exclusion of any studies with relevant overall survival outcomes?

A21. **Priority question.** Please explain how the values for age>65 years in Table 17 were obtained from the studies by Barnias (2007), DeSantis et al (2009-2012), Kim (2013) and Lee (2012) since these do not match the information reported in the study publications.

A22. **Priority question.** Please explain the following discrepancies between the values reported in Table 17 and those in the Bellmunt et al (2009) study:

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(a) Age ≥65 years was 0.49 in the best supportive care arm and 0.47 in the vinflunine + best supportive care arm, not 0.44 as stated in the Table 17.

(b) The ERG cannot find the value of 0.78 for gender, either in the main publication or in a secondary publication not cited in Table 17 (J Clin Oncol 2010;28:1850-55).

(c) Table 17 states that the proportion of people with liver metastases was NA (not applicable); however, the secondary publication (not cited in the table: J Clin Oncol 2010;28:1850-55) states that across both study arms the value was 0.29. Why was this value not used in the analysis?

(d) The proportion of people with ECOG PS≥1 was 0.62 in the best supportive care arm and 0.72 in the vinflunine +best supportive care arm, not 0.69 as stated in Table 17.

A23. **Priority question.** Table 17 states that the proportion with liver metastases in the Lee (2012) study was NA (not applicable); however, the Lee (2012) publication reports liver metastases as 0.30. Why was this value not used in the analysis?

A24. The text below Table 17 states that "there are a number of differences between included trials that require some caution when interpreting the results, such as differences in patient populations including baseline risk, treatment history, differences in trial designs, particularly in regard to primary efficacy outcome(s) measurements." This appears to suggest considerable heterogeneity but this is not transparent as baseline characteristics from the comparator studies are not presented in the company submission. Please explain the rationale for including these studies in the network meta-analysis if the populations were heterogeneous?

A25. **Priority question:** Please provide full details of the study design and population baseline demographic characteristics of each comparator study in section 4.10.5. This should include sample sizes, interventions (including dosage), key inclusion/exclusion criteria, and length of follow up. Please highlight the differences that are referred to in the company submission (i.e. the differences mentioned in the text below Table 17).

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A26. In Figure 4 please explain how the different categories of heterogeneity are defined, and how the combined category of risk of bias and heterogeneity is defined?

A27. Please provide a critical appraisal of both the IMvigor210 and PCD4989g studies, including an assessment of the risk of bias.

A28. Table 19 explaining the methodology of the network meta-analysis for the overall survival outcome shows three different prior distributions for between-study heterogeneity, one of which was used in the base case. Please explain:

- Why the other two prior distributions are presented?
- Were they subject to sensitivity analysis? If so, please provide the results.

Please also answer these questions for the progression-free survival outcome (Table 7 in Appendix 8.4).

A29. The prior distributions were obtained from Turner et al (2015) and the authors emphasise in their publication the value of using these prior distributions to support random-effects meta-analysis. Please explain why random-effects analyses were not used in the base case given that the prior distributions were available?

A30. **Priority question.** The text immediately above Table 23 states that a random effects model was explored in sensitivity analysis; however this is not reported in the company submission. Please provide the random-effects analysis, for each population and for each comparator where possible.

A31. The company submission states in section 4.10.3 that missing covariate values were imputed by generating, at every bootstrap iteration, a random value from a uniform distribution, with boundaries defined by the range of reported values across the studies included in the analysis. What is the justification for this approach? Please provide results based on an alternative means of imputation, such as probabilistic multiple imputation, sensitivity analyses of other imputation approaches or provide justification for why these alternative imputation methods were not considered.

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A32. Please provide the overall survival and progression-free survival results for each study included in the network meta-analysis, indicating in each case the data from both the original study arm and the simulated atezolizumab arm. A format such as that given in Table 1 of the publication by Jansen et al (2011) (cited in the company submission reference list) would be appropriate for summarising all the studies in a concise format.

A33. Please provide a table of the contrast estimate parameters and posterior correlations for overall survival for the first-line population, in the same format as the data provided for second-line population as given in Table 24.

Non-randomised and non-controlled evidence

A34. Please provide the median follow up time and range for each data cut of the IMvigor210 study as detailed in Table 26.

A35. Please explain why two versions of the RECIST criteria were used in the IMvigor210 study.

A36. **Priority question.** Please explain where the 10% historical control rate used in hypothesis testing in IMvigor210 came from, as this is not mentioned in the primary publication. Please justify why this 10% value was chosen and whether any alternatives are available.

A37. Please explain what is meant in the company submission by “intention-to-treat population”, given that intention-to-treat is generally understood to refer to the randomisation groups to which patients are allocated and analysed whereas IMvigor210 had only a single arm and no randomisation.

A38. Please explain whether the fact that 15.1% of cisplatin-ineligible patients in IMvigor210 had received prior cisplatin would affect interpretation of the results? Is a subgroup available that excludes these patients?

A39. Please provide the results of the subgroup analyses mentioned in the sections 4.11.10.2 and 4.11.10.3 of the company submission for the first-line and second-line populations.

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A40. Please provide the inclusion and exclusion criteria for the PCD4989g study. Please also clarify whether patients' disease had progressed and/or if they were cisplatin-ineligible.

A41. The text beneath Table 26 in the company submission suggests that not all of the participants in the PCD4989g study received the licensed dose. Please clarify how many participants did not receive the licensed dose and how this would affect interpretation of the results. Are results available for the subgroup that did receive the licensed dose?

A42. The protocol for study PCD4989g is listed in the reference list of the company submission but was not included with the submission. Please provide the protocol.

A43. Please provide the numbers and percentage of patients who experienced each type of grade 3/4 adverse event, serious adverse event, adverse event of special interest, and adverse event which led to discontinuation, for both the IMvigor210 and PCD4989g studies.

A44. Please explain what "N/A" means in Table 29 and why these data on prior radical treatment (cystectomy or nephroureterectomy) and haemoglobin level are not provided for cohort 1 of the IMvigor210 study.

Section B: Clarification on cost-effectiveness data

B1. **Priority question.** Tables 50, 51 and 71 state that a generalised gamma distribution was used for progression-free survival for both the first-line and second-line populations, but the economic models for both populations use gamma distributions. Please clarify which distribution was used.

B2. **Priority question.** Table 69 states that the source of the health home visit cost is Curtis 2016 but the Curtis 2016 publication does not report this. Please provide the source of this data.

B3. **Priority question.** Table 69 provides references for costs of a community nurse visit, dietician, oncologist consultation and hospice care. However, these references are

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not included in the company submission reference list, and the ERG have been unable to locate these costs. Please provide the sources of these costs.

B4. **Priority question.** Table 70 provides references for costs of adverse events for alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increased, diarrhoea, electrolyte abnormalities, hypophosphataemia, infection, peripheral neuropathy (sensory or motor) and renal failure. However, these references are not included in the company submission reference list, and the ERG have been unable to locate these costs. Please provide the sources of these costs.

B5. **Priority question.** In table 70, the source of the adverse event costs is given as the nivolumab NSCLC appraisal (for adverse events such as fatigue and leucopenia) but the values in the table are slightly higher than those in the source appraisal. The company submission does not state whether these costs were increased. Please clarify this difference.

B6. **Priority question.** Please clarify the pathway of care for patients who stop atezolizumab treatment, either at first-line or second-line.

B7. **Priority question.** For time to treatment discontinuation the company submission states that a generalised gamma distribution provides the best fit for both first-line and second-line cohorts for the atezolizumab arm. However, Tables 66 and 67 of the company submission report gamma distributions instead of generalised gamma distributions for both cohorts. This is inconsistent with the stated generalised gamma distribution for time to treatment discontinuation of atezolizumab reported in Table 71. The economic models for both first and second-line populations use a gamma distribution. Please clarify which distribution is used.

B8. **Priority question.** Please provide a scenario analysis of an unadjusted (naive) comparison between atezolizumab and its comparators for the first-line and second-line populations using the observed study data (i.e. based on the unadjusted meta-analysis requested in clarification question A14 (a)).

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B9. Please provide the references for the 7 cost-effectiveness studies identified in the company's systematic review of cost-effectiveness studies.

B10. A mixed cure rate model with a 0% cure rate fraction based on a gamma distribution would be expected to give the same results as a standard gamma distribution. However, the results reported in the company submission for these two methods are different. Please explain this difference.

Section C: Textual clarifications and additional points

C1. Please explain the meaning of the missing footnotes a. and b. for Figure 18.

C2. The PCD4989g study is not marked as confidential in section 4.11.11, but it is marked as academic in confidence in section 4.12.3.1. Please clarify which is correct.

Single technology appraisal

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Response to clarification questions

Dear Helen,

Please find below responses to the clarification questions received from the Evidence Review Group, Southampton Health Technology Assessments Centre, for the above appraisal. A reference file was additionally submitted to NICE Docs as part of this response.

Our responses include commerical in confidence information as highlighted below. We therefore also include a redacted version of these responses and the confidential information checklist.

A1. Please clarify the role of the expert clinical advisory panel and explain if there were disagreements about any of the issues covered in the company submission.

The expert clinical advisory panel included 12 physicians experienced in the treatment of mUC patients. A one-day advisory meeting was held to solicit clinical opinion on key clinical parameters of the economic model and submission. Topics for discussion included: clarification of the UK patient pathway in metastatic urothelial carcinoma (mUC) and standard of care; appropriate description of patient health states; anticipated pattern of response to atezolizumab and duration of treatment; validation of extrapolated survival curves and expected long-term survival of atezolizumab treated mUC patients; expected utility of mUC patients; and healthcare resource use for mUC patients.

Advisor opinions were broadly consistent. The most significant variance was opinion regarding anticipated long-term survival for atezolizumab treated mUC patients, as reflected in the range of values reported in Table 77 of company submission.

A2. Please define best supportive care for the second-line population (people whose disease has progressed after platinum-based chemotherapy or people for whom cisplatin-based chemotherapy is unsuitable and whose disease has progressed after platinum-based therapy).

For clarity, the second line (2L) population includes the following:

- Patients whose disease has progressed after platinum-based chemotherapy
- Patients for whom cisplatin-based chemotherapy is unsuitable and whose disease has progressed after non-platinum-based therapy

In both above populations the definition of best supportive care is consistent. Patients will receive best supportive care when they are not suitable for active 2L treatment due to clinical considerations of their disease, co-morbidities, or performance status. For these patients the aim of treatment is to relieve symptoms of their disease, and would include support from oncology and palliative care teams including consultants and specialist nurses, palliative radiotherapy for the relief of symptoms, analgesia, support in the community, and hospice admission. This is consistent with the definition of best support care discussed during the scoping consultation, and workshop for this appraisal.
As described in section 5.2.3 and 5.5.4, within the economic model no additional costs have been accounted for with the comparator best supportive care. As such, costs for this

comparator are accrued only from health-state costs. Details of the resources used for health state costs are found in section 5.5.7, Table 69 of company submission.
This is a conservative approach, by not assuming any additional cost for patients who receive best-supportive care following first line treatment.

A3. Please clarify what the numbers in the following sentence refer to: "Taxane choice for patients recruited from the UK is heavily weighted towards paclitaxel ([redacted]) vs. docetaxel ([redacted])" (page 22 of company submission).

These values refer to the UK patients recruited into the IMvigor 211 study, for which the comparator arm is investigator choice of vinflunine, paclitaxel or docetaxel. Investigators are required to pre-specify chemotherapy choice, prior to randomisation to either atezolizumab or the control arm of the study. Of the 84 UK patients enrolled into this study, the investigators pre-specified that they would treat 46 with vinflunine, 36 with paclitaxel and 2 with docetaxel.

A4. Please provide an explanation for the statement in the company submission that the European Society of Medical Oncology Guidelines are not relevant to UK clinical practice.

The European Society of Medical Oncology (ESMO) guidelines are described as not being relevant to UK practice, because they recommend vinflunine as the only approved agent in the 2L. Whilst vinflunine has European Medicines Agency (EMA) approval for use following chemotherapy failure, it was not recommended by NICE (TA272), is not included in the appraisal scope, and as such is not part of routine UK clinical practice.

Whilst vinflunine vs BSC represents the only phase III trial which has been conducted in the 2L setting, a statistically significant survival advantage of 2 months was not reached within the trial (Bellmunt J 2009). Furthermore, there are associated toxicities, such that even when available in the UK through an expanded access programme, there was not wide uptake of the drug.

A5. Please provide the search strategy used to identify relevant sources of clinical effectiveness evidence, indicating the number of records identified for each search line.

The following tables display the search strategy including search terms and number of records per search line:

Table 1 Medline; Table 2 Embase; Table 3 Cochrane; Table 4 ICTRP; Table 5 EU clinical trial register; Table 6 US NUH; and Table 7 conference abstracts.

Table 1: Medline database search results (includes Medline-in-Process and other non-indexed citations [with status: publisher, in-data review or PubMed-not-Medline]), Search date: June 20, 2016 (Date range: 1960–2016)

#	Search terms	Hits
1	ME60	26154128
2	CT=CARCINOMA, TRANSITIONAL CELL	16661
3	CT=URINARY BLADDER NEOPLASMS	46902
4	CT=URETERAL NEOPLASMS	4255
5	CT=URETHRAL NEOPLASMS	2367
6	CT D KIDNEY NEOPLASMS AND (CT=KIDNEY PELVIS OR KIDNEY PELVIS/(TI; AB; UT) OR RENAL PELVIS/(TI; AB; UT))	2815
7	CT=UROLOGIC NEOPLASMS	3777
8	CT=UROGENITAL NEOPLASMS	3524
9	TRANSITIONAL # # CELL # # (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	10001
10	BLADDER ?, (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	50305
11	UROTHELIAL ?, (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	9695
12	UROTHELIUM ?, (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	1309
13	URETER## ?, (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	4679
14	URETHRA# ?, (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	2514
15	RENAL PELVIS ?, (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	1939
16	KIDNEY PELVIS ?, (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	111
17	URINARY TRACT # # (CARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)./(TI; AB; UT)	1729
18	**2 TO 17**	**80036**
19	CT D ANTINEOPLASTIC PROTOCOLS	115788
20	TE=ANTINEOPLASTIC AGENTS	218217
21	CT D ANTIBODIES, MONOCLONAL	194288
22	CT D MOLECULAR TARGETED THERAPY	14623

23	CT D CANCER VACCINES	11023
24	CT D IMMUNOTHERAPY	233260
25	CT D PROTEIN KINASE INHIBITORS	53192
26	CT D ANGIOGENESIS INHIBITORS	38608
27	CT D ANTIBIOTICS, ANTINEOPLASTIC	136171
28	CT D ANTIMETABOLITES, ANTINEOPLASTIC	134057
29	CT D ANTIMITOTIC AGENTS	79111
30	CT D ANTINEOPLASTIC AGENTS, ALKYLATING	84703
31	CT D ANTINEOPLASTIC AGENTS, PHYTOGENIC	93166
32	CT D VINCA ALKALOIDS	33772
33	CT D TAXOIDS OR TAXANE#/(TI; AB; UT)	32152
34	CT D ORGANOPLATINUM COMPOUNDS OR CT=PLATINUM COMPOUNDS OR PLATINUM/(TI; AB)	45349
35	(CHEMOTHERAP### OR SYSTEMIC # THERAP### OR SYSTEMIC # TREATMENT# OR ANTINEOPLASTIC # # PROTOCOL# OR ANTI NEOPLASTIC # # PROTOCOL# OR ANTI NEOPLASTIC AGENT# OR ANTINEOPLASTIC AGENT# OR CANCER TREATMENT PROTOCOL# OR ANTINEOPLASTIC TREATMENT# OR ANTI NEOPLASTIC TREATMENT# OR CANCER VACCINE# OR CANCER IMMUNOTHERAP### OR IMMUNE THERAP### OR PROTEIN # KINASE INHIBITOR# OR CHEMOIMMUNOTHERAP### OR SERINE THRENOINE KINASE INHIBITOR# OR TYROSINE KINASE INHIBITOR# OR TARGETED THERAPY)/(UT; TI; AB) AND STATUS=ALERT	38332
36	TE=MPDL3280A	23
37	(ATEZOLIZUMAB? OR TECENTRIQ? OR MPDL 3280# OR MPDL3280# OR RG 7446 OR RG7446)/(TI; AB; UT)	56
38	RNO=52CMI0WC3Y	0
39	CR=1380723-44-3	0
40	TE=NIVOLUMAB	163
41	NIVOLUMAB?/(TI; AB; UT)	451
42	(MDX-1106 OR MDX1106 OR ONO-4538 OR ONO4538 OR BMS-936558 OR BMS936558 OR OPDIVO?)/(TI; AB; UT)	41
43	RNO=31YO63LBSN	163
44	CR=946414-94-4	0
45	TE=PEMBROLIZUMAB	102
46	(PEMBROLIZUMAB OR KEYTRUDA? OR LAMBROLIZUMAB OR MK 3475 OR MK3475 OR MERCK 3475 OR SCH 900475)/(TI; AB; UT)	325
47	RNO=DPT0O3T46P	102
48	CR=1374853-91-4	0
49	TE=VINFLUNINE	129

50	(VINFLUNIN# OR JAVLOR? OR DIHYDROVINORELBINE OR F12158 OR F-12158 OR BMS-710485)/(TI; AB; UT)	214
51	RNO=33MG53C7XW OR RNO=5BF646324K	129
52	CR=194468-36-5 OR CR=162652-95-1	129
53	CT=VINBLASTINE	11990
54	(VINBLASTIN? OR LE29060 OR LE 29060 OR 29060 LE OR LEUKOBLASTIN? OR VIN##LEU%OBLASTIN# OR VIN%ALEU%OBLASTIN# OR VELBAN? OR VELSAR? OR VLB? OR ROZEVIN?)/(TI; AB; UT; TE)	18688
55	RNO=5V9KLZ54CY	11990
56	CR=865-21-4	11990
57	TE=GEMCITABINE	8535
58	(GEMCITABIN? OR LY188011 OR LY 188011 OR NSC #613327 OR GEMZAR? OR GEMCITE?)/(TI; AB; UT)	11664
59	RNO=B76N6SBZ8R OR RNO=U347PV74IL	8535
60	CR=95058-81-4 OR CR=122111-03-9	0
61	CT=PEMETREXED	1458
62	(PEMETREXED? OR ALIMTA? OR CIAMBRA? OR LY 231514 OR LY231514 OR ROLAZAR OR TIFOLAR)/(TI; AB; UT; TE)	2391
63	RNO=04Q9AIZ7NO OR RNO=2PKU919BA9	1458
64	CR=137281-23-3 OR CR=150399-23-8	1458
65	TE=DOCETAXEL	8074
66	(DOCETAX%L? OR TAXOTERE? OR XRP6976 OR DOCEFREZ? OR HDSB 6965 OR NSC 628503 OR NSC628503 OR RP 56976 OR RP56976 OR DOCECAD? OR TEXOT?)/(TI; AB; UT)	11351
67	RNO=15H5577CQD OR RNO=699121PHCA	8074
68	CR=148408-66-6 OR CR=114977-28-5	0
69	CT D PACLITAXEL OR CT=ALBUMIN-BOUND PACLITAXEL	21423
70	(PACLITAXEL? OR BMS 181339-01 OR BMS181339-01 OR HSDB 6839 OR NSC 125973 OR NSC12973 OR ANZATAX? OR ASOTAX? OR BRISTAXOL? OR CAPXOL? OR CYCLOPAX? OR MEDIPHAXEL? OR ONXOL? OR PACLIVIS? OR PAXENE? OR PAXTEL? OR PRAXEL? OR TAXOL?)/(TI; AB; UT)	26237
71	(NAB-PACLITAXEL OR NAB-PAC OR ALBUMIN-BOUND PACLITAXEL OR ALBUMIN-STABILIZED NANOPARTICLE PACLITAXEL OR NANOPARTICLE ALBUMIN-BOUND PACLITAXEL OR NANOPARTICLE PACLITAXEL OR PROTEIN-BOUND PACLITAXEL OR ABRAXAN? OR ABI 007 OR ABI007)/(TI; AB; UT)	699
72	RNO=P88XT4IS4D	21416
73	CR=33069-62-4	0
74	CT=IFOSFAMIDE	4448

75	(IFOSFAMID? OR IPHOSPHAMID? OR CUANTIL? OR CYFOS? OR HOLOXAN? OR MITOXANA OR IFOXAN? OR NCI-C01638 OR NCIC01638 OR NSC 109724 OR NSC109724 OR Z 4942 OR Z4942 OR MJF 9325 OR MJF9325 OR IFEX OR ISOENDOXAN)/(TI; AB; UT)	5348
76	RNO=UM20QQM95Y	4448
77	CR=3778-73-2	4448
78	CT=FLUOROURACIL	36898
79	(FLUOROURACIL? OR 5FLUOROURACIL? OR FLUORO URACIL? OR 5-FU OR 5FU OR FLU#RACIL? OR FLURIS? OR ADRUCIL? OR ARUMEL? OR EFUDEX? OR FLUOROPLEX? OR FLUOROBLASTIN? OR RO 2-9757 OR RO2-9757 OR RO 29757 OR RIBOFLUOR? OR TIMAZIN? OR ONKOFLUOR? OR NEOFLUOR?)/(TI; AB; UT)	37200
80	RNO=U3P01618RT	36898
81	CR=51-21-8	36898
82	CT=METHOTREXATE	33636
83	(METHOTREXAT? OR MTX OR NSC-740 OR NSC740 PR ABOTREXAT? OR AMETHOPTERIN? OR ANTIFOLAN? OR BRIMEXAT? OR CL 14377 OR CL14377 OR EMT#EXAT? OR FARMITREXAT? OR FOLEX? OR LANTAREL? OR METHYLAMINOPTERIN? OR METOTREX? OR MEXATE? OR RASUVO? OR RHEUMATREX? OR TEXATE? OR TREXERON OR TRIXILEM? OR WR-19039 OR WR19039)/(TI; AB; UT)	36306
84	RNO=YL5FZ2Y5U1	33636
85	CR=59-05-2	33636
86	CT D CARBOPLATIN	9815
87	(CARBOPLAT? OR NSC 201345 OR NSC201345 OR NSC 241240 OR NSC241240 OR PARAPLATIN OR BLASTOCARB? OR CARBOSIN? OR CARBOTEC? OR CBDCA? OR CYCLOPLAT? OR ERCAR? OR JM 8 OR JM8 OR NEOCARBO?)/(TI; AB; UT)	12384
88	RNO=BG3F62OND5	9815
89	CR=41575-94-4	9815
90	CT D CISPLATIN	43844
91	(CISPLATIN? OR CIS-PLATIN? OR CIS-DIAMINODICHLOROPLATIN? OR CDDP OR CIS-DICHLORODIAMINOPLATIN? OR PLATINUM DIAMMINODICHLORIDE OR NCI C55776 OR NCIC55776 OR NSC 119875 OR NSC119875 OR ABIPLATIN? OR BRIPLATIN? OR LEDERPLATIN? OR NEOPLATIN? OR PLATINEX? OR PLATINOL? OR PLATOSIN? OR PLATIDIAM?)/(TI; AB; UT)	53755
92	RNO=Q20Q21Q62J	43844
93	CR=15663-27-1	43844
94	MVAC/(TI; AB; CT; UT; TE) OR M VAC/(TI; AB; CT; UT; TE)	584
95	CT D DOXORUBICIN	46638

96	(DOXORUBICIN? OR CAELYX? OR CAELIX OR DOXIL? OR ADRIABLASTIN? OR ADRIAMYCIN? OR CCRIS 739 OR FI 106 OR FI106 OR NCI C01514 OR NCIC01514 OR NDC 38242 874 OR NDC38242874 OR NSC 123127 OR NSC123127 OR DOXOTEC? OR RUBEX? OR MYOCET? OR ONKODOX? OR RIBODOXO?)/(TI; AB; UT)	46155
97	RNO=80168379AG OR RNO=82F2G7BL4E	43058
98	CR=23214-92-8 OR CR=25316-40-9	43058
99	CT D GRANULOCYTE COLONY-STIMULATING FACTOR	13947
100	(GRANULOCYTE # # COLONY # # STIMULATING # # FACTOR OR G CSF OR AVI-014)/(TI; AB; UT)	29802
101	CR=143011-72-7	13929
102	TE="N-(4-BROMO-2-FLUOROPHENYL)-6-METHOXY-7-((1-METHYLPIPERIDIN-4-YL)METHOXY)QUINAZOLIN-4-AMINE"	399
103	(VANDETANIB? OR CAPRELSA? OR ZACTIMA OR HSDB 8198 OR ZD 6474 OR ZD6474)/(TI; AB; UT)	621
104	RNO=YO460OQ37K	0
105	CR=443913-73-3 OR CR=338992-00-0	0
106	TE=BIBW 2992	239
107	(AFATINIB? OR BIBW 2992 OR BIBW2992 OR TOVOK? OR TOMTOVOK? OR GIOTRIF? OR GILOTRIF?)/(TI; AB; UT)	504
108	RNO=41UD74L59M	0
109	CR=850140-72-6	0
110	TE=PAZOPANIB	420
111	(PAZOPANIB OR VOTRIENT OR GW786034# OR GW 786034# OR GW7 86034# OR GW 780604 OR GW 780604 OR HSDB 8210 OR VOTRIENT? OR PATORMA? OR ARMALA?)/(TI; AB; UT)	875
112	RNO=7RN5DR86CK OR RNO=33Y9ANM545	420
113	CR=444731-52-6 OR CR=635702-64-6	0
114	(AVELUMAB OR MSB-0010718C OR MSB0010718C)/(TI; AB; UT)	9
115	RNO=KXG2PJ551I	0
116	CR=1537032-82-8	0
117	TE=RAMUCIRUMAB	68
118	(RAMUCIRUMAB OR CYMRANZA? OR IMC 1121B OR IMC1121B)/(TI; AB; UT)	226
119	RNO=D99YVK4L0X	68
120	CR=947687-13-0	0
121	TE=PALBOCICLIB	110
122	(PALBOCICLIB OR IBRANCE? OR PD 332991 OR PD332991 OR PD 0332991 OR PD0332991)/(TI; AB; UT)	206

123	RNO=G9ZF61LE7G	110
124	CR=571190-30-2	0
125	CT=EVEROLIMUS	2867
126	EVEROLIMUS?/(TI; AB; UT)	4032
127	(RAD 001 OR RAD001 OR SDZ RAD OR AFINITOR? OR CERTICAN? OR ZORTRESS? OR VOTUBIA?)/(TI; AB; UT)	602
128	RNO=9HW64Q8G6G	2867
129	CR=159351-69-6	0
130	TE=GEFITINIB	3496
131	GEFITINIB?/(TI; AB; UT)	4508
132	(ZD1839 OR ZD 1839 OR I#RESSA?)/(TI; AB; UT)	924
133	RNO=S65743JHBS	3496
134	CR=184475-35-2	3496
135	CT=ERLOTINIB HYDROCHLORIDE	2830
136	ERLOTINIB?/(TI; AB; UT)	4319
137	(OSI 774 OR OSI774 OR CP 358774 OR TARCEVA?)/(TI; AB; UT)	340
138	RNO=DA87705X9K	2830
139	CR=183319-69-9	0
140	CT=CETUXIMAB	3169
141	CETUXIMAB?/(TI; AB; UT)	4454
142	(C225 OR IMC-C225 OR IMCC225 OR HSDB 7454 OR HSDB7454 OR ERBITUX?)/(TI; AB; UT)	548
143	RNO=PQX0D8J21J	3169
144	CR=205923-56-4	0
145	TE=PANITUMUMAB	658
146	PANITUMUMAB/(TI; AB; UT)	1036
147	(ABX-EGF? OR ABENIX? OR VECTIBIX?)/(TI; AB; UT)	78
148	RNO=6A901E312A	0
149	CR=339177-26-3	0
150	CT=TRASTUZUMAB	4701
151	TRASTUZUMAB?/(TI; AB; UT)	6567
152	(212PB-TCMC? OR HSDB 8142 OR HSDB8142 OR PF 05280014 OR HERCEPTIN?)/(TI; AB; UT)	1637
153	RNO=P188ANX8CK	4701
154	CR=180288-69-1	0
155	TE=LAPATINIB?/(TI; AB; UT)	0
156	LAPATINIB?/(TI; AB; UT)	1749

157	(GSK 572016 OR GSK572016 OR GW 572016 OR GW572016 OR HSDB 8209 OR HSDB8209 OR TYKERB?)/(TI; AB; UT)	107
158	RNO=0VUA21238F	1137
159	CR=231277-92-2	0
160	TE="4-AMINO-5-FLUORO-3-(5-(4-METHYLPIPERAZIN-1-YL)-1H-BENZIMIDAZOL-2-YL)QUINOLIN-2(1H)-ONE"	63
161	DOVITINIB?/(TI; AB; UT)	94
162	(TK-258 OR TK258 OR CHIR 258 OR CHIR258)/(TI; AB; UT)	15
163	RNO=I35H55G906	0
164	CR=405169-16-6	0
165	CT=BEVACIZUMAB	8082
166	BEVACIZUMAB?/(TI; AB; UT)	11122
167	(HSDB 8080 OR HSDB8080 OR RHUMAB-VEGF OR AVASTIN?)/(TI; AB; UT)	1284
168	RNO=2S9ZZM9Q9V	8082
169	CR=216974-75-3	0
170	TE=AFLIBERCEPT	420
171	AFLIBERCEPT?/(TI; AB; UT)	772
172	(AVE 0005 OR AVE0005 OR BAY 86-5321 OR BAY86-5321 OR BAY865321 OR VEGF TRAP? OR ZALTRAP?)/(TI; AB; UT)	268
173	RNO=15C2VL427D	420
174	CR=862111-32-8	0
175	TE=SUNITINIB	2499
176	SUNITINIB?/(TI; AB; UT)	3892
177	(PHA-290940AD OR PHA290940AD OR SU 011248 OR SU011248 OR SU 11248 OR SU11248 OR SU010398 OR SU 010398 OR SU 10398 OR SU10398 OR SUTENT?)/(TI; AB; UT)	257
178	RNO=LVX8N1UT73	0
179	CR=341031-54-7	0
180	TE=CABOZANTINIB	103
181	CABOZANTINIB?/(TI; AB; UT)	252
182	(BMS 907351 OR BMS907351 OR XL 184 OR XL184 OR CABOMETYX? OR COMETRIQ?)/(TI; AB; UT)	65
183	RNO=1C39JW444G OR RNO=DR7ST46X58	103
184	CR=1140909-48-3 OR CR=849217-68-1	0
185	TE=CABAZITAXEL	217
186	CABAZITAXEL?/(TI; AB; UT)	470
187	(XRP-6258 OR XRP6258 OR TXD258 OR TXD 258 OR RPR 116258A OR JEVTANA?)/(TI; AB; UT)	34

188	RNO=51F690397J	217
189	CR=183133-96-2	0
190	TE=ERIBULIN	175
191	ERIBULIN?/(TI; AB; UT)	276
192	(B 1939 OR B1939 OR E 7389 OR E7389 OR ER 086526 OR ER 086526)/(TI; AB; UT)	52
193	RNO=LR24G6354G	0
194	CR=253128-41-5	0
195	TE=IPILIMUMAB	764
196	IPILIMUMAB/(TI; AB; UT)	1255
197	(MDX 010 OR MDX010 OR MDX-CTLA 4 OR MDXCTLA4 OR MDX-CTLA4 OR YERVOY?)/(TI; AB; UT)	69
198	RNO=6T8C155666	0
199	CR=477202-00-9	0
200	19 TO 199	1182261
201	DT=RANDOMIZED CONTROLLED TRIAL	413363
202	DT=CONTROLLED CLINICAL TRIAL	90426
203	RANDOMI%ED/(TI; AB; UT)	451446
204	PLACEBO/(TI; AB; UT)	176099
205	QF=DRUG THERAPY	1846450
206	RANDOMLY/(TI; AB)	254001
207	TRIAL/(TI; AB)	428996
208	GROUPS/(TI; AB)	1599413
209	201 TO 208	3824130
210	209 NOT (CT D ANIMALS NOT CT=HUMANS)	3299499
211	**18 AND 200 AND 210**	**7193**
212	CT=EPIDEMIOLOGIC STUDIES	7054
213	CT D CASE-CONTROL STUDIES	775439
214	CT D COHORT STUDIES	1525325
215	CASE CONTROL/(TI; AB; UT)	93493
216	COHORT (STUDY; STUDIES)/(TI; AB; UT)	119199
217	COHORT ANALY?/(TI; AB; UT)	4817
218	FOLLOW U% (STUDY; STUDIES)/(TI; AB; UT)	41699
219	OBSERVATIONAL (STUDY; STUDIES)/(TI; AB; UT)	62433
220	LONGITUDINAL/(TI; AB; UT)	173453
221	RETROSPECTIVE##/(TI; AB; UT)	492619
222	CROSS-SECTIONAL/(TI; AB; UT)	222912
223	CT=CROSS-SECTIONAL STUDIES	213779

224	CT=OBSERVATIONAL STUDIES? OR DT=OBSERVATIONAL STUDY	22829
225	NO%-RANDOMI%ED ?, (TRIAL#; STUD###; DESIGN)./(TI; AB; UT)	7903
226	UNCONTROLLED ?, (TRIAL; STUDY; DESIGN)./(TI; AB) OR NON-CONTROLLED ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	5371
227	NON-RCT/(TI; AB; UT) OR NRCT/(TI; AB; UT)	163
228	SINGLE # ARM?/(TI; AB; UT)	3852
229	DT=CLINICAL TRIAL	498256
230	DT=CLINICAL TRIAL, PHASE I%#	36754
231	PHASE 2 ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	4509
232	PHASE II ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	25879
233	PHASE 3 ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	3512
234	PHASE III ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	12864
235	PHASE 4 ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	282
236	PHASE IV ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	771
237	PHASE 2 # # # (TRIAL; STUDY; DESIGN)/UT OR PHASE 3 # # # (TRIAL; STUDY; DESIGN)/UT OR PHASE 4 # # # (TRIAL; STUDY; DESIGN)/UT OR PHASE II # # # (TRIAL; STUDY; DESIGN)/UT OR PHASE III # # # (TRIAL; STUDY; DESIGN)/UT OR PHASE IV # # # (TRIAL; STUDY; DESIGN)/UT	192
238	OPEN LABEL/(TI; AB; UT)	30007
239	OPEN # # # (TRIAL; STUDY; DESIGN)/(TI; AB; UT)	32564
240	PARALLEL GROUP#/(TI; AB)	13739
241	(CROSSOVER OR CROSS OVER)/(TI; AB; UT)	68789
242	CONTROLLED ?, (TRIAL; STUDY; DESIGN)./(TI; AB)	203267
243	212 TO 242	2820869
244	243 NOT (CT D ANIMALS NOT CT=HUMANS)	2749788
245	**18 AND 200 AND 244**	**3107**
246	**211 OR 245**	**7826**

Embase database – Search for RCT and non RCT

Table 2: Embase database search results, Search date: June 20, 2016 (Date range: 1974–2016)

#	Search terms	Hits
1	'transitional cell carcinoma'/exp	20439
2	'bladder cancer'/exp OR 'bladder tumor'/de	71293
3	'kidney pelvis carcinoma'/de OR 'kidney pelvis cancer'/de OR 'kidney pelvis tumor'/de	1761

4	'kidney cancer'/exp AND ('kidney pelvis'/exp OR 'kidney pelvis tumor'/de OR 'kidney pelvis':ab,ti OR 'renal pelvis':ab,ti)	1640
5	'ureter cancer'/exp OR 'ureter tumor'/de	4074
6	'urethra cancer'/exp OR 'urethra tumor'/de	2339
7	'urinary tract cancer'/de OR 'urinary tract tumor'/de	5102
8	'urothelial cancer':de OR 'urothelial carcinoma':de OR 'metastatic urothelial cancer':de OR 'advanced urothelial cancer':de OR 'metastatic urothelial carcinoma':de OR 'advanced urothelial carcinoma':de	469
9	(transitional NEXT/3 cell NEXT/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	11969
10	(bladder NEAR/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	58960
11	(urothelial NEAR/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	13741
12	(urothelium NEAR/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	843
13	(ureter* NEAR/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	4027
14	(urethra* NEAR/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	1819
15	('renal pelvis' NEAR/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	1885
16	('kidney pelvis' NEAR/4 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	87
17	('urinary tract' NEXT/1 (carcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignanc*)):ab,ti	1386
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	100428
19	'cancer chemotherapy'/exp	300189
20	'cancer combination chemotherapy'/exp	75422
21	'cancer immunotherapy'/exp	45320
22	'immunotherapy'/de	62222
23	'protein kinase inhibitor'/de OR 'protein serine threonine kinase inhibitor'/de OR 'protein tyrosine kinase inhibitor'/de	34334
24	'chemotherapy'/de	120154
25	'antineoplastic agent'/de	237391
26	'chlormethine derivative'/exp	235213
27	'alkylating agent'/exp	330652

28	'angiogenesis inhibitor'/exp	108333
29	'antineoplastic alkaloid'/exp	215165
30	'anthracycline antibiotic agent'/exp	201256
31	'antineoplastic antimetabolite'/exp	431759
32	'antineoplastic metal complex'/exp	189749
33	'molecularly targeted therapy'/exp	13704
34	'monoclonal antibody'/exp	404625
35	'cancer vaccine'/de	11872
36	'vinca alkaloid'/exp	4325
37	'taxoid'/exp	2147
38	'platinum complex'/exp OR 'platinum'/exp	29147
39	'atezolizumab'/de	445
40	atezolizumab*:tn,ab,ti	40
41	tecentriq*:tn,ab,ti OR (mpdl NEXT/1 3280*):tn,ab,ti OR mpdl3280*:tn,ab,ti OR 'rg 7446':tn,ab,ti OR rg7446:tn,ab,ti	344
42	'1380723-44-3':rn	139
43	'nivolumab'/exp	1907
44	nivolumab*:tn,ab,ti	702
45	mdx-1106':tn,ab,ti OR mdx1106:tn,ab,ti OR 'ono 4538':tn,ab,ti OR ono4538:tn,ab,ti OR 'bms 936558':tn,ab,ti OR bms936558:tn,ab,ti OR opdivo*:tn,ab,ti	591
46	'946414-94-4':rn	1414
47	'pembrolizumab'/exp	1412
48	pembrolizumab:tn,ab,ti OR keytruda*:tn,ab,ti OR lambrolizumab:tn,ab,ti OR 'mk 3475':tn,ab,ti OR mk3475:tn,ab,ti OR 'merck 3475':tn,ab,ti OR 'sch 900475':tn,ab,ti	841
49	'1374853-91-4':rn	1026
50	'vinflunine'/exp	651
51	vinflunin*:tn,ab,ti OR javlor*:tn,ab,ti OR dihydrovinorelbine:tn,ab,ti OR f12158:tn,ab,ti OR 'f 12158':tn,ab,ti OR 'bms-710485':tn,ab,ti	364
52	'194468-36-5':rn OR '162652-95-1':rn	553
53	'vinblastine'/exp	32978
54	vinblastin*:tn,ab,ti OR le29060:tn,ab,ti OR (le NEAR/1 29060):tn,ab,ti OR leukoblastin*:tn,ab,ti OR vincaleukoblastin*:tn,ab,ti OR vincaleucoblastin*:tn,ab,ti OR vinleukoblastin*:tn,ab,ti OR vinleucoblastin:tn,ab,ti OR velban*:tn,ab,ti OR velsar*:tn,ab,ti OR vlb*:tn,ab,ti OR rozevin*:tn,ab,ti	15220
55	'865-21-4':rn	32035
56	'gemcitabine'/exp	40645

57	gemcitabine*:tn,ab,ti OR ly188011:tn,ab,ti OR 'ly 188011':tn,ab,ti OR 'nsc 613327':tn,ab,ti OR 'nsc 0613327':tn,ab,ti OR gemzar*:tn,ab,ti OR gemcite*:tn,ab,ti	20184
58	'95058-81-4':rn OR '122111-03-9':rn	0
59	'pemetrexed'/exp	8879
60	pemetrexed*:tn,ab,ti OR alimta*:tn,ab,ti OR ciambra*:tn,ab,ti OR (ly NEXT/1 231514):tn,ab,ti OR ly231514:tn,ab,ti OR rolazar*:tn,ab,ti OR tifolar:tn,ab,ti	5069
61	'137281-23-3':rn OR '150399-23-8':rn	6964
62	'docetaxel'/exp	42416
63	docetaxel*:tn,ab,ti OR docetaxol*:tn,ab,ti OR taxotere*:tn,ab,ti OR xrp6976:tn,ab,ti OR docefrez*:tn,ab,ti OR (hdsb NEXT/1 6965):tn,ab,ti OR (nsc NEXT/1 628503):tn,ab,ti OR nsc628503:tn,ab,ti OR 'rp 56976':tn,ab,ti OR rp56976:tn,ab,ti OR docecad*:tn,ab,ti OR texot*:tn,ab,ti	21138
64	'148408-66-6':rn OR '114977-28-5':rn	35421
65	'paclitaxel'/exp	78968
66	'bms 181339 01':tn,ab,ti OR 'bms181339 01':tn,ab,ti OR 'hsdb 6839':tn,ab,ti OR 'nsc 125973':tn,ab,ti OR nsc12973:tn,ab,ti OR anzatax*:tn,ab,ti OR asotax*:tn,ab,ti OR bristaxol*:tn,ab,ti OR capxol*:tn,ab,ti OR cyclopax*:tn,ab,ti OR mediphaxel*:tn,ab,ti OR onxol*:tn,ab,ti OR paclivis*:tn,ab,ti OR paxene*:tn,ab,ti OR paxtel*:tn,ab,ti OR praxel*:tn,ab,ti OR taxol*:tn,ab,ti	12788
67	'nab-paclitaxel':tn,ab,ti OR 'nab-pac':tn,ab,ti OR 'albumin-bound paclitaxel':tn,ab,ti OR 'albumin-stabilized nanoparticle paclitaxel':tn,ab,ti OR 'albumin-stabilised nanoparticle paclitaxel':tn,ab,ti OR 'nanoparticle albumin-bound paclitaxel':tn,ab,ti OR 'nanoparticle paclitaxel':tn,ab,ti OR 'protein-bound paclitaxel':tn,ab,ti OR abraxan*:tn,ab,ti OR 'abi 007':tn,ab,ti OR abi007:tn,ab,ti	2396
68	'33069-62-4':rn	68809
69	taxane*:tn,ab,ti	11755
70	'ifosfamide'/exp	25418
71	ifosfamid*:tn,ab,ti OR iphosphamid*:tn,ab,ti OR cuantil*:tn,ab,ti OR cyfos*:tn,ab,ti OR holoxan*:tn,ab,ti OR mitoxana*:tn,ab,ti OR ifoxan*:tn,ab,ti OR 'nci-c01638':tn,ab,ti OR ncic01638:tn,ab,ti OR 'nsc 109724':tn,ab,ti OR nsc109724:tn,ab,ti OR 'z 4942':tn,ab,ti OR z4942:tn,ab,ti OR 'mjf 9325':tn,ab,ti OR mjf9325:tn,ab,ti OR ifex*:tn,ab,ti OR isoendoxan*:tn,ab,ti	0
72	'3778-73-2':rn	24051
73	'fluorouracil'/exp	116353

74	fluorouracil*:tn,ab,ti OR 5fluorouracil*:tn,ab,ti OR (fluoro NEXT/1 uracil):tn,ab,ti OR '5-fu':tn,ab,ti OR 5fu:tn,ab,ti OR fluracil*:tn,ab,ti OR fluoracil*:tn,ab,ti OR fluris*:tn,ab,ti OR adrucil*:tn,ab,ti OR arumel*:tn,ab,ti OR efudex*:tn,ab,ti OR fluoroplex*:tn,ab,ti OR fluoroblastin*:tn,ab,ti OR 'ro 2-9757':tn,ab,ti OR 'ro2-9757':tn,ab,ti OR 'ro 29757':tn,ab,ti OR ribofluor*:tn,ab,ti OR timazin*:tn,ab,ti OR onkofluor*:tn,ab,ti OR neofluor*:tn,ab,ti	50341
75	'51-21-8':rn	107985
76	'methotrexate'/exp	146768
77	methotrexate*:tn,ab,ti OR mtx:tn,ab,ti OR 'nsc-740':tn,ab,ti OR nsc740:tn,ab,ti OR abotrexat*:tn,ab,ti OR amethopterin*:tn,ab,ti OR antifolan*:tn,ab,ti OR brimexat*:tn,ab,ti OR 'cl 14377':tn,ab,ti OR cl14377:tn,ab,ti OR emthexate*:tn,ab,ti OR emtexat*:tn,ab,ti OR farmitrexat*:tn,ab,ti OR folex*:tn,ab,ti OR lantarel*:tn,ab,ti OR methylaminopterin*:tn,ab,ti OR metotrex*:tn,ab,ti OR mexate*:tn,ab,ti OR rasuvo*:tn,ab,ti OR rheumatrex*:tn,ab,ti OR texate*:tn,ab,ti OR trexeron*:tn,ab,ti OR trixilem*:tn,ab,ti OR 'wr-19039':tn,ab,ti OR wr19039:tn,ab,ti	55344
78	'59-05-2':rn	132577
79	'carboplatin'/exp	51751
80	carboplat*:tn,ab,ti OR 'nsc 201345':tn,ab,ti OR nsc201345:tn,ab,ti OR 'nsc 241240':tn,ab,ti OR nsc241240:tn,ab,ti OR paraplatin*:tn,ab,ti OR blastocarb*:tn,ab,ti OR carbosin*:tn,ab,ti OR carbotec*:tn,ab,ti OR cbdca*:tn,ab,ti OR cycloplat*:tn,ab,ti OR ercar*:tn,ab,ti OR 'jm 8':tn,ab,ti OR jm8:tn,ab,ti OR neocarbo*:tn,ab,ti	20103
81	'41575-94-4':rn	46120
82	'cisplatin'/exp	143157
83	cisplatin*:tn,ab,ti OR (cis NEXT/1 platin):tn,ab,ti OR (cis NEXT/1 diaminodichloroplatin*):tn,ab,ti OR cddp:tn,ab,ti OR (cis NEXT/1 dichlorodiaminoplatin*):tn,ab,ti OR 'platinum diamminodichloride':tn,ab,ti OR 'nci c55776':tn,ab,ti OR ncic55776:tn,ab,ti OR 'nsc 119875':tn,ab,ti OR nsc119875:tn,ab,ti OR abiplatin*:tn,ab,ti OR briplatin*:tn,ab,ti OR lederplatin*:tn,ab,ti OR neoplatin*:tn,ab,ti OR platinex*:tn,ab,ti OR platinol*:tn,ab,ti OR platosin*:tn,ab,ti OR platidiam*:tn,ab,ti	71559
84	'15663-27-1':rn	129031
85	'antineoplastic metal complex'/exp	189749
86	platinum:ab,ti	40111
87	mvac:tn,ab,ti OR (m NEXT/1 vac):de,tn,ab,ti	876
88	'doxorubicin'/exp	152810

89	doxorubicin*:tn,ab,ti OR caelyx*:tn,ab,ti OR caelix*:tn,ab,ti OR doxil*:tn,ab,ti OR adriablastin*:tn,ab,ti OR adriamycin*:tn,ab,ti OR 'ccris 739':tn,ab,ti OR 'fi 106':tn,ab,ti OR fi106:tn,ab,ti OR 'nci c01514':tn,ab,ti OR ncic01514:tn,ab,ti OR 'ndc 38242 874':tn,ab,ti OR ndc38242874:tn,ab,ti OR 'nsc 123127':tn,ab,ti OR nsc123127:tn,ab,ti OR doxotec*:tn,ab,ti OR rubex*:tn,ab,ti OR myocet*:tn,ab,ti OR onkodox*:tn,ab,ti OR ribodoxo*:tn,ab,ti	67090
90	'23214-92-8':rn OR '25316-40-9':rn	142761
91	'granulocyte colony stimulating factor'/exp	36552
92	'g csf':ab,ti OR (colony NEAR/3 stimulating NEAR/3 factor):ab,ti OR (granulocyte NEAR/3 colony* NEAR/3 factor):ab,ti	45146
93	'143011-72-7':rn	0
94	'vandetanib'/exp	3540
95	vandetanib*:tn,ab,ti OR caprelsa*:tn,ab,ti OR zactima*:tn,ab,ti OR 'hsdb 8198':tn,ab,ti OR 'zd 6474':tn,ab,ti OR zd6474:tn,ab,ti	2367
96	'443913-73-3':rn OR '338992-00-0':rn	3202
97	'afatinib'/exp	2123
98	afatinib*:tn,ab,ti OR bibw:tn,ab,ti AND 2992:tn,ab,ti OR bibw2992:tn,ab,ti OR tovok*:tn,ab,ti OR tomtovok*:tn,ab,ti OR giotrif*:tn,ab,ti OR gilotrif*:tn,ab,ti	657
99	'pazopanib'/exp	4457
100	pazopanib:tn,ab,ti OR gw786034*:tn,ab,ti OR (gw NEXT/1 786034*):tn,ab,ti OR (gw7 NEXT/1 86034*):tn,ab,ti OR 'gw 780604':tn,ab,ti OR gw780604:tn,ab,ti OR 'hsdb 8210':tn,ab,ti OR votrient*:tn,ab,ti OR patorma*:tn,ab,ti OR armala*:tn,ab,ti OR '850140-72-6':rn	3757
101	'444731-52-6':rn OR '635702-64-6':rn	3587
102	avelumab*:tn,ab,ti OR 'msb-0010718c':tn,ab,ti OR msb0010718c:tn,ab,ti	66
103	'1537032-82-8':rn	48
104	'ramucirumab'/exp	921
105	ramucirumab*:tn,ab,ti OR cymranza*:tn,ab,ti OR 'imc 1121b':tn,ab,ti OR imc1121b:tn,ab,ti	516
106	'947687-13-0':rn	701
107	'palbociclib'/exp	867
108	palbociclib*:tn,ab,ti OR ibrance*:tn,ab,ti OR 'pd 332991':tn,ab,ti OR pd332991:tn,ab,ti OR 'pd 0332991':tn,ab,ti OR pd0332991:tn,ab,ti	689
109	'571190-30-2':rn	411
110	'everolimus'/exp	18481
111	everolimus*:tn,ab,ti OR 'rad 001':tn,ab,ti OR rad001:tn,ab,ti OR 'sdz rad':tn,ab,ti OR afinitor*:tn,ab,ti OR certican*:tn,ab,ti OR zortress*:tn,ab,ti OR votubia*:tn,ab,ti	11974

112	'159351-69-6':rn	12679
113	'gefitinib'/exp	18533
114	gefitinib*:tn,ab,ti OR zd1839:tn,ab,ti OR 'zd 1839':tn,ab,ti OR iressa*:tn,ab,ti OR irressa*:tn,ab,ti	11377
115	'184475-35-2':rn	16219
116	'erlotinib'/exp	20055
117	erlotinib*:tn,ab,ti OR 'osi 774':tn,ab,ti OR osi774:tn,ab,ti OR 'cp 358774':tn,ab,ti OR tarceva*:tn,ab,ti	11495
118	'183319-69-9':rn	16287
119	'cetuximab'/exp	20560
120	cetuximab*:tn,ab,ti OR c225:tn,ab,ti OR 'imc-c225':tn,ab,ti OR imcc225:tn,ab,ti OR 'hsdb 7454':tn,ab,ti OR hsdb7454:tn,ab,ti OR erbitux*:tn,ab,ti	11627
121	'205923-56-4':rn	16681
122	'panitumumab'/exp	5981
123	panitumumab*:tn,ab,ti OR (abx NEXT/1 egf*):tn,ab,ti OR abenix*:tn,ab,ti OR vectibix*:tn,ab,ti	2986
124	'339177-26-3':rn	4997
125	'339177-26-3':rn	4997
126	trastuzumab*:tn,ab,ti OR (212pb NEXT/1 tcmc*):tn,ab,ti OR 'hsdb 8142':tn,ab,ti OR hsdb8142:tn,ab,ti OR 'pf 05280014':tn,ab,ti OR herceptin*:tn,ab,ti	17856
127	'180288-69-1':rn	22438
128	'lapatinib'/exp	8932
129	lapatinib*:tn,ab,ti OR 'gsk 572016':tn,ab,ti OR 'gsk572016':tn,ab,ti OR 'gw 572016':tn,ab,ti OR gw572016:tn,ab,ti OR 'hsdb 8209':tn,ab,ti OR hsdb8209:tn,ab,ti OR tykerb*:tn,ab,ti	4608
130	'231277-92-2':rn	7342
131	'dovitinib'/exp	713
132	dovitinib*:tn,ab,ti OR 'tk-258':tn,ab,ti OR tk258:tn,ab,ti OR 'chir 258':tn,ab,ti OR chir258:tn,ab,ti	329
133	'405169-16-6':rn OR '804551-71-1':rn	480
134	'bevacizumab'/exp	40016
135	bevacizumab*:tn,ab,ti OR 'hsdb 8080':tn,ab,ti OR hsdb8080:tn,ab,ti OR 'rhumab vegf':tn,ab,ti OR avastin*:tn,ab,ti	24236
136	'216974-75-3':rn	32473
137	'aflibercept'/exp	2704

138	aflibercept*:tn,ab,ti OR 'ave 0005':tn,ab,ti OR ave0005:tn,ab,ti OR 'bay 86-5321':tn,ab,ti OR 'bay86-5321':tn,ab,ti OR bay865321:tn,ab,ti OR (vegf NEXT/1 trap*):tn,ab,ti OR zaltrap*:tn,ab,ti	1474
139	'862111-32-8':rn	2229
140	'sunitinib'/exp	9999
141	sunitinib*:tn,ab,ti OR 'pha-290940ad':tn,ab,ti OR pha290940ad:tn,ab,ti OR 'su 011248':tn,ab,ti OR su011248:tn,ab,ti OR 'su 11248':tn,ab,ti OR su11248:tn,ab,ti OR su010398:tn,ab,ti OR 'su 010398':tn,ab,ti OR 'su 10398':tn,ab,ti OR su10398:tn,ab,ti OR sutent*:tn,ab,ti	12973
142	'341031-54-7':rn	1466
143	'cabozantinib'/exp	977
144	cabozantinib*:tn,ab,ti OR 'bms 907351':tn,ab,ti OR bms907351:tn,ab,ti OR 'xl 184':tn,ab,ti OR xl184:tn,ab,ti OR cabometyx*:tn,ab,ti OR cometriq*:tn,ab,ti	1005
145	'1140909-48-3':rn OR '849217-68-1':rn	1508
146	'cabazitaxel'/exp	1096
147	cabazitaxel*:tn,ab,ti OR 'xrp-6258':tn,ab,ti OR xrp6258:tn,ab,ti OR txd258:tn,ab,ti OR 'txd 258':tn,ab,ti OR 'rpr 116258a':tn,ab,ti OR jevtana*:tn,ab,ti	1004
148	'183133-96-2':rn	1102
149	'eribulin'/exp	760
150	eribulin*:tn,ab,ti OR 'b 1939':tn,ab,ti OR b1939:tn,ab,ti OR 'e 7389':tn,ab,ti OR e7389:tn,ab,ti OR 'er 086526':tn,ab,ti OR er086526:tn,ab,ti	696
151	'253128-41-5':rn	5177
152	'ipilimumab'/exp	2877
153	ipilimumab*:tn,ab,ti OR 'mdx 010':tn,ab,ti OR mdx010:tn,ab,ti OR 'mdx ctla 4':tn,ab,ti OR mdxctla4:tn,ab,ti OR 'mdx ctla4':tn,ab,ti OR yervoy*:tn,ab,ti	4001
154	'477202-00-9':rn	

155	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #152 OR #153 OR #154	1630124
156	'clinical trial'/de	860403
157	'randomized controlled trial'/de	403594
158	'randomization'/de	69941
159	'single blind procedure'/de	22164
160	'double blind procedure'/de	129209
161	'crossover procedure'/de	46929
162	'placebo'/de	289886
163	((randomized OR randomised) NEXT/1 controlled NEXT/1 trial*):tn,ab,ti	136225
164	rct:tn,ab,ti	20696
165	'random allocation':tn,ab,ti OR 'randomly allocated':tn,ab,ti OR 'allocated randomly':tn,ab,ti	28610
166	(allocated NEAR/2 random):tn,ab,ti	839
167	((single OR double) NEXT/1 blind*):tn,ab,ti	183991
168	((treble OR triple) NEXT/1 blind*):tn,ab,ti	576
169	placebo*:tn,ab,ti	237637
170	'prospective study'/de	327547
171	randomized:ti OR randomised:ti	167279
172	#156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171	1606935
173	#172 NOT ('case study'/de OR 'case report':ab,dn,ti OR 'abstract report':it OR letter:it)	1565960
174	#18 AND #155 AND #173	4227
175	**#174 NOT ('animal'/exp NOT 'human'/exp)**	**4195**
176	'clinical study'/de	130511
177	'case control study'/de	100080

178	'family study'/de	12969
179	'longitudinal study'/de	86865
180	'retrospective study'/de	453346
181	'prospective study'/exp NOT 'randomized controlled trial'/de	290693
182	'cohort analysis'/de	242637
183	(cohort NEXT/1 (study OR studies)):tn,ab,ti	161868
184	(case NEXT/1 control NEXT/1 (study OR studies)):tn,ab,ti	94050
185	(follow NEXT/1 up NEXT/1 (study OR studies)):tn,ab,ti OR (followup NEXT/1 (study OR studies)):tn,ab,ti	53620
186	(observational NEXT/1 (study OR studies)):tn,ab,ti	91297
187	(epidemiologic* NEXT/1 (study OR studies)):tn,ab,ti	85680
188	(cross NEXT/1 sectional NEXT/1 (study OR studies)):tn,ab,ti	119504
189	'observational study'/de	92539
190	(single NEXT/2 arm*):de,ab,ti	7862
191	('non-randomized' NEAR/3 (trial* OR study OR studies OR design)):ab,ti OR ('non-randomised' NEAR/3 (trial* OR study OR studies OR design)):ab,ti	9283
192	'non-rct':ab,ti OR nrct:ab,ti	246
193	(uncontrolled NEAR/3 (trial* OR study OR studies OR design)):ab,ti OR ('non-controlled' NEAR/3 (trial* OR study OR studies OR design)):ab,ti	6784
194	'controlled clinical trial':de OR 'controlled study':de	4990988
195	(controlled NEAR/3 (trial* OR study OR design)):ab,ti	307765
196	'clinical trial'/de	860403
197	'intervention study'/de OR 'major clinical study'/de	2534774
198	'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp	73980
199	('phase 2' NEAR/3 (trial* OR study OR design)):ab,ti	8792
200	('phase ii' NEAR/3 (trial* OR study OR design)):ab,ti	45361
201	('phase 3' NEAR/3 (trial* OR study OR design)):ab,ti	10371
202	('phase iii' NEAR/3 (trial* OR study OR design)):ab,ti	30807
203	('phase 4' NEAR/3 (trial* OR study OR design)):ab,ti	362
204	('phase iv' NEAR/3 (trial* OR study OR design)):ab,ti	1141
205	'open label':de,ab,ti	50498
206	(open NEXT/3 (trial* OR study OR design)):ab,ti	40033
207	(parallel NEXT/1 group*):ab,ti	18167
208	crossover:de,ab,ti OR 'cross-over':de,ab,ti	89669

209	#176 OR #177 OR #178 OR #179 OR #180 OR #181 OR #182 OR #183 OR #184 OR #185 OR #186 OR #187 OR #188 OR #189 OR #190 OR #191 OR #192 OR #193 OR #194 OR #195 OR #196 OR #197 OR #198 OR #199 OR #200 OR #201 OR #202 OR #203 OR #204 OR #205 OR #206 OR #207 OR #208	7859933
210	#18 AND #155 AND #209	10282
211	**#210 NOT ('animal'/exp NOT 'human'/exp)**	**9851**
212	**#175 OR #211**	**10105**

Cochrane Library

Table 3: Cochrane Library search results (includes Cochrane Reviews, DARE, Cochrane Central Register of Controlled Trials, HTA Database, NHSEED), Search date: June 20, 2016 (Date range: No restriction)

#	Search terms	Hits
1	[mh ^"Carcinoma, Transitional Cell"]	440
2	[mh ^"urinary bladder neoplasms "]	1161
3	[mh ^"ureteral neoplasms"]	12
4	[mh ^"urethral neoplasms"]	2
5	[mh "kidney neoplasms"] and [mh ^"kidney pelvis"]	0
6	[mh "kidney neoplasms"] and pelvis:ab,ti,kw	4
7	[mh ^"urologic neoplasms"]	63
8	(transitional next/3 cell next/3 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	407
9	(bladder near/4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	2163
10	(urothelial near/4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	275
11	(urothelium near/4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	43
12	(ureter* near/4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	44
13	(urethra* near/4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	62
14	(renal next pelvis near/4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	0
15	(kidney next pelvis near/4 (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	7
16	("urinary tract" next (carcinoma* or cancer* or neoplasm* or tumor* or tumour* or malignanc*)):ab,ti,kw	60

17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	2397
18	[mh "Carcinoma, Transitional Cell"/DT]	241
19	[mh "urologic neoplasms"/DT]	861
20	[mh "antineoplastic protocols"]	12124
21	[mh "antineoplastic agents"]	11397
22	[mh "antibodies, monoclonal"]	6300
23	[mh "molecular targeted therapy"]	98
24	[mh "cancer vaccines"]	259
25	[mh immunotherapy]	7481
26	[mh "protein kinase inhibitors"]	604
27	[mh "angiogenesis inhibitors"]	858
28	[mh "antibiotics, antineoplastic"]	741
29	[mh "antimetabolites, antineoplastic"]	1009
30	[mh "antimitotic agents"]	85
31	[mh "antineoplastic agents, alkylating"]	413
32	[mh "antineoplastic agents, phytogenic"]	722
33	[mh "vinca alkaloids"]	2862
34	[mh taxoids] or taxane*:ab,ti,kw	3345
35	[mh "organoplatinum compounds"] or [mh "platinum compounds"] or platinum:ab,ti	6471
36	mpdl3280*:ab,ti,kw	4
37	atezolizumab*:ab,ti,kw	4
38	(tecentriq* or "mpdl 3280" or "mpdl 3280a" or "rg 7446" or rg7446):ab,ti,kw	5
39	nivolumab*:ab,ti,kw	67
40	("mdx-1106" or mdx1106 or "ono-4538" or ono4538 or "bms-936558" or bms936558 or opdivo*):ab,ti,kw	17
41	pembrolizumab*:ab,ti,kw	35
42	(keytruda* or lambrolizumab or "mk 3475" or mk3475 or "merck 3475" or "sch 900475"):ab,ti,kw	26
43	vinflunin*:ab,ti,kw	38
44	(javlor* or dihydrovinorelbine or f12158 or "f 12158" or "bms-710485"):ab,ti,kw	3
45	[mh vinblastine]	908
46	(vinblastin* or le29060 or (le near/1 29060) or leukoblastin* or vincaleukoblastin* or vincaleucoblastin* or vinleukoblastin* or vinleucoblastin or velban* or velsar* or vlb* or rozevin*):ab,ti,kw	2037
47	Gemcitabin*:ab,ti,kw	2299
48	(ly188011 or "ly 188011" or "nsc 613327" or "nsc 0613327" or gemzar* or gemcite*):ab,ti,kw	29

49	[mh pemetrexed]	165
50	(pemetrexed* or alimta* or ciambra* or (ly next/1 231514) or ly231514 or rolazar* or tifolar):ab,ti,kw	548
51	docetaxel*:ab,ti,kw	3008
52	(docetaxol* or taxotere* or xrp6976 or docefrez* or (hdsb next/1 6965) or (nsc next/1 628503) or nsc628503 or "rp 56976" or rp56976 or docecad* or texot*):ab,ti,kw	194
53	[mh paclitaxel] or [mh "albumin-bound paclitaxel"]	1695
54	(paclitaxel or "bms 181339 01" or "bms181339 01" or "hsdb 6839" or "nsc 125973" or nsc12973 or anzatax* or asotax* or bristaxol* or capxol* or cyclopax* or mediphaxel* or onxol* or paclivis* or paxene* or paxtel* or praxel* or taxol*):ab,ti,kw	4478
55	("nab-paclitaxel" or "nab-pac" or "albumin-bound paclitaxel" or "albumin-stabilized nanoparticle paclitaxel" or "albumin-stabilised nanoparticle paclitaxel" or "nanoparticle albumin-bound paclitaxel" or "nanoparticle paclitaxel" or "protein-bound paclitaxel" or abraxan* or "abi 007" or abi007):ab,ti,kw	156
56	[mh ifosfamide]	411
57	(ifosfamid* or iphosphamid* or cuantil* or cyfos* or holoxan* or mitoxana* or ifoxan* or "nci-c01638" or ncic01638 or "nsc 109724" or nsc109724 or "z 4942" or z4942 or "mjf 9325" or mjf9325 or ifex* or isoendoxan*):ab,ti,kw	971
58	[mh fluorouracil]	4208
59	(fluorouracil* or 5fluorouracil* or (fluoro next/1 uracil) or "5-fu" or 5fu or fluracil* or fluoracil* or fluris* or adrucil* or arumel* or efudex* or fluoroplex* or fluoroblastin* or "ro 2-9757" or "ro2-9757" or "ro 29757" or ribofluor* or timazin* or onkofluor* or neofluor*):ab,ti,kw	8331
60	[mh methotrexate]	3050
61	(methotrexate* or mtx or "nsc-740" or nsc740 or abotrexat* or amethopterin* or antifolan* or brimexat* or "cl 14377" or cl14377 or emthexate* or emtexat* or farmitrexat* or folex* or lantarel* or methylaminopterin* or metotrex* or mexate* or rasuvo* or rheumatrex* or texate* or trexeron* or trixilem* or "wr-19039" or wr19039):ab,ti,kw	6711
62	[mh carboplatin]	1113
63	(carboplat* or "nsc 201345" or nsc201345 or "nsc 241240" or nsc241240 or paraplatin* or blastocarb* or carbosin* or carbotec* or cbdca* or cycloplat* or ercar* or "jm 8" or jm8 or neocarbo*):ab,ti,kw	3196
64	[mh cisplatin]	3531
65	(cisplatin* or (cis next/1 platin) or (cis next/1 diaminodichloroplatin*) or cddp or (cis-NEXT/1 dichlorodiaminoplatin*) or "platinum diamminodichloride" or "nci c55776" or ncic55776 or "nsc 119875" or nsc119875 or abiplatin* or briplatin* or lederplatin* or neoplatin* or platinex* or platinol* or platosin* or platidiam*):ab,ti,kw	8546
66	mvac:ab,ti,kw or (m next/1 vac):ab,ti,kw	101
67	[mh doxorubicin]	3545

68	(doxorubicin* or caelyx* or caelix* or doxil* or adriablastin* or adriamycin* or "ccris 739" or "fi 106" or fi106 or "nci c01514" or ncic01514 or "ndc 38242 874" or ndc38242874 or "nsc 123127" or nsc123127 or doxotec* or rubex* or myocet* or onkodox* or ribodoxo*):ab,ti,kw	6009
69	[mh "granulocyte colony stimulating factor"]	1191
70	("g csf" or (colony near/3 stimulating near/3 factor) or (granulocyte near/3 colony* near/3 factor)):ab,ti	3046
71	vandetanib:ab,ti,kw	99
72	(caprelsa* or zactima* or "hsdb 8198" or "zd 6474" or zd6474):ab,ti,kw	20
73	afatinib:ab,ti,kw	103
74	(bibw 2992 or bibw2992 or tovok* or tomtovok* or giotrif* or gilotrif*):ab,ti,kw	21
75	pazopanib:ab,ti,kw	154
76	(votrient* or gw786034* or (gw next/1 786034*) or (gw7 next/1 86034*) or "gw 780604" or gw780604 or "hsdb 8210" or votrient* or patorma* or armala*):ab,ti,kw	10
77	(avelumab* or "msb-0010718c" or msb0010718c):ab,ti,kw	0
78	Ramucirumab:ab,ti,kw	66
79	(cymranza* or "imc 1121b" or imc1121b):ab,ti,kw	13
80	palbociclib:ab,ti,kw	21
81	(ibrance* or "pd 332991" or pd332991 or "pd 0332991" or pd0332991):ab,ti,kw	9
82	[mh everolimus]	390
83	(everolimus or "rad 001" or rad001 or "sdz rad" or afinitor* or certican* or zortress* or votubia*):ab,ti,kw	1445
84	(gefitinib or "zd1839" or "zd 1839" or iressa* or irressa*):ab,ti,kw	388
85	[mh "erlotinib hydrochloride"]	168
86	(erlotinib* or "osi 774" or osi774 or "cp 358774" or tarceva*):ab,ti,kw	626
87	[mh cetuximab]	186
88	(cetuximab* or c225 or "imc-c225" or imcc225 or "hsdb 7454" or hsdb7454 or erbitux*):ab,ti,kw	857
89	(panitumumab* or abx-egf* or abenix* or vectibix*):ab,ti,kw	230
90	[mh trastuzumab]	189
91	(trastuzumab* or (212pb next/1 tcmc*) or "hsdb 8142" or hsdb8142 or "pf 05280014" or herceptin*):ab,ti,kw	1020
92	(lapatinib* or "gsk 572016" or gsk572016 or "gw 572016" or gw572016 or "hsdb 8209" or hsdb8209 or tykerb*):ab,ti,kw	364
93	(dovitinib* or "tk-258" or tk258 or "chir 258" or chir258):ab,ti,kw	17
94	[mh bevacizumab]	577
95	(bevacizumab* or "hsdb 8080" or hsdb8080 or "rhumab-vegf" or avastin*):ab,ti,kw	2048

96	(aflibercept or "ave 0005" or ave0005 or "bay 86-5321" or "bay86-5321" or bay865321 or (vegf next/1 trap*) or zaltrap*):ab,ti,kw	155
97	(sunitinib* or "pha-290940ad" or pha290940ad or "su 011248" or su011248 or "su 11248" or su11248 or su010398 or "su 010398" or "su 10398" or su10398 or sutent*):ab,ti,kw	414
98	(cabozantinib* or "bms 907351" or bms907351 or "xl 184" or xl184 or cabometyx* or cometriq*):ab,ti,kw	47
99	(cabazitaxel* or "xrp-6258" or xrp6258 or txd258 or "txd 258" or "rpr 116258a" or jevtana*):ab,ti,kw	52
100	(eribulin* or "b 1939" or b1939 or "e 7389" or e7389 or "er 086526" or er 086526):ab,ti,kw	63
101	(ipilimumab* or "mdx 010" or mdx010 or "mdx-ctla 4" or mdxctla4 or "mdx-ctla4" or yervoy*):ab,ti,kw	173
102	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101	58529
103	**#17 and #102**	**927**

Study registries – International Clinical Trials Registry Platform (ICTRP)

Table 4: ICTRP search results, Search date: July 13, 2016

Study registry	International Clinical Trials Registry Platform Search Portal
Search strategy	bladder cancer OR bladder carcinoma OR urothelial cancer OR urothelial carcinoma OR urothelium cancer OR urothelium carcinoma OR ureter cancer OR ureter carcinoma OR urethral cancer OR urethral carcinoma OR kidney pelvis cancer OR kidney pelvis carcinoma OR renal pelvis cancer OR renal pelvis carcinoma OR transitional cell carcinoma OR transitional cell cancer OR TCC
No. of hits	**1378 hits = 1119 trials according to website, The download actually retrieved 1121 trials**

Study registries – EU Clinical Trial Register

Table 5: EU Clinical Trial Register search results, Search date: July 6, 2016

Study registry	International Clinical Trials Registry Platform Search Portal
Search strategy A	“bladder cancer”
No. of hits	160 studies
Search strategy B	“bladder carcinoma”
No. of hits	131 studies
Search strategy C	“urothelial cancer”
No. of hits	64 hits
Search strategy D	“urothelial carcinoma”
No. of hits	62 hits
Search strategy E	“urothelium cancer”
No. of hits	27 hits
Search strategy F	“urothelium carcinoma”
No. of hits	30 hits
Search strategy G	“ureter cancer”
No. of hits	24 hits
Search strategy H	“ureter carcinoma”
No. of hits	26 hits
Search strategy I	“urethral cancer”
No. of hits	8 hits
Search strategy J	“urethral carcinoma”
No. of hits	5 hits
Search strategy K	“kidney pelvis cancer”
No. of hits	11 hits
Search strategy L	“kidney pelvis carcinoma”
No. of hits	9 hits
Search strategy M	“renal pelvis cancer”
No. of hits	114 hits
Search strategy N	“renal pelvis carcinoma”
No. of hits	96 hits
Search strategy O	“transitional cell cancer”
No. of hits	85 hits
Search strategy P	“transitional cell carcinoma”
No. of hits	93 hits
Search strategy Q	TCC
No. of hits	58 hits

Total findings of all searches	**286 hits (without duplicates)** **1003 hits (including duplicates)**

Study registries – US National Institute of Health's (NUH) clinical trial registry

Table 6: US NUH search results, Search date: July 5, 2016

Study registry	Clinicaltrials.gov
Search strategy (Expert Search)	(((bladder OR urothelial OR urothelium OR ureter OR urethral OR "kidney pelvis" OR "renal pelvis" OR "transitional cell") AND (cancer OR cancers OR carcinoma OR carcinomas OR neoplasm OR neoplasms OR tumor OR tumors)) [DISEASE] AND EXACT (Phase 2 OR Phase 3 OR Phase 4) [PHASE]) OR (((bladder OR urothelial OR urothelium OR ureter OR urethral OR "kidney pelvis" OR "renal pelvis" OR "transitional cell") AND (cancer OR cancers OR carcinoma OR carcinomas OR neoplasm OR neoplasms OR tumor OR tumors)) [DISEASE] AND (NOT EXACT (Phase 1 OR Phase 0) [PHASE] AND Drug [TREATMENT]))
No. of hits	**565 hits (including 72 studies with results)**

Conference abstracts

Table 7: conference abstracts search results, event dates from 2015–2016

Number of references found	Meetings	Date of search	Search strategy	Number of references found
American Society of Clinical Oncology (ASCO)				
2016	Genitourinary Cancer Symposium	July 25, 2016	Search Strategy: Choice of topic: Urothelial Carcinoma	114 hits
2016	Cancer Survivorship Symposium	July 25, 2016	Search for: Abstract: transitional cell: 0 hits Abstract: TCC 0 hits Abstract: urothelial: 0 hits Abstract: urinary: 0 hits Abstract: ureteral: 0 hits Abstract: urethral: 0 hits	0 hits

			Abstract: urologic: 0 hits Abstract: urogenital: 0 hits Abstract: bladder: 0 hits Abstract: renal: 0 hits Abstract: kidney: 0 hits	
2016	Cancer Survivorship Symposium	July 25, 2016	Search for: Keywords: transitional cell: 0 hits Keywords: TCC: 0 hits Keywords: urothelial: 0 hits Keywords: urinary: 6 hits Keywords: ureteral: 1 hit Keywords: urethral: 0 hits Keywords: urologic: 5 hits Keywords: urogenital: 0 hits Keywords: bladder: 3 hits Keywords: renal: 1 hit	17 hits (including 2 duplicates)
2016	ASCO Annual Meeting	July 25, 2016	Search Strategy: Choice of topic (left side): Bladder cancer: 69 hits Other GU cancers: 8 hits Search for: Keywords: renal pelvis: 3 hits Keywords: kidney pelvis: 0 hits	80 hits
2015	Genitourinary Cancer Symposium	July 25, 2016	Search Strategy: Choice of topic (left side): Urothelial carcinoma	85 hits
2015	ASCO Annual Meeting	July 25, 2016	Search Strategy: Choice of topic (left side): Bladder cancer: 70 hits Other GU cancers: 15 hits Search for: Keywords: renal pelvis: 6 hits Keywords: kidney pelvis: 0 hits	91 hits (including 5 duplicates)
2015	Palliative Care in Oncology Symposium	July 25, 2016	Search for: Abstract: transitional cell: 0 hits Abstract: TCC 0 hits Abstract: urothelial: 0 hits Abstract: urinary: 0 hits Abstract: ureteral: 0 hits Abstract: urethral: 0 hits Abstract: urologic: 0 hits Abstract: urogenital: 0 hits Abstract: bladder: 0 hits	0 hits

			Abstract: renal: 0 hits Abstract: kidney: 0 hits	
European Society of Medical Oncology (ESMO)/ECCO				
2016	ESMO Symposium on Signalling Pathways in Cancer 2016, 4-5 March 2016, Sitges-Barcelona, Spain	July 26, 2016	Event: ESMO Symposium on Signalling Pathways in Cancer Session Types: all included (all screened)	0 hits
2015	European Cancer Congress 2015 (ECC 2015), 25-29 September 2015, Vienna, Austria	July 26, 2016	Search Menu: transitional cell: 4 hits TCC: 8 hits urothelial: 32 hits urinary: 43 hits ureteral: 2 hits (but not visible or accessible!) urethral: 4 hits urologic: 19 hits urogenital: 14 hits bladder: 49 hits renal pelvis: 2 hits kidney pelvis: 2 hits	128 hits excluding duplicates (177 hits including duplicates)
2015	ESMO Asia 2015, 18-21 December 2015, Singapore	July 29, 2016	Search This Issue: Transitional TCC urothelial urinary ureteral urethral urologic urogenital bladder pelvis	13 hits
2015	ESMO Symposium on Immuno-Oncology 2015, 20-21 Nov 2015, Lausanne, Switzerland	July 29, 2016	Search This Issue: Transitional TCC urothelial urinary ureteral urethral urologic urogenital bladder pelvis	1 hit
European Association of Urology (EAU)				
2016	5th Meeting of the EAU Section of Uro-Technology (ESUT) EAU16, 31st Congress 2016,	July 28, 2016	Search strategies in ScienceDirect expert search: Search 1 – 97 hits: (pub-date > 2015 and ISSN (1569-9056) AND (vis (15 AND 3) OR vis (15 AND 5) OR vis (15 AND 6)) AND LIMIT-TO(topics, "bladder cancer"))	148 hits (excluding 97 duplicates) (245 hits including duplicates)

	Munich (DE) 3rd EAU Baltic Meeting 2016, Tallinn (EST)		Search 2 – 148 hits: ((pub-date > 2015 and ISSN (1569-9056) AND (vis (15 AND 3) OR vis (15 AND 5) OR vis (15 AND 6)) AND (tak (transitional cell) OR tak (TCC) OR tak (urothelial) OR tak (ureteral) OR tak (urethral) OR tak (bladder) OR tak (renal pelvis) OR tak (kidney pelvis))) AND (pub-date > 2015 and ISSN (1569-9056) AND (vis (15 AND 3) OR vis (15 AND 5) OR vis (15 AND 6)) AND (tak (cancer) OR tak (carcinoma) OR tak (neoplasm) OR tak (tumor) OR tak (malignancy))))	
2015	EAU15, 30th Congress 2015, Madrid (ES) 12th ERUS Meeting 2015, Bilbao (ES) 3rd EULIS Meeting 2015, Alicante (ESP) 15th CEM 2015, Budapest (HUN) 11th SEEM 2015, Antalya (TUR) EAU Baltic Meeting 2015, Riga (LVA)	July 28, 2016	Search strategies in ScienceDirect expert search: Search 1 – 90 hits: (pub-date = 2015 and ISSN (1569-9056) AND (vis (14 AND 2) OR vis (14 AND 3) OR vis (14 AND 4) OR vis (14 AND 5) OR vis (14 AND 6) OR vis (14 AND 9)) AND LIMIT-TO(topics, "bladder cancer")) Search 2 – 138 hits: ((pub-date = 2015 and ISSN (1569-9056) AND (vis (14 AND 2) OR vis (14 AND 3) OR vis (14 AND 4) OR vis (14 AND 5) OR vis (14 AND 6) OR vis (14 AND 9)) AND (tak (transitional cell) OR tak (TCC) OR tak (urothelial) OR tak (ureteral) OR tak (urethral) OR tak (bladder) OR tak (renal pelvis) OR tak (kidney pelvis))) AND (pub-date = 2015 and ISSN (1569-9056) AND (vis (14 AND 2) OR vis (14 AND 3) OR vis (14 AND 4) OR vis (14 AND 5) OR vis (14 AND 6) OR vis (14 AND 9)) AND (tak (cancer) OR tak (carcinoma) OR tak (neoplasm) OR tak (tumor) OR tak (malignancy))))	138 hits excluding 90 duplicates (228 hits including 90 duplicates)
European Multidisciplinary Meeting on Urological Cancers (EMUC)				
2015	7th European Multidisciplinary Meeting on Urological Cancers (EMUC), 12-15	July 25, 2016	Events: 7th European Multidisciplinary Meeting on Urological Cancers Media Types: Abstracts Media Types: Posters	178 abstracts (116 corresponding hits for posters were found, one

	Nov 2015, Barcelona, Spain			was broken and also a duplicate)
American Urological Association (AUA)				
2016	Joint Meeting of the Society for Pediatric Urology and American Urological Association, New Orleans, Lousiana 15–17 May 2015 Annual Meeting American Urological Association, Program Abstracts. Volume 195, Issue 4, Supplement, Pages e1-e1192 (April 2016) 2016 Annual Meeting Program Abstracts, AUA Annual Meeting San Diego, CA 6–10 May 2016	July 28, 2016	Search strategies in ScienceDirect expert search: Search 1: 306 hits (pub-date > 2015 and ISSN (0022-5347) AND (SPECISS-NAME (Papers Presented at the Joint Meeting of the Society for Pediatric Urology and American Urological Association*) OR SPECISS-NAME (2016 Annual Meeting Program Abstracts*)) AND LIMIT-TO(topics, "bladder cancer")) Search 2: 248 hits ((pub-date > 2015 and ISSN (0022-5347) AND (SPECISS-NAME (Papers Presented at the Joint Meeting of the Society for Pediatric Urology and American Urological Association*) OR SPECISS-NAME (2016 Annual Meeting Program Abstracts*)) AND (tak (transitional cell) OR tak (TCC) OR tak (urothelial) OR tak (ureteral) OR tak (urethral) OR tak (bladder) OR tak (renal pelvis) OR tak (kidney pelvis))) AND (pub-date > 2015 and ISSN (0022-5347) AND (SPECISS-NAME (Papers Presented at the Joint Meeting of the Society for Pediatric Urology and American Urological Association*) OR SPECISS-NAME (2016 Annual Meeting Program Abstracts*)) AND (tak (cancer) OR tak (carcinoma) OR tak (neoplasm) OR tak (tumor) OR tak (malignancy))))	330 excl. duplicates (554 incl.
2015	Joint Meeting of the Society for Pediatric Urology and American Urological Association, Papers Presented.	July 28, 2016	Search strategies in ScienceDirect expert search: Search 1: 313 hits (pub-date = 2015 and ISSN (0022-5347) AND (SPECISS-NAME (Papers Presented at the Joint Meeting of the Society for Pediatric Urology and American Urological Association*) OR	330 excl. duplicates (563 incl. duplicates)

	Orlando, FL 16–18 May 2014 Annual Meeting American Urological Association, Program Abstracts. New Orleans, LA 15–19 May 2015		SPECISS-NAME (2015 Annual Meeting Program Abstracts*)) AND LIMIT-TO(topics, "bladder cancer")) Search 2: 250 hits ((pub-date = 2015 and ISSN (0022-5347) AND (SPECISS-NAME (Papers Presented at the Joint Meeting of the Society for Pediatric Urology and American Urological Association*) OR SPECIES-NAME (2015 Annual Meeting Program Abstracts*)) AND (tak (transitional cell) OR tak (TCC) OR tak (urothelial) OR tak (ureteral) OR tak (urethral) OR tak (bladder) OR tak (renal pelvis) OR tak (kidney pelvis))) AND (pub-date = 2015 and ISSN (0022-5347) AND (SPECISS-NAME (Papers Presented at the Joint Meeting of the Society for Pediatric Urology and American Urological Association*) OR SPECISS-NAME (2015 Annual Meeting Program Abstracts*)) AND (tak (cancer) OR tak (carcinoma) OR tak (neoplasm) OR tak (tumor) OR tak (malignancy))))	

A6. Please clarify the following relating to the eligibility screening process for selecting studies to include in the systematic literature review:

- **Were all of the eligibility criteria that are reported in the company submission specified *a priori*?**
- **The number of reviewers that assessed titles/abstracts and full texts**
- **The parts of Figure 3 in the company submission that correspond to the title/abstract and full-text screening steps**

1. All of the eligibility criteria were specified a priori through the research question of the systematic literature search based on PICO(S) elements.
2. Titles/abstracts and full texts were assessed by two reviewers
3. The “screening” section of Figure 3 corresponds to the title/abstract screening steps and the “eligibility” section of Figure 3 corresponds to the full-text screening step. After

excluding duplicates (n=4,984) and screening against inclusion/exclusion criteria 18,050 titles/abstracts were excluded. 864 citations were found eligible for the screening on full-text level.

A7. Figure 3 in the company submission states that 631 publications were excluded from the systematic literature review but reasons for exclusion are only given for 373 of these. Please explain why the remaining publications were excluded.

The remaining 258 records (254 from searching study registers, and 4 from internet search) were excluded due to 'outcomes', meaning the publications did not provide information on any of the outcomes of interest as listed in the systematic literature review inclusion criteria (Table 10 of company submission).

A8. Figure 3 in the company submission suggests that 233 publications were included in a qualitative synthesis, but no qualitative synthesis with the corresponding number of publications is reported. Please give details of the qualitative synthesis, and if possible provide the results.

No search restrictions were applied to the systematic literature review relating to interventions. The final search resulted in 233 publications, but included studies with a wide range of interventions, many of which not of interest to the appraisal decision problem. As outlined on page 57 of the company submission, the studies were divided into two categories based on the study interventions: priority 1 and priority 2. Priority 1 studies included any of the comparators as listed in Table 8 below, and these studies were taken forward for assessment for inclusion in the network meta-analysis (NMA). There were 74 publications, of 43 studies categorised as priority 1 studies. The remaining 159 publications were priority 2, and were not further evaluated.

Table 8: Categorisation of SLR results by intervention

Priority 1 studies	Priority 2 studies
2nd Line chemo failure Best supportive care Carboplatin plus paclitaxel Docetaxel Paclitaxel Nab-paclitaxel Vinflunine Gemcitabine Gemcitabine plus paclitaxel MVAC (Cisplatin, doxorubicin, methotrexate, and vinblastine)	Any remaining intervention not included as priorty 1

Carboplatin, cisplatin, oxaliplatin (platin-based re-challenge if >12 months since last dose) Pembrolizumab Nivolumab Gemcitabine plus cisplatin **1st Line cis-ineligible** Gemcitabine plus carboplatin Best supportive care Gemcitabine plus paclitaxel (after re-treatment)	

A9. The reasons for exclusion of studies from the network meta-analysis, listed in Appendix 8.2, are not clear, as the following explanations are ambiguous: connector "not of interest", "poor reporting", "poor data" and "poor reporting and data inconsistency". Please provide a more detailed description of the above reasons.

Due to challenges with the limited available data for comparators, and the interventions of interest, potential bridging studies which might enable an indirect link were initially selected and included. These studies were evaluated regarding their feasibility for the NMA and excluded if they did not provide enough information. Thus these studies were excluded by following reasons

- "Connector not of interest" = Intervention (since the drug is not in priority 1 list as described in A8 above)

Some studies selected for 2L treatment did not provide sufficient information for inclusion within the NMA. The following reasons were applied for the exclusion during feasibility analysis of the NMA:

- "Poor data" = no prognostic factors were reported (as required for prediction model)
- "Poor reporting and data inconsistency" = applied for Naiki 2016 and Lida 2016 representing two publications for one gemcitabine + paclitaxel study. The KM curve reporting within the publications was of low quality, with inconsistent results. For example it was unclear whether the x-axis unit of the overall survival (OS) KM curve represented weeks or months. Assuming the units were weeks, converting the 4 deaths and 9 censors to months results in 1 death in [0,2.16] months, the second death in [2.16,3.79] months, the third death in [3.79,4.72] months and the fourth death in [4.72,5.7] months. This does not coincide with the reported median of 10.8 months. Exclusion of Naiki 2016 did not change the network due to other included Gemcitabine + Paclitaxel studies.

A10. Table 16 in the company submission lists the studies providing evidence for the comparators for the second-line population that are eligible for inclusion in a network meta-analysis of overall survival and progression-free survival. However, when compared with Table 14 it appears that Table 16 has omitted seven studies that reported either overall survival or progression-free survival but not both (Joly 2009, McCaffery 1997, Srinivas 2005, Suyama 2009, Sternberg 2002, Takahashi 2006, Vaughn 2002). Please explain the reasons for this.

As described on page 69 of the company submission, in order to include comparator studies within the time-to-event analyses, KM curves were required for progression-free-survival (PFS) and / or OS. Table 14 in the company submission describes studies which included any of the outcomes of interest – OS, PFS, 12 month OS, objective response rate (ORR). Table 16 in the company submission describes 2L studies which include KM curves for PFS or OS. The studies listed in question A10 above did not report KM curves for either outcome, as such could not be included in the time-to-event analysis.

For clarity, the titles of Table 15 and 16 could be amended to read:

- Table 15:Studies included for OS and / or PFS NMA (1L)
- Table 16: Studies included for OS and / or PFS NMA (2L+)

A11. Priority question. The ERG has identified the following studies that appear to meet the eligibility criteria for inclusion in the network meta-analysis using the criteria given in the company submission which are not listed in the company submission or appendices. Please explain whether these studies were identified and checked for eligibility and, if so, please explain why they were excluded:

Please see Table 9 for the rationale for exclusion of the ERG identified studies.

All studies listed were identified during the company submission systematic literature review, except for the studies by Plimack et al. and Sharma et al. which were not yet published at the date of the search (June 2016 to August 2016).

Table 9: ERG identified studies with rationale for exclusion

Study	Reason for exclusion
Bamias A, Dafni U, Karadimou A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol 2013; 24:1011.	• Population (excluded at full-text level) • "No previous chemotherapy for advanced disease was allowed" => treatment naïve but not cisplatin ineligible • Treatment included cisplatin
Calabrò F, Lorusso V, Rosati G, et al. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 2009; 115:2652.	• Population (excluded at full-text level) • Patients were required to have received no previous systemic cytotoxic or biologic treatment for advanced disease. But cis-ineligibility was not required
Gebbia, V et al. Single agent 2',2'-difluorodeoxycytidine in the treatment of metastatic urothelial carcinoma: a phase II study. La Clinica terapeutica. 1999; 150(1): 11-15.	• Study type (excluded at full-text level) • Consecutive study (e.g. consecutive patients in prospective observational study (hospital, region, practice.)
Gondo, T et al. The efficacy and safety of gemcitabine plus cisplatin regimen for patients with advanced urothelial carcinoma after failure of M-VAC regimen. International Journal of Clinical Oncology 2011; 16(4): 345-351.	• Study type (excluded at abstract level) • Retrospective: (e.g. chart review; hospital database; registry)
Halim, A. Methotrexate-paclitaxel-epirubicin-carboplatin as second-line chemotherapy in patients with metastatic transitional cell carcinoma of the bladder pretreated with cisplatin-gemcitabine: A phase II study. Asia-Pacific Journal of Clinical Oncology 2013; 9(1): 60-65.	• Included at full-text level • Excluded at final step because the drug "Methotrexate-paclitaxel-epirubicin-carboplatin" is not a comparator of interest to the decision problem
Kanai, K et al. Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. International Journal of Clinical Oncology 2008; 13(6): 510-514.	• Study type (excluded at full-text level) • Consecutive study (e.g. consecutive patients in prospective observational study (hospital, region, practice.)
Kaufman, DS et al. A multi-institutional phase II trial of gemcitabine plus paclitaxel in patients with locally advanced or metastatic urothelial cancer. Urologic Oncology 2004; 22(5): 393-397.	• Population (excluded at full-text level) • Only 6 patients received previous therapy; cisplatin ineligibility could not be determined
Krege S, Rembrink V, Börgermann C, et al. Docetaxel and ifosfamide as second line treatment for patients with advanced or metastatic urothelial cancer after failure of platinum chemotherapy: a phase 2 study. J Urol 2001; 165:67.	• Included at full-text level • Excluded at final step because the drug "ifosfamide" is not a comparator of interest to the decision problem
Li J, Juliar B, Yiannoutsos C, et al. Weekly paclitaxel and gemcitabine in advanced transitional-cell	• Population (excluded at full text level)

carcinoma of the urothelium: a phase II Hoosier Oncology Group study. J Clin Oncol 2005; 23:1185.	• No prior therapy for metastatic disease was permitted. But cis-ineligibility was not reported
Lin CC, Hsu CH, Huang CY, et al. Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study. Anticancer Drugs 2007; 18:487.	• Population (excluded at full-text level) • No prior therapy for metastatic disease was permitted. But cis-ineligibility was not reported
Plimack ER, Bellmunt J, Gupta S, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol 2017.	• This source was not yet published during the search process in June 2016
Pronzato P, Vigani A, Pensa F, et al. Second line chemotherapy with ifosfamide as outpatient treatment for advanced bladder cancer. Am J Clin Oncol 1997; 20:519.	• Population (excluded at abstract level) • Drug “ifosfamide” is not a comparator of interest to the decision problem
Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016; 17:1590.	• This source was not yet published during the search process in June 2016
Soga, N et al. Paclitaxel Carboplatin chemotherapy as a second-line chemotherapy for advanced platinum resistant urothelial cancer in Japanese cases. International Journal of Urology 2007; 14(9): 828-832.	• Study type (excuded at full-text level) • Consecutive study (e.g. consecutive patients in prospective observational study (hospital, region, practice.)
Sweeney CJ, Roth BJ, Kabbinavar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol 2006; 24:3451.	• Found and extracted • Pemetrexed is not a comparator of interest to the decision problem
Tsuruta, H et al. Combination therapy consisting of gemcitabine, carboplatin, and docetaxel as an active treatment for advanced urothelial carcinoma. International Journal of Clinical Oncology 2011; 16(5): 533-538.	• Included at full-text level • Patients had had to discontinue a first-line chemotherapy with MVAC or HD-MVAC because of tumor progression or unacceptable toxicity or the disease had relapsed in patients after first-line chemotherapy with MVAC or HD-MVAC • Drug combination not a comparator of interest to the decision problem
Uhm, JE et al. Paclitaxel with cisplatin as salvage treatment for patients with previously treated advanced transitional cell carcinoma of the urothelial tract. Neoplasia 2007; 9(1): 18-22.	• Included at full-text level. • Excluded at the final step because the drug “paclitaxel with cisplatin” is not a comparator of interest to the decision problem.
Witte RS, Elson P, Bono B, et al. Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol 1997; 15:589.	• Included at full-text level • Excluded at the final step because the drug “ifosfamide” is not a comparator of interest to the decision problem

A12. Please explain the rationale for conducting a network meta-analysis of the binary outcomes objective response rate and 12-month overall survival, given that these outcomes do not inform the economic model.

The intention of the NMA was to inform the economic model, and to more broadly assess comparative effectiveness of atezolizumab vs other interventions. Therefore, endpoints not of interest to the economic model were included, such as ORR and 12-month OS. ORR was the primary endpoint in the IMvigor210 study and therefore deemed an important endpoint to include.

For cancer immunotherapies, characterization of long-term survival is important. Milestone survival was included because this new endpoint has been suggested in the literature for assessing and comparing long-term benefit. (Chen TT. 2015)

The additional analyses of binary outcomes in the NMA did not impact the time-to-event analyses. As such their inclusions or exclusion have no bearing on the results of the NMA and subsequent incorporation of NMA results into the economic model.

A13. The rationale given in the company submission for conducting the fractional polynomial analysis was that the proportional hazards assumption was likely to be violated. However, zero-order fractional polynomial analysis was conducted for all comparisons, which also assumes proportional hazards. Please explain the rationale for conducting this analysis given the apparent contradiction.

The zero-order fractional polynomial models were included to allow for a statistical assessment of the proportional hazards assumption. Since the zero-, first- and second-order fractional polynomial models were all fitted to the same data, statistical measures of fit such as the DIC can be compared between models. Whilst the proportional hazards assumption was not anticipated to hold between cancer immunotherapies and chemotherapies, the zero-order fractional polynomial model was included such that this issue could be assessed with statistical techniques.

A14. Priority question. The fractional polynomial network meta-analysis consists largely of direct comparisons. Please explain why this approach to network meta-analysis was chosen instead of direct comparison meta-analyses between the simulated atezolizumab arm and each comparator.

The company submission NMA was based on a star-shaped network with atezolizumab as the common link. Thus, the network reference is atezolizumab. In such a network, every competitor treatment adds a new basic parameter. As there are no closed loops, these parameters are estimated only from direct evidence, and there is no indirect evidence on the basic parameters. Therefore, the fixed effects NMA is, mathematically, equivalent to a series of pairwise fixed-effects meta-analysis, and both approaches would lead to the same results.

One joint fit was preferential as compared to a series of separate model fits. This ensured consistency in model structure between the different comparisons and allowed model selection to be based on a joint assessment of fit for all data.

The joint model also allowed for heterogeneity inclusion via random effects models. The random effects variance was assumed to be the same across the network, which is a strong but common assumption in network meta-analysis. With this assumption the degrees of freedom were small but sufficient to estimate heterogeneity. In contrast, the number of trials per comparison would have been too limited to include random effects in pairwise meta-analysis.

A15. Priority question. Please provide the following analyses for each cohort:

(a) An unadjusted direct comparison of overall survival and progression-free survival from the IMvigor210 trial and each of the relevant comparator studies.

(b) An adjusted direct meta-analysis comparison between the simulated atezolizumab arm and comparator arm for each of the relevant comparator studies.

Alternatively, provide justification why these analyses are not considered appropriate.

Please consider clarification questions A30 and A31 below before providing these analyses, as these raise issues related to the analysis approach.

a) As per section 4.10.7 of the company submission, use of unadjusted direct comparisons is not recommended, and was not included within the company submission. This analysis has not been conducted, as per the justification below.

Literature on network meta-analysis emphasizes the importance of indirect comparisons being adjusted (or “anchored”) (Song et al. 2003). The International Society For Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect

Treatment Comparisons Good Research Practices states that "*Using data only from the treatment arms of interest to draw comparisons, omitting the data from the control or placebo arms, is called a "naïve indirect comparison," results in bias, and should be avoided.*" (Jansen et al. 2011). Whilst the majority of evidence within the company submission NMA is single arm (thus does not include control or placebo arms), the guidance regarding avoidance of naïve indirect comparison is adhered to. Jansen et al developed a questionnaire to assess relevance and credibility of ITCs/NMAs to inform health care decision making (Jansen et al. 2014). Item 7 in the questionnaire to assess credibility, declares naïve comparisons as analysis methods with a "*fatal flaw*".

In the absence of a connected network, model based methods seek to adjust for population differences. The approach presented within the company submission is based on outcome regression, which can be considered a type of Simulated Treatment Comparison (STC). Despite the limitations of model based adjustments, unadjusted methods do correspond to naïve comparisons and should be avoided.

b) As discussed in the response to question A14, the pairwise meta-analysis comparing the simulated atezolizumab arm and comparator arm for each relevant comparator are expected to lead to the same estimates as the joint fit.

To confirm this assumption the pairwise meta-analysis for OS 2L+ was conducted. Table 10 below is a reproduction of Table 24 within the company submission, along with the results obtained from 3 separate pairwise meta-analyses (using the same FE fractional polynomial model).

These results demonstrate the two analyses lead to consistent results. The minor numerical differences are due to Monte Carlo error as the estimates are based on Markov chain Monte Carlo methods: however, when rounded to two digits, results are identical.

Table 10: Contrast estimates and posterior correlations for OS, from pairwise meta-anslyses for comparators of interest (2L+)

Company submission Table 24: Contrast estimates and posterior correlations for OS under FE fractional polynomial model for comparators of interest (2L+)							
Treatment	**Intercept (median)**	**Intercept (lower bound)**	**Intercept (upper bound)**	**Slope (median)**	**Slope (lower bound)**	**Slope (upper bound)**	**Correlation between intercept and slope**

BSC	0.547	0.238	0.848	-0.002	-0.038	0.034	-0.736
paclitaxel	0.333	-0.280	0.901	0.003	-0.073	0.070	-0.738
docetaxel	-0.168	-0.581	0.234	0.044	-0.008	0.092	-0.787

New analysis: results from three separate pairwise meta-analysis, one for each comparator of interest, using the same model.

Treatment	**Intercept (median)**	**Intercept (lower bound)**	**Intercept (upper bound)**	**Slope (median)**	**Slope (lower bound)**	**Slope (upper bound)**	**Correlation between intercept and slope**
BSC	0.551	0.241	0.851	-0.002	-0.039	0.034	-0.736
paclitaxel	0.325	-0.283	0.900	0.003	-0.073	0.070	-0.738
docetaxel	-0.169	-0.588	0.228	0.044	-0.007	0.093	-0.784

A16. Priority question. The rationale given in sections 3.5.3 and 4.10.4 of the company submission for identifying the prognostic factors used to match patients in the atezolizumab trials to those in comparator trials, is based on two publications. Please provide evidence that no known prognostic factors or effect modifiers have been missed from the prediction model.

Prognostic factors for the outcomes associated with 2L treatment of advanced or metastatic UC were reported in the paper by Bellmunt et al (Bellmunt et al, 2010). To identify similar papers and determine the suitability of these prognostic factors, the following targeted searches of the literature were performed in 2015:

1) PubMed search to identify articles that linked directly to the Bellmunt publication ("similar articles"; n=177)

2) A search of Thomson Reuters' Web of Science™ Core Collection for articles that referenced the Bellmunt article (n=96)

3) An OVID MEDLINE search using a variety of keywords and MeSH terms used to describe the Bellmunt study (published in 2014 or 2015; n=821).

The studies identified in these 3 searches were reviewed based on title and abstract. Any papers considered to report prognostic factors with respect to 2L treatment were reviewed in full-text.

This search identified an additional three articles which were deemed relevant (Agarwal, 2014; Pond, 2014; Witjes 2014). The primary reasons for exclusion of the vast majority of studies were: 1) a different UC population; 2) biomarker and diagnostic test validation studies, 3) review articles; and 4) clinical trials. Many of the trials published after 2010 performed analyses informed by the prognostic factors reported by Bellmunt et al; but no additional prognostic factors were reported.

Two (Agarwal et al, 2014 and Witjes et al, 2014) of the three additional identified papers were clinical treatment guidelines which discussed the use and relevance of prognostic factors. The third paper (Pond et al. 2014) described the development of a nomogram which included Bellmunt's prognostic factors, as well as the time since last treatment as a factor of importance. A summary of the relevant factors in the in the different studies is provided in Table 11 below.

Table 11: Literature described mUC prognostic factors

	Liver involvement	ECOG PS (≤1)	Haemoglobin (<10g/dL)^	No. organs involved[&]	Age	Gender
Bellmunt,2010	X	X	X	X		
Agarwal,2014*	X	X	X			
Pond, 2014*	X	X	X			
Witjes, 2014*	X	X	X			
Internal expert opinion#					X	X

* Articles cite prognostic factors reported by Bellmunt et al. (2010)

^ Excluded from analysis since trials typically excluded all patients with baseline haemoglobin <10g/dL

& Excluded from analysis since variable not found to be statistically significant in Bellmunt study.

Roche internal clinical expert, distinct to the expert panel as discussed in questions A1

A17. Priority question. Please provide evidence to justify the cut-off used in section 4.10.4 of the company submission for the age covariate of the prediction model (65 years or older).

The EMA defines elderly patients as those over 65. As per section 4.2 of the Summary of Product Characteristics for EMA approved medicines, 'Special population, Elderly patients' is

defined as those aged 65 years and older'. As such, this was deemed a clinical important cut-off for the age covariate.

A18. Priority question. Please provide evidence to justify the cut-off used for the prior chemotherapies covariate of the prediction model (2 or more).

Cohort 2 of the IMvigor210 study assessed atezolizumab as a 2L treatment option in mUC. However, the study did not restrict to patients having received only one prior chemotherapy, and enrolled patients at the 3rd and later lines (3L+) of treatment. The cut-off of 2 or more prior chemotherapies was used to assess the impact of having a larger or lower proportion of patients being 3L+, in contract to only 2L.

A19. Please clarify why liver metastasis was selected as a prognostic factor rather than visceral metastasis (i.e. bone, liver or lung) which is mentioned as a prognostic factor in section 3.5.3 of the company submission. Would specification of liver rather than visceral metastasis be unnecessarily restrictive given the already poor evidence base and could this have led to exclusion of any otherwise relevant studies?

The inclusion of liver metastasis (rather than visceral metastatic) as a prognostic factor for mUC is consistent with the available literature; as discussed in response to question A16. Both the prognostic model in Bellmunt et al, 2010 and the nomogram presented in Pond et al, 2014 utilised liver metastasis.

The two other articles identified (Agarwal, 2014 and Witjes, 2014) discussed prognostic factors, but did not present a prognostic model.

A20. Please explain why in section 4.10.5 overall survival at 12 months was selected as an outcome instead of also including overall survival measured at other time points? Could this have led to exclusion of any studies with relevant overall survival outcomes?

As described in section 4.10.5 of the company submission, selection of literature for inclusion within the NMA was based not only on the availability of 12 month OS results, but also KM curves for OS. As such, any paper not reporting 12 month OS, but reporting OS KM curves was selected during the systematic literature review. Therefore inclusion of OS measured at alternative time points would not lead to inclusion of additional papers for the time-to-event analysis, this being the analysis which informed the economic model.

As discussed in section 4.10.9 of the company submission, and in response to question A12, binary outcomes were not incorporated into the economic analysis. These were included within the NMA to provide complete assessment of the relative effectiveness of atezolizumab to comparators. 12 months OS was included to assess long-term survival. Whilst later time-points would ideally provide evidence of this long-term survival, the available sample sizes become very small and so uncertainty becomes very large. 12 month OS was a pragmatic compromise, and is consistent with the literature citation on milestone survival for cancer immunotherapies (Chen TT. 2015).

A21. Priority question. Please explain how the values for age>65 years in Table 17 were obtained from the studies by Barnias (2007), DeSantis et al (2009-2012), Kim (2013) and Lee (2012) since these do not match the information reported in the study publications.

The studies list in question A21 (Barnias et al, 2007; DeSantis et al (2009-2012); Kim et al, 2013; Lee et al, 2012) did not report the proportion of patients >65 years old. When such information was missing, the age covariate defined as proportion of study patients age > 65 years, was calculated using the below described approach:

- Reconstructed assuming normal distribution of age within the study population, based on the reported mean and standard deviation (SD).
- When the mean was not reported, the median was used as a proxy (valid under normality).
- When standard deviation was not reported, it was reconstructed the following way:
    - If standard error (SE) was reported, SD was calculated from sample size n as: $\mathrm{SD} = \mathrm{SE} \times \sqrt{\mathrm{n}}$.
    - Else, if minimum and maximum ages were reported, SD was calculated using SE approximated by [16]: $\mathrm{SE} = (\max - \min)/4$.

Missing proportions for binary outcomes were recalculated from sample sizes where available. Missing confidence intervals for proportions were derived using the Wilson score interval except for 12-month survival outcomes which were derived using Clopper-Pearson intervals as they are expected to be more conservative.

A22. Priority question. Please explain the following discrepancies between the values reported in Table 17 and those in the Bellmunt et al (2009) study:

(a) Age ≥65 years was 0.49 in the best supportive care arm and 0.47 in the vinflunine + best supportive care arm, not 0.44 as stated in the Table 17.

(b) The ERG cannot find the value of 0.78 for gender, either in the main publication or in a secondary publication not cited in Table 17 (J Clin Oncol 2010;28:1850-55).

(c) Table 17 states that the proportion of people with liver metastases was NA (not applicable); however, the secondary publication (not cited in the table: J Clin Oncol 2010;28:1850-55) states that across both study arms the value was 0.29. Why was this value not used in the analysis?

(d) The proportion of people with ECOG PS≥1 was 0.62 in the best supportive care arm and 0.72 in the vinflunine +best supportive care arm, not 0.69 as stated in Table 17.

a) In order to be consistent and use a uniform approach across studies, the method described in response to question A21 was utilised to derive the proportion of patients >65 years in the Bellmunt 2009 study. Since several studies did not report age > 65 it was initially planned to handle published clinical studies in a uniform approach with the proportion of patients >65 years were estimated as described in answer A21. In a second approach, the data describing the % above 65 years were extracted from the finally selected studies. Exceptionally, for Bellmunt 2009 the imputed data for age >65 were used. In the update the data available in the paper were unfortunately overlooked.

b) The EMA CHMP Assessment Report for Javlor reports the proportion of men in the vinflunine + BSC group as 77.9% (page 41 of report). Therefore the rounded value of 78% has been used (Javlor CHMP Report, 2009).

c) The Bellmunt 2010 reference as cited in question A22 c) was excluded during the systematic literature review at abstract level. The rationale for exclusion was this publication being a secondary analysis of study data, for which the objective was to identify prognostic factors. This did not meet the systematic literature review inclusion criteria, as per Table 10 in the company submission.

To note, inclusion of this value would not lead to a difference in the model prediction. The reported proportion of patients with liver metastasis in the Bellmunt 2010 publication (29%) is similar to the reported proportion in the IMvigor 210 study (31%), thus no further adjustment of the curves would be required if included. Should this adjustment be included it would favour the outcomes of the Bellmunt 2010 study, and penalise the

IMvigor 210 outcomes. As such, non-inclusion of this adjustment is considered a conservative approach.

d) For included randomised controlled trials (RCTs) in which both treatment arms were of interest, the weighted mean of the covariates was calculated. This was to adjust for the study (not for each arm separately) as the prediction model aimed at imputing a hypothetical missing atezolizumab arm for the study as a whole. Taking the sample sizes of the groups into account (n=117 for the BSC group and n=253 for vinflunine+BSC), the weighted average proportion of ECOG PS ≥1 is 69%.

A23. Priority question. Table 17 states that the proportion with liver metastases in the Lee (2012) study was NA (not applicable); however, the Lee (2012) publication reports liver metastases as 0.30. Why was this value not used in the analysis?

This has been an unfortunate typographical error. This result was included in the systematic literature review dataset, but was overseen during transfer to the final analysis dataset.

Although an error, we do not expect this accidental omission to significantly affect the analyses. The reported proportion of patients with liver metastasis in the Lee 2012 publication (30%) is similar to the reported proportion in the IMvigor 210 study (31%), thus no further adjustment of the curves would be required if included.

A24. **The text below Table 17 states that "there are a number of differences between included trials that require some caution when interpreting the results, such as differences in patient populations including baseline risk, treatment history, differences in trial designs, particularly in regard to primary efficacy outcome(s) measurements." This appears to suggest considerable heterogeneity but this is not transparent as baseline characteristics from the comparator studies are not presented in the company submission. Please explain the rationale for including these studies in the network meta-analysis if the populations were heterogeneous?**

There are limited available data for the appraisal comparators, and within available data KM curves for OS or PFS were required in order to include studies within the NMA for the time-to-event analysis. Consequently, it was necessary to include studies of heterogeneous populations due to the lack of alternative data. Bias and heterogeneity are explored and

described in 4.10.6 of the company submission, but inclusion of such studies was unavoidable in order to conduct a comparison against the comparators of interest.

A25. Priority question: Please provide full details of the study design and population baseline demographic characteristics of each comparator study in section 4.10.5. This should include sample sizes, interventions (including dosage), key inclusion/exclusion criteria, and length of follow up. Please highlight the differences that are referred to in the company submission (i.e. the differences mentioned in the text below Table 17).

Table 12: Drug dosing in included first line studies

Reference	Study drugs	Study drug dosing
(Bamias, 2007):	Carboplatin plus gemcitabine	Patients received gemcitabine at a dose of 1,250 mg/m2, followed by carboplatin at an area under the curve of 2.5, according to the Calvert formula. Treatment was repeated every 2 weeks for at least 8 cycles unless there was disease progression or unacceptable toxicity.
De Santis, 2012	Carboplatin plus gemcitabine versus methotrexate plus carboplatin and vinblastine	Patients who were given M-CAVI received methotrexate 30 mg/m2 intravenously on days 1, 15, and 22. Carboplatin was dosed in milligrams (4.5 x[GFR +25]) and given over 1 hour intravenously on day 1 in both treatment arms, once every 4 weeks. Vinblastine 3mg/m2 intravenously was given on days 1, 15, and 22. Patients allocated to the GC arm received gemcitabine 1,000 mg/m2 over 30 minutes intravenously on days 1 and 8, followed by carboplatin on day 1, every 3 weeks

Table 13: Study design for included 1L comparator studies

Author and year [author, year]	Compared interventions [name]	Study design [RCT/Single arm/ Observational]	Blinding [DB/SB/OL]	Explanation on blinding status	Multicenter [MC/SC]	Study setting [primary care center/tertiary referral center]	Study phase [phase 1, phase 2, phase 3, phase 4]	Crossover?	Duration of controlled period	Duration of controlled period [unit]	Duration of long term follow-up	Duration of long term follow-up [unit]
Bamias, 2007	GEMCITABINE + CARBOPLATIN	Single arm	NR	NR	Single centre	Academic hospital	Phase 2	No	16	Weeks	NR	NR
EORTC Study 30986												
De Santis, 2009	GEMCITABINE + CARBOPLATIN	RCT	Open-label	NR	Multicenter	NR	Phase 2	NR	NR	NR	NR	NR
De Santis 2010	GEMCITABINE + CARBOPLATIN vs METHOTREXATE + CARBOPLATIN + VINBLASTINE	RCT	NR	NR	Multicenter	NR	Phase 3	NR	NR	NR	4.5 (median)	Years
De Santis, 2012	GEMCITABINE + CARBOPLATIN M-CAVI	RCT	Open-label	NR	Multicenter	NR	Phase 2/3	NR	NR	NR	7.8	Years

Table 14: Drug dosing in included first line studies

Reference	Study drugs	Study drug dosing
Bellmunt, 2013	Vinflunine plus best supportive care versus best supportive care alone	Vinflunine was given at 320 mg/m2 every 3 weeks, or 280 mg/m2 every 3 weeks if the patient had an ECOG PS of 1 or an ECOG PS of 0 and pelvic irradiation had been previously administered. If the first administration at 280 mg/m2 was well tolerated, then the dose was subsequently increased at 320 mg/m2. BSC was set up at each institution and included palliative radiotherapy, antibiotics, analgesics, corticosteroids and/or transfusions. In the study arm, treatment was given until documented progression, unacceptable toxicity or withdrawal of patient's consent
Choueiri, 2012	Docetaxel plus vandetanib versus docetaxel plus placebo	Patients on both arms underwent 21-day dosing cycles with docetaxel 75 mg/m2 via 1-hour infusion on day 1 and dexamethasone 8 mg at about 12, 3, and 1 hour before docetaxel. Vandetanib and matching placebo were given as 100-mg tablets orally once daily. Patients receiving placebo tablets were assigned to take them on the same schedule as the patients receiving vandetanib. Treatment was administered until documented progression, unacceptable toxicity, or patient refusal
Kim, 2016	Weekly docetaxel	Patients received docetaxel 30 mg/m2 by way of a 1-hour infusion on days 1 and 8 every 3 weeks. Patients received premedications, including corticosteroid and antihistamines. The docetaxel dose was reduced to 80% in patients with grade 4 neutropenia, febrile neutropenia, grade 3 thrombocytopenia, grade 2 peripheral neuropathy, or other grade 3 nonhematologic toxicity.
Noguchi, 2016	Personalized Peptide Vaccination (PPV) versus best supportive care	The administration schedule of PPV in the PPV plus BSC arm comprised 8 doses at 1-week intervals followed by 4 doses at 2-week intervals; total administration was 12 doses. BSC was including palliative radiotherapy, antibiotics, analgesics, corticosteroids, and transfusion
Lee, 2012	Paclitaxel (cremophor-free, polymeric micelle formulation of paclitaxel	Patients received Genexol-PM 240 mg/m2 intravenously over 3 h every 3 weeks without premedication

Table 15: Study design for included 2L comparator studies

Author and year	Compared interventions [name]	Study design [RCT/Single arm/ Observational]	Blinding [DB/SB/OL]	Explanation on blinding status	Multicenter [MC/SC]	Study setting [primary care center/tertiary referral center]	Study phase [phase 1, phase 2, phase 3, phase 4]	Crossover?	Duration of controlled period	Duration of controlled period [unit]	Duration of long term follow-up	Duration of long term follow-up [unit]
NCT00315237												
Bellmunt, 2008	VINFLUNINE + BEST SUPPORTIVE CARE	RCT	Open-label	NR	Multicenter	NR	Phase 3	No	NR	NR	NR	NR
Bellmunt, 2009	VINFLUNINE + BEST SUPPORTIVE CARE	RCT	Open-label	NR	Multicenter	NR	Phase 3	No	NR	NR	NR	NR
Bellmunt, 2013	VINFLUNINE + BEST SUPPORTIVE CARE	RCT	Open-label	NR	Multicenter	NR	Phase 3	No	NR	NR	NR	NR
Culine, 2010	VINFLUNINE + BEST SUPPORTIVE CARE	RCT	Open-label	NR	Multicenter	NR	Phase 3	No	NR	NR	NR	NR
Fougeray, 2012	VINFLUNINE + BEST SUPPORTIVE CARE	RCT	NR	NR	Multicenter	NR	Phase 3	NR	NR	NR	NR	NR
NCT00880334												
Choueiri 2011	VANDETANIB + DOCETAXEL vs DOCETAXEL + PLACEBO	RCT	Double-blind	Masking: Double Blind (Subject, Investigator)	Multicenter	NR	Phase 2	NR	NR	NR	NR	NR
Choueiri 2012	VANDETANIB +	RCT	Double-blind	NR	Multicenter	NR	Phase 2	yes	NR	NR	NR	NR

Author and year	Compared interventions [name]	Study design [RCT/Single arm/ Observational]	Blinding [DB/SB/OL]	Explanation on blinding status	Multicenter [MC/SC]	Study setting [primary care center/tertiary referral center]	Study phase [phase 1, phase 2, phase 3, phase 4]	Crossover?	Duration of controlled period	Duration of controlled period [unit]	Duration of long term follow-up	Duration of long term follow-up [unit]
	DOCETAXEL											
NCT01711112												
Kim, 2013	DOCETAXEL	Single arm	NR	NR	Multicenter	NR	Phase 2	No	NR	NR	NR	NR
Kim, 2016	DOCETAXEL	Single arm	NR	NR	Multicenter	NR	Phase 2	No	NR	NR	NR	NR
NCT01426126												
Lee, 2011	PACLITAXEL (POLYMERIC MICELLE FORMULATION)	Single arm	NR	NR	NR	Academic medical centres	Phase 2	No	NR	NR	NR	NR
Lee, 2012	PACLITAXEL (POLYMERIC MICELLE FORMULATION)	Single arm	NR	NR	MC	Academic medical centres	Phase 2	No	24	week	NR	NR
UMIN000003157												
Noguchi, 2014	PERSONALIZED PEPTIDE VACCINATION + BEST SUPPORTIVE CARE	RCT	Open-label	NR	Multicenter	NR	Phase 2	No	NR	NR	NR	NR

Author and year	Compared interventions [name]	Study design [RCT/Single arm/ Observational]	Blinding [DB/SB/OL]	Explanation on blinding status	Multicenter [MC/SC]	Study setting [primary care center/tertiary referral center]	Study phase [phase 1, phase 2, phase 3, phase 4]	Crossover?	Duration of controlled period	Duration of controlled period [unit]	Duration of long term follow-up	Duration of long term follow-up [unit]
Noguchi, 2016	PERSONALIZED PEPTIDE VACCINATION + BEST SUPPORTIVE CARE	RCT	Open-label	NR	Multicenter	NR	Phase 2	No	NR	NR	NR	NR

Table 16: Patients in- and exclusion criteria (1L)

		Inclusion criteria				Exclusion criteria			
Author and year	Compared interventions [name]	Clinical Criteria	Diagnostic criteria	Disease Stage	Prior Treatment	Main exclusion criterion	Subgroup data [yes/no]	Subgroup data prespecified [yes/no]	Subgroup data [type]
Bamias, 2007	GEMCITABINE + CARBOPLATIN	ECOG > or = 2, creatinine clearance < 50 ml/min, other comorbidities precluding cisplatin	Histologically proven TCC of urothelium	Disease was unresectable, recurrent, or metastatic	Previous neoadjuvant or adjuvant treatment, but 12-month treatment-free interval	No previous chemotherapy	Yes	Yes	PFS
De Santis, 2009	GEMCITABINE + CARBOPLATIN	All patients had to be ineligible (unfit) for cisplatin-based chemotherapy, defined by either aWHOPS2 and/or an impaired renal function(GFR>30 but<60 mL/min). GFR	Patients with histologically proven transitional-cell carcinoma of the urinary tract (including renal pelvis, ureters,	Patients with histologically proven transitional-cell carcinoma of the urinary tract (including renal pelvis, ureters,	Patients ineligible for cisplatin therapy Lesions occurring in tissues that had been previously irradiated were to	Patients with previous systemic chemotherapy (including adjuvant and neoadjuvant chemotherapy); inadequate bone	Yes	Unclear	Bajorin Risk Groups (0-2)

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
		could be assessed by direct measurement (ethylenediaminetetra-acetate or creatinine clearance) or, if not available, by calculation from serum/plasma creatinine.24 Corrected serum calcium was to be within the normal limits. Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule was required. Fertile men and potentially childbearing women were required to use an appropriate contraceptive method during and for 6 months after completion of chemotherapy.	urinary bladder), unresected lymph node(s) (N), distant metastases (M1, stage IV) or unresectable primary bladder cancer (T3-4), and with measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST)	urinary bladder), unresected lymph node(s) (N), distant metastases (M1, stage IV) or unresectable primary bladder cancer (T3-4)	be assessed only if irradiation treatment had been completed at least 3 months earlier and if the lesions had since progressed or were new. No previous systemic treatment, either cytotoxic or biologic, was allowed.	marrow function (WBC <4,000/ L or platelets <125,000/ L); liver function impairment (bilirubin >1.25 upper limit of normal [ULN] and/or AST/ALT >3 ULN; in the case of known liver metastases AST/ALT >5 ULN); presence of brain metastases or other CNS lesions; a concomitant, second, or previous malignancy except for cured basal-cell skin cancer; carcinoma in situ of the cervix; and pregnant or lactating women were all ineligible.			
De Santis 2010	GEMCITABINE + CARBOPLATIN vs METHOTREXATE +	measurable disease and an impaired renal	NR	NR	Ineligible for cisplatin protocol	NR	No	NR	NR

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
	CARBOPLATIN + VINBLASTINE	function (GFR<60 but >30 ml/min) and/or PS 2							
De Santis, 2012	GEMCITABINE + CARBOPLATIN	All patients had to be ineligible (unfit) for cisplatin-based chemotherapy, defined by either aWHOPS2 and/or an impaired renal function(GFR>30 but<60 mL/min). GFR could be assessed by direct measurement (ethylenediaminetetra-acetate or creatinine clearance) or, if not available, by calculation from serum/plasma creatinine.24 Corrected serum calcium was to be within the normal limits. Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule was required. Fertile men and potentially childbearing women were required to use an appropriate contraceptive method	Patients with histologically proven transitional-cell carcinoma of the urinary tract (including renal pelvis, ureters, urinary bladder), unresected lymph node(s) (N), distant metastases (M1, stage IV) or unresectable primary bladder cancer (T3-4), and with measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST)	Patients with histologically proven transitional-cell carcinoma of the urinary tract (including renal pelvis, ureters, urinary bladder), unresected lymph node(s) (N), distant metastases (M1, stage IV) or unresectable primary bladder cancer (T3-4)	Patients ineligible for cisplatin therapy Lesions occurring in tissues that had been previously irradiated were to be assessed only if irradiation treatment had been completed at least 3 months earlier and if the lesions had since progressed or were new. No previous systemic treatment, either cytotoxic or biologic, was allowed.	Patients with previous systemic chemotherapy (including adjuvant and neoadjuvant chemotherapy); inadequate bone marrow function (WBC <4,000/ L or platelets <125,000/ L); liver function impairment (bilirubin >1.25 upper limit of normal [ULN] and/or AST/ALT >3 ULN; in the case of known liver metastases AST/ALT >5 ULN); presence of brain metastases or other CNS lesions; a concomitant, second, or previous malignancy except for cured	Yes	Unclear	Bajorin Risk Groups (0-2)

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
		during and for 6 months after completion of chemotherapy.				basal-cell skin cancer; carcinoma in situ of the cervix; and pregnant or lactating women were all ineligible.			
De Santis, 2012	METHOTREXATE + CARBOPLATIN + VINBLASTINE	All patients had to be ineligible (unfit) for cisplatin-based chemotherapy, defined by either aWHOPS2 and/or an impaired renal function(GFR>30 but<60 mL/min). GFR could be assessed by direct measurement (ethylenediaminetetra-acetate or creatinine clearance) or, if not available, by calculation from serum/plasma creatinine.24 Corrected serum calcium was to be within the normal limits. Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule was required. Fertile men and potentially	Patients with histologically proven transitional-cell carcinoma of the urinary tract (including renal pelvis, ureters, urinary bladder), unresected lymph node(s) (N), distant metastases (M1, stage IV) or unresectable primary bladder cancer (T3-4), and with measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST)	Patients with histologically proven transitional-cell carcinoma of the urinary tract (including renal pelvis, ureters, urinary bladder), unresected lymph node(s) (N), distant metastases (M1, stage IV) or unresectable primary bladder cancer (T3-4)	No previous cytotoxic or biologic systemic treatment was allowed. All patients had to be ineligible (unfit) for cisplatin-based chemotherapy,	Patients with previous systemic chemotherapy (including adjuvant and neoadjuvant chemotherapy); inadequate bone marrow function (WBC <4,000/ L or platelets <125,000/ L); liver function impairment (bilirubin >1.25 upper limit of normal [ULN] and/or AST/ALT >3 ULN; in the case of known liver metastases AST/ALT >5 ULN); presence of brain metastases or other CNS lesions; a concomitant,	Yes	Unclear	Bajorin Risk Groups (0-2)

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
		childbearing women were required to use an appropriate contraceptive method during and for 6 months after completion of chemotherapy.				second, or previous malignancy except for cured basal-cell skin cancer; carcinoma in situ of the cervix; and pregnant or lactating women were all ineligible.			

Table 17: Patients in- and exclusion criteria (2L)

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
NCT00315237									
Bellmunt, 2008	VINFLUNINE + BEST SUPPORTIVE CARE	NR	Advanced transitional cell carcinoma of the urothelium	NR	Prior platinum-based therapy	NR	No	NR	NR
Bellmunt, 2009	VINFLUNINE + BEST SUPPORTIVE CARE	ECOG PS of 0 or 1	Locally advanced or metastatic TCCU	Advanced disease stage, not further specified	Progression after a first-line platinum-based schedule	NR	No	NR	NR

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
Bellmunt, 2013	VINFLUNINE + BEST SUPPORTIVE CARE	ECOG PS of 0 or 1	Advanced transitional cell carcinoma of the urothelium	Advanced disease stage, not further specified	Prior platinum-based therapy	NR	No	NR	NR
Culine, 2010	VINFLUNINE + BEST SUPPORTIVE CARE	NR	Advanced transitional cell carcinoma of the urothelium	NR	Prior platinum-based therapy	NR	No	NR	NR
Fougeray, 2012	VINFLUNINE + BEST SUPPORTIVE CARE	NR	Advanced transitional cell carcinoma	Advanced disease stage, no further description	Prior Cisplatin-Based Therapy possible	NR	NR	NR	NR
Von der Maase, 2008	VINFLUNINE + BEST SUPPORTIVE CARE	NR	Advanced transitional cell carcinoma of the urothelium	NR	Prior platinum-based therapy	NR	No	NR	NR
NCT00880334									
Choueiri 2011	VANDETANIB + DOCETAXEL vs DOCETAXEL + PLACEBO	18 Years and older. Measurable or evaluable disease, as defined by RECIST.	Histologically or cytologically confirmed TCC. ECOG PS 0 or 1	Histologically or cytologically confirmed TCC	Must have received chemotherapy treatment for TCC and have stage IV TCC at the time of study entry. 1-3 prior systemic chemotherapeutic or investigational treatment regimens for TCC are allowed.	History of treatment with a VEGF-axis active agent, including antibodies to VEGF, antibodies to VEGF receptors, or VEGF receptor tyrosine kinase inhibitors. History of	No	No	No

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
Choueiri 2012	VANDETANIB + DOCETAXEL	* Participants must be ≥18 years * Participants must have measurable disease defined as at least one target lesion that has not been irradiated and can be accurately measured in at least one dimension by RECIST v1.1 criteria ;	Participants must have histologically documented metastatic or locally inoperable advanced urothelial carcinoma (bladder, urethra, ureter and renal pelvis) (T4b, N2, N3, or M1 disease. NOTE: Aberrant differentiation such as squamous, glandular	Metastatic or locally inoperable advanced urothelial carcinoma (bladder, urethra, ureter and renal pelvis) (T4b, N2, N3, or M1 disease.	* Participants must have received prior systemic chemotherapy treatment for metastatic urothelial carcinoma. NOTE: Up to 2 prior systemic chemotherapeutic regimens given in the metastatic disease setting for urothelial carcinoma are allowed ;	treatment of TCC (in any setting- neoadjuvant, adjuvant or for metastatic disease) with docetaxel. Any concomitant medication that may cause QTc prolongation, induce Torsades de Pointes or induce CYP3A4 function * History of treatment with docetaxel in any setting. Participants treated with prior paclitaxel are eligible ; * Prior enrollment in the OncoGenex Phase 2 Study OGX-427-02 ; * Participants may not be receiving other investigational agents ;	NR	NR	NR

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
			(adenocarcinoma), and micropapillary are eligible unless the tumor is considered a pure histological variant according to the pathology report. Participants with small cell histology are not eligible ;			* Participants with known brain or spinal cord metastases are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. NOTE: Brain imaging is not required unless the patient has symptoms or physical signs of central nervous system (CNS) disease ; * History of allergic reactions or severe hypersensitivity reactions to drugs			

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
						formulated with polysorbate 80 or antisense oligonucleotides ; * Peripheral neuropathy ≥Grade 2 ; * Uncontrolled intercurrent illness including, but not limited to ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements ; * Cerebrovascular accident or pulmonary embolus within 3 months of randomization ; * Pregnant women and breast feeding women are excluded from this study because of the			

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
						risk to a fetus due to docetaxel chemotherapy and OGX-427 systemic treatment (fertility toxicology studies have not been completed for OGX-427) ; * Active second malignancy (except non-melanomatous skin cancer or incidental prostate cancer found on cystectomy): active secondary malignancy is defined as a current need for cancer therapy or a high possibility (>30%) of recurrence during the study.			

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
NCT01426126									
Lee, 2011	PACLITAXEL (POLYMERIC MICELLE FORMULATION)	NR	NR	NR	NR	NR	NR	37	
Lee, 2012	PACLITAXEL (POLYMERIC MICELLE FORMULATION)	NR	NR	NR	NR	NR	NR	37	NR
NCT01711112									
Kim, 2013	DOCETAXEL	NR	Measurable UCC, progressive	Advanced disease	Progressive after one prior platinum-based chemotherapy for advanced disease	NR	No	NR	NR
Kim, 2016	DOCETAXEL	Age 18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; adequate bone marrow (absolute neutrophil count 1500/mL and platelet count 100,000/mL), normal hepatic (bilirubin 1.5 times the upper limit of normal [ULN] and hepatic transaminase 3 times the ULN), and renal (serum creatinine, < 1.5	Histologically confirmed metastatic UC with measurable lesions;	Metastatic urothelial carcinoma with measureable lesions	Documented progression after 1 previous platinum-based chemotherapy regimens for advanced or metastatic disease (adjuvant or neoadjuvant therapy counted as first-line of therapy if the patient developed progression within 6 months of the last dose);	Patients were excluded from the study if they had undergone previous treatment with taxanes (docetaxel and paclitaxel) or had brain metastases, an uncontrolled comorbid illness, or another malignancy.	Yes	Unclear	Prognostic model subgroups: According to the prognostic model by Sonpavde et al, the following 4 prognostic factors were examined for the prognostic grouping of patients: time from previous chemotherapy (TFPC) < 3

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
		mg/dL) function; and an estimated life expectancy of 3 months.							months, ECOG PS > 0, hemoglobin < 10 g/dL, and the presence of liver metastasis. We categorized the subgroups according to the presence of 0, 1, 2, and 3 to 4 factors.
UMIN000003157									
Noguchi, 2014	PERSONALIZED PEPTIDE VACCINATION + BEST SUPPORTIVE CARE	Patients with advanced metastatic bladder cancer who failed or progressed after first-line platinum-containing regimens	NR	NR	First-line platinum-containing regimens	NR	NR	NR	NR
Noguchi, 2016	PERSONALIZED PEPTIDE VACCINATION + BEST SUPPORTIVE CARE	Eligible patients were ages 18 years, and had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1, life expectancy of at least 12 weeks, and adequate bone marrow function,	Histologically proven metastatic urothelial carcinoma of the bladder and were documented within 12 months after first-line platinum-containing chemotherapy. Patients were also	Metastatic disease	First-line platinum-containing chemotherapy	Acute infection, a history of severe allergic reactions, pulmonary, cardiac or other systemic diseases, and other inappropriate conditions for enrollment as	No	NR	NR

		Inclusion criteria				Exclusion criteria			
Author and year	**Compared interventions [name]**	**Clinical Criteria**	**Diagnostic criteria**	**Disease Stage**	**Prior Treatment**	**Main exclusion criterion**	**Subgroup data [yes/no]**	**Subgroup data prespecified [yes/no]**	**Subgroup data [type]**
		hepatic function, and renal function.	required to have measurable disease to be eligible for the trial			judged by clinicians.			

Table 18: Age, gender, and ethnicity of the studies included in the feasibility assessment (baseline) (1L)

			Age				Female gender (Dichotomous baseline characteristic)			Ethnicity								
Author and year	**Compared interventions [name]**	**Sample size**	**mean**	**median**	**range [lower]**	**range [upper]**	**n**	**N**	**%**	**N**	**White [n]**	**White [%]**	**Black [n]**	**Black [%]**	**Asian [n]**	**Asian [%]**	**Other [n]**	**Other [%]**
Bamias, 2007	GEMCITABINE + CARBOPLATIN	34	NR	75.5	57	84	6	34	17.0%	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Santis, 2009	GEMCITABINE + CARBOPLATIN	119	NR	71	36	85	19	88	21.60%	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Santis 2010	GEMCITABINE + CARBOPLATIN vs METHOTREXATE + CARBOPLATIN + VINBLASTINE	119	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Santis, 2012	GEMCITABINE + CARBOPLATIN	119	NR	70	36	87	29	119	24.40%	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 19: Age, gender, and ethnicity of the studies included in the feasibility assessment (baseline) (2L)

			Age				Female gender (Dichotomous baseline characteristic)			Ethnicity								
Author and year	**Compared interventions [name]**	**Sample size**	**mean**	**median**	**range [lower]**	**range [upper]**	**n**	**N**	**%**	**N**	**White [n]**	**White [%]**	**Black [n]**	**Black [%]**	**Asian [n]**	**Asian [%]**	**Other [n]**	**Other [%]**
NCT00315237																		
Bellmunt, 2008	VINFLUNINE + BEST SUPPORTIVE CARE	253 117	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bellmunt, 2009	VINFLUNINE + BEST SUPPORTIVE CARE		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bellmunt, 2013	VINFLUNINE + BEST SUPPORTIVE CARE		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Culine, 2010	VINFLUNINE + BEST SUPPORTIVE CARE		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fougeray, 2012	VINFLUNINE + BEST SUPPORTIVE CARE		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Von der Maase, 2008	VINFLUNINE + BEST SUPPORTIVE CARE		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NCT00880334																		
Choueiri	VANDETANIB + DOCETAXEL vs DOCETAXEL + PLACEBO	74 75	NR	NR	NR	NR	**45**	142	31.7%	142	128	1.0%	3	2.1%	3	2.1%	NR	NR

			Age				Female gender (Dichotomous baseline characteristic)			Ethnicity								
Author and year	**Compared interventions [name]**	**Sample size**	**mean**	**median**	**range [lower]**	**range [upper]**	**n**	**N**	**%**	**N**	**White [n]**	**White [%]**	**Black [n]**	**Black [%]**	**Asian [n]**	**Asian [%]**	**Other [n]**	**Other [%]**
Choueiri 2012	VANDETANIB + DOCETAXEL		NR	NR	NR	NR	**22**	**70**	**31.4%**	NR	NR	NR	NR	NR	NR	NR	NR	NR
Choueiri 2012	DOCETAXEL		NR	NR	NR	NR	**23**	**72**	**31.9%**	NR	NR	NR	NR	NR	NR	NR	NR	NR
NCT01426126																		
Lee, 2011	PACLITAXEL (POLYMERIC MICELLE FORMULATION)	37	NR	NR	NR	NR	NR	NR	NR	37	NR	NR	NR	NR	NR	NR	NR	NR
Lee, 2012	PACLITAXEL (POLYMERIC MICELLE FORMULATION)		NR	57	44	78	8	37	22.0%	37	NR	NR	NR	NR	NR	NR	NR	NR
NCT01711112																		
Kim, 2013	DOCETAXEL	31	NR	64	40	79	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kim, 2016	DOCETAXEL		NR	64	40	79	7	31	23.0%	31	NR	NR	NR	NR	31	1.0%	NR	NR
UMIN000003157																		
Noguchi, 2014	PERSONALIZED PEPTIDE VACCINATION + BEST SUPPORTIVE CARE	39 41	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Noguchi, 2016	PERSONALIZED PEPTIDE VACCINATION + BEST		NR	65	51	84	11	39	28.2%	NR	NR	NR	NR	NR	NR	NR	NR	NR

			Age				Female gender (Dichotomous baseline characteristic)			Ethnicity								
Author and year	**Compared interventions [name]**	**Sample size**	**mean**	**median**	**range [lower]**	**range [upper]**	**n**	**N**	**%**	**N**	**White [n]**	**White [%]**	**Black [n]**	**Black [%]**	**Asian [n]**	**Asian [%]**	**Other [n]**	**Other [%]**
Noguchi, 2016	SUPPORTIVE CARE BEST SUPPORTIVE CARE		NR	65	46	81	8	41	19.5%	NR	NR	NR	NR	NR	NR	NR	NR	NR

A26. In Figure 4 please explain how the different categories of heterogeneity are defined, and how the combined category of risk of bias and heterogeneity is defined?

The risk of bias regarding the NMA was assessed in a three step approach:

1) Critical quality appraisal of each individual study included in the feasibility assessment of the NMA (intrinsic validity).

   As described in section 4.10.6 of company submission, the tools applied for the critical study appraisals were based on the NICE and Cochrane checklists for randomised clinical studies and on an adapted assessment checklist developed by National Institutes of Health (NIH) for single arm studies.

   Criteria for quality assessment included adequacy of randomisation method, allocation concealment, homogeneity of baseline characteristics between treatment groups and blinding in RCTs. The quality assessment of single arm studies was based on the adequate description and comparability of included study populations, and adequate description of the underlying methods and outcomes. The study quality assessment was conducted by two independent assessors.

   The study quality was assigned to one of following categories:

   - high
   - moderate to high
   - moderate
   - low to moderate
   - low

2) Step 2 was a qualitative assessment of the heterogeneity across studies (i.e. age, sex, ECOG PS, proportion of all metastatic sites and liver metastasis as well as treatment dosage and frequency of administration).

   The degree of heterogeneity between studies was assigned to one of following categories*:

   - Low
   - low to moderate
   - moderate

- moderate to high
- high

* The category of heterogeneity has been qualitatively assessed as follows:
a) The more baseline information regarding population characteristics and treatment schedule and b) the more homogenous the values are between the studies the lower was the degree of heterogeneity.

3) Step 3 was an assessment of the risk of bias for each individual network, which was qualitatively evaluated based on the study quality (step 1) of each study included in the network and the heterogeneity between the studies (step 2) considered for a network.

   The risk of bias for each individual network of the NMA was described by combining the rating of the study quality and the degree of heterogeneity, defined as:

   - Low
   - low to moderate
   - moderate
   - moderate to high
   - high

A27. Please provide a critical appraisal of both the IMvigor210 and PCD4989g studies, including an assessment of the risk of bias.

Incorporation of atezolizumab clinical parameters into the economic model is from only the IMvigor 210 study. The phase I PCD4989g study is included descriptively as supportive data within the available evidence-base for atezolizumab in mUC. However it is acknowledged there are limitations to the assessment of outcomes from phase I studies, as such no clinical parameters from the phase I PCD4989g study are incorporated into the NMA or economic model. As such a critical appraisal and assessment of the risk of bias was not conducted for this study.

Table 20 below is taken from appendix 8.3 of the company submission, and shows the NIH quality assessment for single arm studies. Assessment was against each available publication of IMvigor 210. Figure 4 of the company submission summarises the critical appraisal, within study heterogeneity and assessment of bias for studies included in the NMA, thus includes the IMvigor 210 study.

Table 20: Single arm study quality assessment for IMvigor 210

Source	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the length of follow-up adequate?	Were the statistical methods well-described?	Were the results well-described?	Count (x from 8 possible)
IMvigor210 study Balar, 2016	yes	no	CD	yes	yes	yes	no	yes	5
Rosenberg, 2016	yes	yes	no	yes	yes	yes	yes	yes	7
IMvigor210, cohort 1 and 2 CSR STUDY IMVIGOR 210 (GO29293)	yes	yes	no	yes	yes	yes	yes	yes	7

A28. Table 19 explaining the methodology of the network meta-analysis for the overall survival outcome shows three different prior distributions for between-study heterogeneity, one of which was used in the base case. Please explain:

- **Why the other two prior distributions are presented?**
- **Were they subject to sensitivity analysis? If so, please provide the results.**

Please also answer these questions for the progression-free survival outcome (Table 7 in Appendix 8.4).

Random effects NMA models were included to allow for between trial heterogeneity. Since the number of degrees of freedom to estimate the random effects variance was small in the network, the informative priors presented by Turner et al were selected (Turner et al. 2015). Two other choices were included to assess the sensitivity of the results to the informative prior. As such, the models with the weakly informative prior and the vague prior in Table 19 of company submission represent the sensitivity analysis to the choice of prior. This framework was followed for the analysis of OS KM curves.

For PFS, the uncertainty in the hazard-ratio estimates over time was substantial even with the fixed effects model. The number of trials in the PFS analysis was too few to allow for the vague prior model. Given the large uncertainty present already in the fixed effect PFS analysis, the random effects models were not deemed appropriate.

A29. The prior distributions were obtained from Turner et al (2015) and the authors emphasise in their publication the value of using these prior distributions to support random-effects meta-analysis. Please explain why random-effects analyses were not used in the base case given that the prior distributions were available?

For the NMA of OS KM curves, the best performing fixed effect fractional polynomial model was subsequently fitted in a random effects framework. Table 21 below displays the DIC, effective number of parameters (pD), and mean deviance estimates from these fits. The DIC values did not support that the more complex random effects models led to better fit than the fixed effect model (Welton et al state that "*if there are only small differences (less than 3) in*

DIC there is probably little to choose between the two models.") (Welton et al. 2012). Therefore, the more parsimonious model was preferred as the base-case.

Table 21: DIC values for fixed and random effects models

Model	FE or RE	DIC	pD	meanDev
First order fractional polynomial, p=1 (Gompertz model)	FE	1654.7	49.9	1604.9
	RE, informative prior (Turner et al.)	1652.8	53.2	1599.6
	RE, vague prior	1653.1	53.3	1599.8
	RE, uniform prior	1653.3	54.7	1598.5

A30. Priority question. The text immediately above Table 23 states that a random effects model was explored in sensitivity analysis; however this is not reported in the company submission. Please provide the random-effects analysis, for each population and for each comparator where possible.

The OS random effects (RE) model was fit with 3 different priors for the first order fractional polynomial with P1=1, equivalent to a Gompertz model:

- Informative prior
- Weakly informative prior
- Vague (uniform) prior

Figure 1and Table 22 present the results of RE model with informative prior, Figure 2 and Table 23 present the results of RE model with weakly informative prior and Figure 3 and Table 24 present the results of RE model with vague prior.

Figure 1, Figure 2 and Figure 3 include additional comparators not of relevance to this appraisal.

Figure 1: Hazard ratio estimates for atezolizumab vs other treatments for OS under RE fractional polynomial model (informative prior)

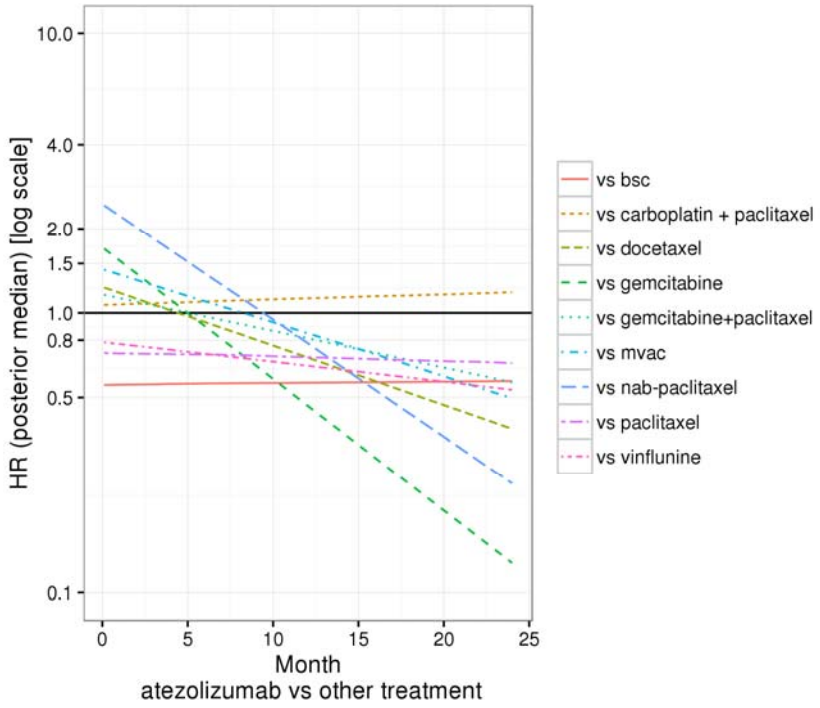


Table 22: Contrast estimates and posterior correlation for OS under RE fractional polynomial model (informative prior

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation
BSC	**0.591**	**0.205**	**0.999**	**-0.001**	**-0.038**	**0.034**	**-0.573**
paclitaxel	**0.328**	**-0.365**	**0.993**	**0.003**	**-0.074**	**0.070**	**-0.651**
docetaxel	**-0.212**	**-0.709**	**0.242**	**0.049**	**-0.002**	**0.098**	**-0.691**

Figure 2: Hazard ratio estimates for atezolizumab vs other treatments for OS under RE fractional polynomial model (weakly informative prior)

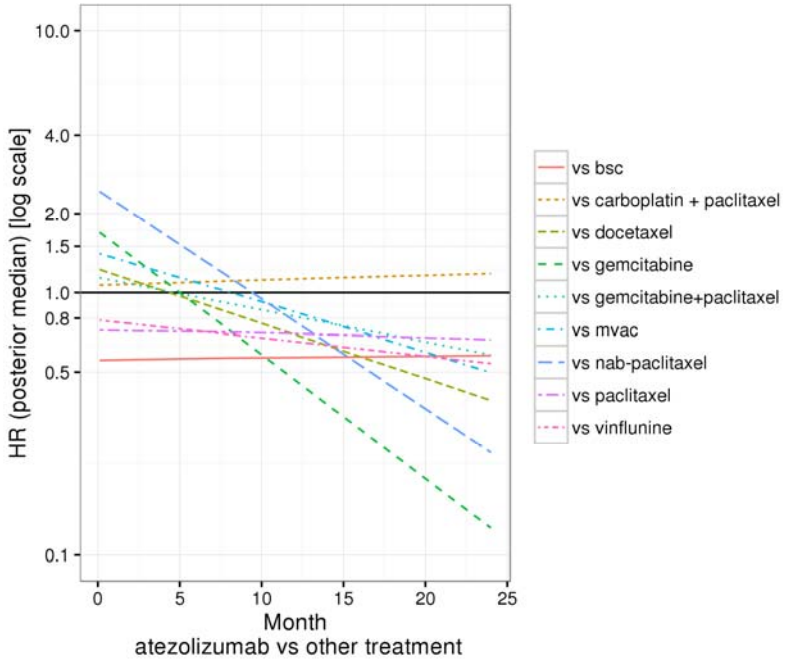


Table 23: Contrast estimates and posterior correlation for OS under RE fractional polynomial model (weakly informative prior)

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation
BSC	0.591	0.194	0.998	-0.002	-0.038	0.034	-0.561
paclitaxel	0.327	-0.369	0.990	0.004	-0.071	0.070	-0.637
docetaxel	-0.207	-0.715	0.251	0.048	-0.005	0.097	-0.691

Figure 3: Hazard ratio estimates for atezolizumab vs other treatments for OS under RE fractional polynomial model (vague [uniform] prior)

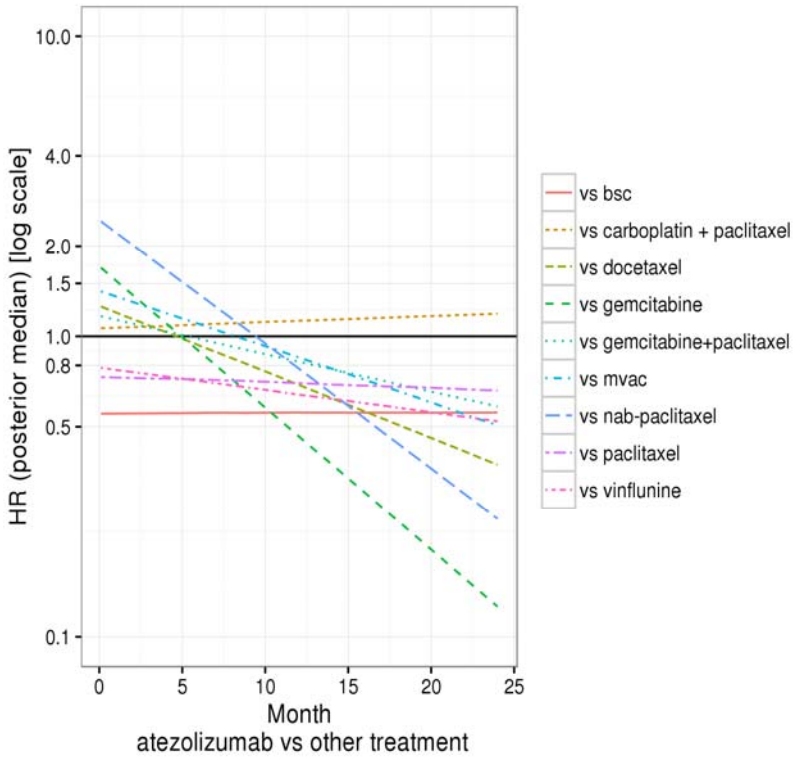


Table 24: Contrast estimates and posterior correlation for OS under RE fractional polynomial model (vague [uniform] prior)

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation
BSC	0.593	0.129	1.072	0.000	-0.037	0.034	-0.466
paclitaxel	0.312	-0.465	1.074	0.004	-0.071	0.071	-0.572
docetaxel	-0.233	-0.801	0.296	0.051	-0.001	0.101	-0.616

A31. The company submission states in section 4.10.3 that missing covariate values were imputed by generating, at every bootstrap iteration, a random value from a uniform distribution, with boundaries defined by the range of reported values across the studies included in the analysis. What is the justification for this approach? Please provide results based on an alternative means of imputation, such as probabilistic multiple imputation, sensitivity analyses of other imputation approaches or provide justification for why these alternative imputation methods were not considered.

The approach used can be considered a basic form of probabilistic multiple imputation, since missing values are simulated within the bootstrap procedure. Sampling a different value at every bootstrap iteration ensures the uncertainty in the predicted missing prognostic factors is captured (in contrast, for example, to single imputation methods). Imputing within the bootstrap implies the uncertainty in the missing covariates - and the uncertainty in the parameter estimates - are captured at the same time. This is similar to Bayesian methods, which treat missing values as unknown parameters.

As relatively few studies qualified for the NMA, the information on the joint distribution of study average covariate values was limited. The multivariate joint distribution needed to impute missing covariate values would not have been well characterized by the available data. Therefore, values were generated from independent uniform distributions. Sampling from more complex regression models would have led to more precise imputations, but would have required stronger, untestable assumptions. The simpler approach was considered more appropriate to avoid such assumptions.

Using uniform distributions is expected to inflate the uncertainty in the model predictions and is therefore conservative compared to other, more complex methods.

A32. Please provide the overall survival and progression-free survival results for each study included in the network meta-analysis, indicating in each case the data from both the original study arm and the simulated atezolizumab arm. A format such as that given in Table 1 of the publication by Jansen et al (2011) (cited in the company submission reference list) would be appropriate for summarising all the studies in a concise format.

The 1L digitalised OS KM curve results are presented in Table 25, with 1L digitalised PFS KM curve results in Table 26. The predicted 1L atezolizumab OS and PFS are presented in Table 27.

The 2L digitalised OS KM curve results are presented in Table 28, with 2L digitalised PFS KM curve results in Table 29. The predicted 2L atezolizumab OS and PFS are presented in Table 30.

Table 25: Digitalised OS KM curves (1L)

[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26: Digitalised PFS KM curves (1L)

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

Table 27: Prediction of atezolizumab OS and PFS (1L)

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 28: Digitalised OS KM curves (2L)

	[redacted]			[redacted]				[redacted]				[redacted]				[redacted]			
Time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 29: Digitalised PFS KM curves (2L)

[redacted]				[redacted]				[redacted]				[redacted]				[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30: Prediction of atezolizumab OS and PFS (2L)

A33. Please provide a table of the contrast estimate parameters and posterior correlations for overall survival for the first-line population, in the same format as the data provided for second-line population as given in Table 24.

Table 31: Contrast estimates and posterior correlations for OS for comparator of interest (1L)

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation between intercept and slope
gemcitabine +carboplatin	0.21	-0.242	0.647	0.051	-0.009	0.112	-0.749

A34. Please provide the median follow up time and range for each data cut of the IMvigor210 study as detailed in Table 26.

5 May 2015 Cohort 1: 4.2 months (0.20-9.72), Cohort 2: 7.1 months (0.23-10.61)
14 Sept 2015 Cohort 1: 8.5 months (0.20-14.26), Cohort 2: 11.7 months (0.23-15.24)
4 July 2016 Cohort 1: 17.2 months (0.2-23.5), Cohort 2: 21.1 months (0.2-24.5)

A35. Please explain why two versions of the RECIST criteria were used in the IMvigor210 study.

The primary endpoint of the IMvigor 210 study was ORR based on two distinct methods:

- Independent review facility-assessed objective response rate according to RECIST v1.1
- Investigator-assessed objective response rate according to immune-modified RECIST criteria to better assess atypical response kinetics described with immunotherapy

Unconventional response patterns have been described in patients treated with anti−cytotoxic T lymphocyte−associated antigen 4 (CTLA-4) (Wolchok et al. 2009), and were observed in the preliminary experience with atezolizumab in the phase I study, PCD4989g. In order to account for the possibility of pseudoprogression / tumor immune infiltration (i.e., radiographic increase in tumor volume due to the influx of immune cells; Hales et al. 2010) and the potential for delayed anti-tumor activity, the IMvigor210 used modified RECIST criteria (in addition to RECIST v1.1) as a co-primary endpoint. The modified RECIST was utilised to accommodate the possible appearance of new lesions and

to allow the apparent increase in tumor burden to be confirmed at a subsequent assessment, prior to designation of progressive disease.

The IMvigor 210 study was designed to characterize these different patterns of response. Treatment beyond apparent RECIST v1.1 progression was permissible in Cohort 2 patients who met all of the following criteria:

- Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease (including worsening of laboratory values [e.g., new or worsening hypercalcemia])
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Cohort 1 patients needed to discontinue study treatment at the first occurrence of unequivocal radiographic progression per RECIST v1.1.

A36. Priority question. Please explain where the 10% historical control rate used in hypothesis testing in IMvigor210 came from, as this is not mentioned in the primary publication. Please justify why this 10% value was chosen and whether any alternatives are available.

Details regarding the 10% historical control rate are included within the study protocol and clinical study report (F. Hoffmann-la Roche ltd. 2014; F. Hoffmann-la Roche ltd. 2015b). At the time the IMvigor 210 study was designed, a 10% historical control was considered the most meaningful estimation of outcomes for the diverse patient group - patients who are cisplatin ineligible and who have progressed after first line treatment.

Acknowledging the limitations of single-arm studies and subsequent challenges with cross trial comparisons, the response rates observed in historical trials of patients with metastatic UC who have progressed following prior platinum chemotherapy are highly consistent and represent a reliable comparison. ORR observed from such taxane or vinflunine studies are summarized in Table 32 below.

Based on results of studies completed by the time of the IMvigor 210 study design (Logothetis 2002; Bellmunt et al. 2009; Choueiri et al. 2012), a historical control ORR for patients experiencing disease progression on, or following a platinum-based chemotherapy regimen (Cohort 2) was estimated to be 10%. Additional trials reported subsequent to the IMvigor 210 study design remained consistent and supportive of the 10% historical control (Petrylak et al. 2016). Of note, the CheckMate 275 study, a single arm phase II study assessing nivolumab in mUC, also used a 10% historical control rate to assess efficacy (Sharma et al, 2017)

Table 32: Second-Line Trials of Taxane or Vinflunine for mUC

Second Line Chemotherapy	ORR (%)	Median DOR (months)	Median PFS (months)	Median OS (months)
Paclitaxel weekly (n=31) (Vaughn et al. 2002)	**10**	**NR**	**2.2**	**7.2**
Docetaxel (n=30) (McCaffrey et al. 1997)	**13**	**4**	**n/a**	**9.0**
Docetaxel (n=72) (Choueiri et al. 2012)	**11**	**NR**	**1.6**	**7.0**
Docetaxel (n=45) (Petrylak et al. 2016)	**8.9**	**4.6**	**2.8**	**9.2**
Vinflunine (n=51) (Culine et al. 2006)	**18**	**9.1**	**3.0**	**6.6**
Vinflunine (n=253) (Bellmunt et al. 2009)	**8.6**	**7.4**	**3.0**	**6.9**

DOR = duration of response; ORR = objective response rate; NR = not reported;
PFS = progression-free survival; OS = overall survival.
a Randomized trial.

A37. Please explain what is meant in the company submission by "intention-to-treat population", given that intention-to-treat is generally understood to refer to the randomisation groups to which patients are allocated and analysed whereas IMvigor210 had only a single arm and no randomisation.

Intention-to-treat is defined as enrolled patients who received any amount of study drug. An exception to this involves ORR analyses, which was performed on the objective response-

evaluable population, defined as ITT patients who have measureable disease per RECIST v1.1 at baseline.

A38. Please explain whether the fact that 15.1% of cisplatin-ineligible patients in IMvigor210 had received prior cisplatin would affect interpretation of the results? Is a subgroup available that excludes these patients?

Cohort 1 inclusion criteria state that for patients who received prior adjuvant/neoadjuvant chemotherapy or chemoradiation for UC, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting (F. Hoffmann-la Roche ltd. 2014).

As described on page 105 of the company submission, the 15.1% of patients who received prior cisplatin are likely to have received this as a previous line of therapy, such as neoadjuvant treatment, at which time they were judged to be eligible to receive cisplatin. Cisplatin-based treatments are known to have adverse effects such as nephrotoxicity, neurotoxicity and ototoxicity (cisplatin SmPC). As such, previously treated patients may subsequently be ineligible for cisplatin at the time of study entry, based on the inclusion criteria of the study. This is representative of a 'real world' UK population of mUC patients, thus the population whom will receive atezolizumab in clinical practice. There is no subgroup analysis available which excludes these patients.

A39. Please provide the results of the subgroup analyses mentioned in the sections 4.11.10.2 and 4.11.10.3 of the company submission for the first-line and second-line populations.

Response rates by baseline characteristics were presented for both Cohort 1 (1L) and Cohort 2 (2L) at the American Society of Clinical Oncology (ASCO) conference, 2016 (Balar et al 2016; Dreicer et al 2016). The data cut off for both cohorts was March 14 2016 which represents an interim data cut off. Subgroup analyses are not available from the most recent data cut off of July 2016. Please note, the company submission primarily reports the most recent data cut off, as such the results presented in Figure 4 and Figure 5 below are from an earlier cut off which is inconsistent with that reported in the company submission.

Figure 4: Results by baseline characteristic of Cohort 1 (1L)

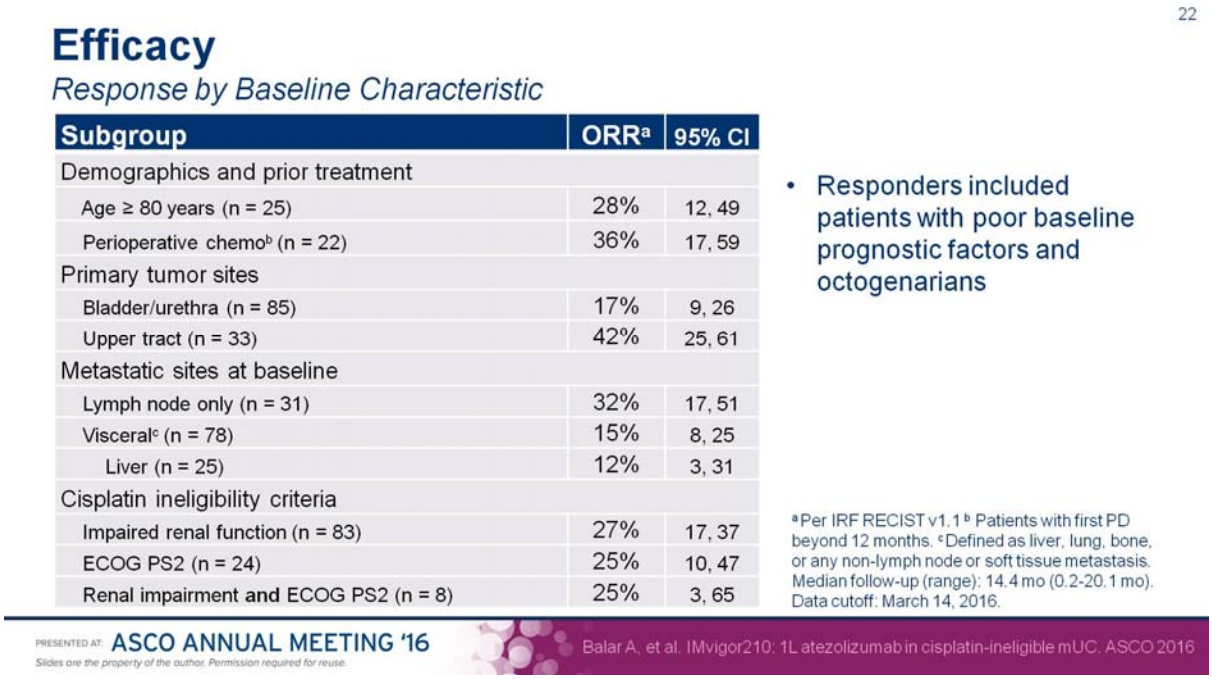
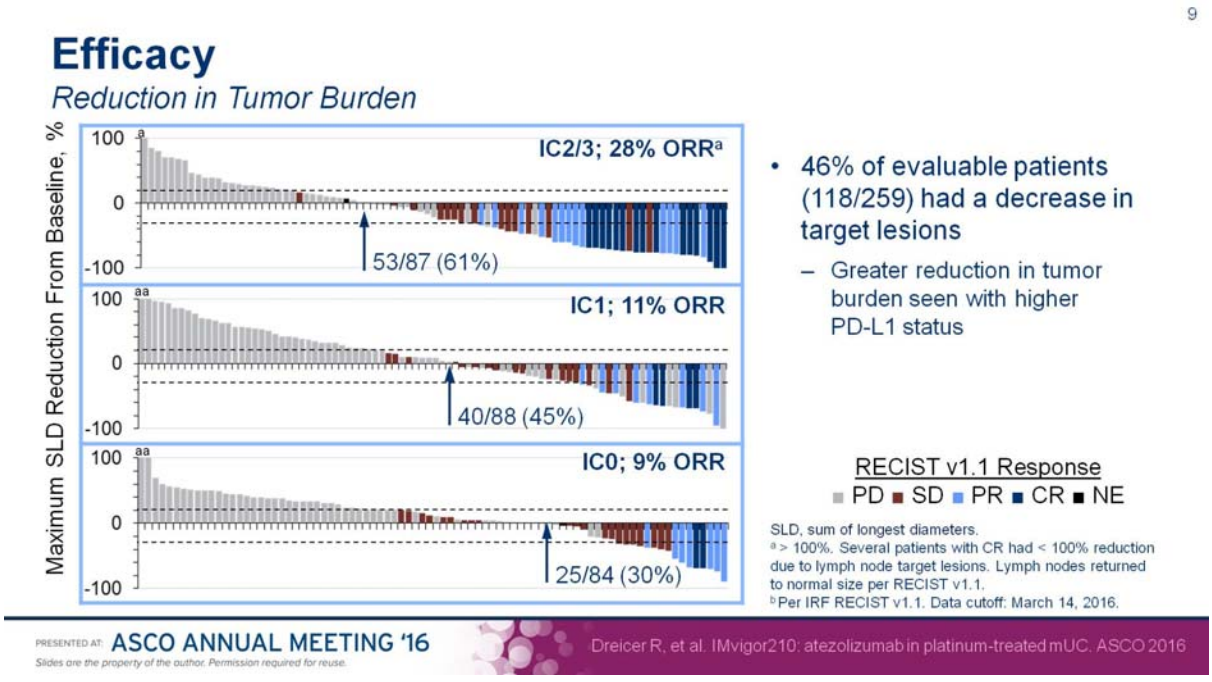


Figure 5: Results by baseline characteristic of Cohort 2 (2L+)



A40. Please provide the inclusion and exclusion criteria for the PCD4989g study. Please also clarify whether patients' disease had progressed and/or if they were cisplatin-ineligible.

As per the baseline characteristics reported in Table 40 of company submission, the majority of patients in PCD4989g study had progressed after prior chemotherapy, with [redacted] of

patients receiving ≥ 6 prior therapies. There were [redacted] of patients who previously received cisplatin-based chemotherapy.

Full inclusions and exclusion criteria can be found in the attached protocol for the PCD4989g study. An abridged version of the criteria is found below:

Inclusion Criteria

- Signed Informed Consent Form
- Age ≥ 18 years
- Histologically or cytologically documented, incurable or metastatic solid tumor or hematologic malignancy that is advanced (non-resectable) or recurrent and progressing since the last anti tumor therapy and for which no recognized standard curative therapy exists.
- Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, requested at any time prior to study entry. Only tissue from core needle, punch, or excisional biopsy sample collection will be accepted.
- Adequate hematologic and end organ function, defined by laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1)
- Measurable disease per RECIST v1.1 for patients with solid malignancies
- Disease specific criteria will be used for patients with prostate cancer, GBM, malignant lymphoma, or multiple myeloma:
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab
- ECOG performance status of 0 or 1
- INR and aPTT ≤ 1.5 × ULN
-

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any approved anti cancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed:
- Adverse events from prior anti cancer therapy that have not resolved to Grade ≤ 1 except for alopecia

- Bisphosphonate therapy for symptomatic hypercalcemia
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease
- Patients with acute leukemia, accelerated/blast phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma
- Known primary CNS malignancy or symptomatic CNS metastases
- Pregnancy, lactation, or breastfeeding
- Known hypersensitivity to pharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Inability to comply with study and follow-up procedures
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory test result giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- History of HIV infection or active hepatitis B (chronic or acute) defined as having a positive hepatitis B surface antigen (HBsAg) test at screening or hepatitis C infection defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening
- Active tuberculosis
- Patients in dose-escalation cohorts: absence of Epstein-Barr virus (EBV) antibodies (negative EBV serology, negative Epstein-Barr nuclear antigen [EBNA] IgG)
- Severe infections within 4 weeks prior to Cycle 1, Day 1 including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
- Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study

- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study or within 5 months following the last dose of atezolizumab
- Malignancies other than disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., CLL Rai Stage 0, prostate cancer with Gleason score ≤ 6, and PSA ≤ 10 mg/mL, etc.)

Exclusion Criteria Related to Medications

- Prior treatment with anti-PD-L1 or anti-PD-1 therapeutic antibody or pathway targeting agents
- Treatment with systemic immunostimulatory agents (including but not limited to IFN-α, IL-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) within 2 weeks prior to Cycle 1, Day 1
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation

A41. The text beneath Table 26 in the company submission suggests that not all of the participants in the PCD4989g study received the licensed dose. Please clarify how many participants did not receive the licensed dose and how this would affect interpretation of the results. Are results available for the subgroup that did receive the licensed dose?

Of the safety evaluable population in PCD4989g (n=95), 86 patients received a dose of 15mg/kg q3w IV, and 9 patients received a dose of 1200mg q3w IV. The PCD4989g protocol was amended during the study on 30 April 2014, to the fixed dose of 1200mg q3wIV. As a result the study patients received relatively less exposure at the anticipated licensed dose of

atezolizumab, of 1200mg q3w. However, with an average patient weight of 80kg, drug exposure is comparable between the 2 doses.

There are no subgroup analyses for the 9 patients who received the fixed dose of 1200mg. Such analysis would be difficult to interpret given the relative size of the group.

Whilst results of the phase I study should be interpreted with caution due to the heavily pre-treated cohort of mUC patients, the results are useful to consider as supportive data within the available evidence base for atezolizumab in mUC.

A42. The protocol for study PCD4989g is listed in the reference list of the company submission but was not included with the submission. Please provide the protocol.

The file has been submitted to NICE Docs as part of this response (F. Hoffmann-la Roche Ltd 2015a.)

A43. Please provide the numbers and percentage of patients who experienced each type of grade 3/4 adverse event, serious adverse event, adverse event of special interest, and adverse event which led to discontinuation, for both the IMvigor210 and PCD4989g studies.

Table 33: IMvigor 210 Cohort 1 grade 3–4 adverse events related to atezolizumab

Grade 3–4 AE	Cohort 1 (n=119)
Any AE	19 (16.0%)
Fatigue	4 (3.4%)
Multiple organ dysfunction syndrome	1 (0.8%)
Diarrhoea	2 (1.7%)
Autoimmune colitis	1 (0.8%)
Pruritus	1 (0.8%)
Rash	1 (0.8%)
Alanine aminotransferase increased	4 (3.4%)
Aspartate aminotransferase increased	3 (2.5%)
Blood alkaline phosphatase increased	1 (0.8%)
Blood bilirubin increased	2 (1.7%)

Blood creatine phosphokinase increased	1 (0.8%)
Blood phosphorus decreased	1 (0.8%)
Decreased appetite	1 (0.8%)
Hypophosphataemia	2 (1.7%)
Acidosis	1 (0.8%)
Rhabdomyolysis	1 (0.8%)
Rheumatoid arthritis	1 (0.8%)
Anaemia	1 (0.8%)
Leukocytosis	1 (0.8%)
Hypotension	1 (0.8%)
Renal failure	2 (1.7%)
Liver disorder	1 (0.8%)
Portal vein disorder	1 (0.8%)
Hypersensitivity	1 (0.8%)

Table 34: IMvigor 210 Cohort 1 serious adverse events related to treatment

AE, Any grade	Cohort 1 (N=119)
Any AEs	12 (10.1%)
Gastrointestinal disorders	5 (4.2%)
Diarrhoea	3 (2.5%)
Autoimmune colitis	1 (0.8%)
Colitis	1 (0.8%)
Investigations	2 (1.7%)
Blood bilirubin increased	1 (0.8%)
Blood creatine phosphokinase increased	1 (0.8%)
Renal and urinary disorders	2 (1.7%)
Renal failure	2 (1.7%)
Blood and lymphatic system disorders	1 (0.8%)
Leukocytosis	1 (0.8%)
General disorders and administration site conditions	1 (0.8%)
Pyrexia	1 (0.8%)
Hepatobiliary disorders	1 (0.8%)
Liver disorder	1 (0.8%)

Immune system disorders	1 (0.8%)
Hypersensitivity	1 (0.8%)
Infections and infestations	1 (0.8%)
Sepsis	1 (0.8%)
Metabolism and nutrition disorders	1 (0.8%)
Dehydration	1 (0.8%)
Musculoskeletal and connective tissue disorders	1 (0.8%)
Rhabdomyolysis	1 (0.8%)

Table 35: IMvigor 210 Cohort 1 adverse events of special interest

AE, any grade	Cohort 1 (n=119)
Any AE	37 (31.1%)
Rash	12 (10.1%)
Rash maculo-papular	5 (4.2%)
Dermatitis	3 (2.5%)
Eczema	1 (0.8%)
Rash Erythematous	1 (0.8%)
Rash macular	1 (0.8%)
Rash popular	1 (0.8%)
Rash pruritic	1 (0.8%)
Alanine aminotransferase increased	9 (7.6%)
Aspartate aminotransferase increased	8 (6.7%)
Blood bilirubin increased	4 (3.4%)
Blood thyroid stimulating hormone increased	1 (0.8%)
Hypothyroidism	9 (7.6%)
Hyperthyroidism	2 (1.7%)
colitis	3 (2.5%)
Autoimmune colitis	1 (0.8%)
Neuropathy peripheral	3 (2.5%)
Pneumonitis	2 (1.7%)
Rheumatoid arthritis	1 (0.8%)

Table 36: IMvigor 210 Cohort 1 adverse events leading to atezolizumab withdrawal

AE, any grade	Cohort 1 (n=119)
Any AE	9 (7.6%)
Cardiac arrest	1 (0.8%)
Myocardial infarction	1 (0.8%)
Autoimmune colitis	1 (0.8%)
Diarrhoea	1 (0.8%)
Fatigue	1 (0.8%)
Hypersensitivity	1 (0.8%)
Sepsis	1 (0.8%)
Rheumatoid arthritis	1 (0.8%)
Respiratory failure	1 (0.8%)

Table 37: IMvigor 210 Cohort 2 grade 3–4 adverse events related to atezolizumab

AE, grade 3–4	Cohort 2 (n=310)
Any AE	56 (18.1%)
Fatigue	5 (1.6%)
Pyrexia	1 (0.3%)
Gait disturbance	1 (0.3%)
Diarrhoea	1 (0.3%)
Vomiting	1 (0.3%)
Abdominal pain	1 (0.3%)
Colitis	2 (0.6)
Colitis ischaemic	1 (0.3%)
Pruritis	1 (0.3%)
Rash	1 (0.3%)
Decreased appetite	2 (0.6%)
Hypophosphataemia	1 (0.3%)
Hypercalcaemia	1 (0.3%)
Hypokalaemia	1 (0.3%)
Metabolic acidosis	1 (0.3%)

Arthralgia	2 (0.6%)
Myalgia	1 (0.3%)
Pain in extremity	1 (0.3%)
Dyspnoea	2 (0.6%)
Pneumonitis	3 (1.0%)
Pulmonary embolism	1 (0.3%)
Haemoptysis	1 (0.3%)
Respiratory failure	1 (0.3%)
Encephalopathy	1 (0.3%)
Diplegia	1 (0.3%)
Paraplegia	1 (0.3%)
Aspartate aminotransferase increased	4 (1.3%)
Alanine aminotransferase increased	4 (1.3%)
Weight decreased	1 (0.3%)
Blood creatinine increased	1 (0.3%)
Blood bilirubin increased	1 (0.3%)
Lymphocyte count decreased	3 (1.0%)
Transaminases increased	1 (0.3%)
Blood alkaline phosphatase increased	1 (0.3%)
White blood cell count decreased	1 (0.3%)
Platelet count decreased	1 (0.3%)
Bacteraemia	1 (0.3%)
Cellulitis	1 (0.3%)
Device related infection	1 (0.3%)
Sepsis	1 (0.3%)
Anaemia	2 (0.6%)
Leukocytosis	1 (0.3%)
Hypotension	2 (0.6%)
Hypertension	3 (1.0%)
Hypothyroidism	1 (0.3%)
Acute kidney injury	1 (0.3%)

Chronic kidney disease	1 (0.3%)
Cytokine release syndrome	1 (0.3%)
Autoimmune hepatitis	1 (0.3%)
Cholecystitis	1 (0.3%)
Hepatitis	1 (0.3%)
Pericardial effusion	1 (0.3%)
Immobile (social circumstances)	1 (0.3%)

Table 38: IMvigor 210 Cohort 2 serious adverse events related to atezolizumab

AE, any grade	Cohort 2 (n=310)
Any AEs	38 (12.3%)
Respiratory thoracic and mediastinal disorders	8 (2.6%)
Pneumonitis	4 (1.3%)
Pulmonary embolism	3 (1.0%)
Dyspnoea	1 (0.3%)
Haemoptysis	1 (0.3%)
Infections and infestations	6 (1.9%)
Bacteraemia	1 (0.3%)
Cellulitis	1 (0.3%)
Device-related infection	1 (0.3%)
Diverticulitis	1 (0.3%)
Sepsis	1 (0.3%)
Urinary tract infection pseudomonal	1 (0.3%)
Nervous system disorders	5 (1.6%)
Encephalopathy	2 (0.6%)
Cerebrovascular accident	1 (0.3%)
Diplegia	1 (0.3%)
Paraplegia	1 (0.3%)
Gastrointestinal disorders	4 (1.3%)
Colitis	2 (0.6%)
Anal incontinence	1 (0.3%)
Colitis ischaemic	1 (0.3%)
Diarrhoea	1 (0.3%)
General disorders and administration site conditions	4 (1.3%)

Pyrexia	2 (0.6%)
Asthenia	1 (0.3%)
Hepatobiliary discorders	2 (0.6%)
Cholecystitis	1 (0.3%)
Hepatitis	1 (0.3%)
Musculoskeletal and connective tissue disorders	2 (0.6%)
Arthralgia	1 (0.3%)
Muscular weakness	1 (0.3%)
Renal and urinary disorders	2 (0.6%)
Acute kidney injury	1 (0.3%)
Chronic kidney disease	1 (0.3%)
Blood and lymphatic system disorders	1 (0.3%)
Leukocytosis	1 (0.3%)
Cardiac disorders	1 (0.3%)
Pericardial effusion	1 (0.3%)
Endocrine disorders	1 (0.3%)
Hypothyroidism	1 (0.3%)
Metabolism and nutrition disorders	1 (0.3%)
Hypercalcaemia	1 (0.3%)
Psychiatric disorders	1 (0.3%)
Confusional state	1 (0.3%)
Skin and subcutaneous tissue disorders	1 (0.3%)
Rash maculo-papular	1 (0.3%)
Vascular disorders	1 (0.3%)
Hypotension	1 (0.3%)

AE, adverse event

Table 39: IMvigor 210 Cohort 2 adverse events of special interest

AE, any grade	Cohort 2 (n=310)
Any AE	93 (30.0%)
Rash	36 (11.6%)
Rash maculo-papular	10 (3.2%)
Rash pruritic	6 (1.9%)
Eczema	2 (0.6%)
Psoriasis	2 (0.6%)

Rask papular	2 (0.6%)
Lichen planus	1 (0.3%)
Rash erythematous	1 (0.3%)
Vitiligo	1 (0.3%)
Alanine aminotransferase increased	16 (5.2%)
Aspartate aminotransferase increased	16 (5.2%)
Blood bilirubin increased	8 (2.6%)
Transaminases increased	6 (1.9%)
Blood thyroid stimulating hormone increased	1 (0.3%)
Hypothyroidism	10 (3.2%)
Hyperthyroidism	1 (0.3%)
Neuropathy peripheral	10 (3.2%)
Pneumonitis	8 (2.6%)
Colitis	3 (1.0%)
Autoimmune hepatitis	1 (0.3%)
Hepatitis	1 (0.3%)
Polymyalgia rheumatica	1 (0.3%)
Sjorgen's syndrome	1 (0.3%)
Cytokine release syndrome	1 (0.3%)

Table 40: IMvigor 210 Cohort 2 adverse events leading to atezolizumab withdrawal

AE, any grade	**Cohort 2 (n=310)**
Any AE	12 (3.9%)
Sepsis	2 (0.6%)
Pulmonary sepsis	1 (0.3%)
Retroperitoneal infection	1 (0.3%)
Colitis	1 (0.3%)
Colitis microscopic	1 (0.3%)
Subileus	1 (0.3%)
Fatigue	1 (0.3%)
Cerebral haemorrhage	1 (0.3%)

Acute kidney injury	1 (0.3%)
Pneumonitis	1 (0.3%)
Pruritis	1 (0.3%)

Table 41: PCD4989g grade 3–4 adverse events related to atezolizumab

AE, grade 3–4	All patients (n=95)
Any AE	9 (9.5%)
Asthenia	2 (2.1%)
Rash maculo-papular	1 (1.1%)
Alanine aminotransferase increased	1 (1.1%)
Aspartate aminotransferase	1 (1.1%)
Blood phosphorus decreased	1 (1.1%)
Gamma-glutamyltransferase	1 (1.1%)
Anaemia	1 (1.1%)
Thrombocytopenia	1 (1.1%)
Lymphopenia	1 (1.1%)
Neutropenia	1 (1.1%)

Table 42: PCD4989g serious adverse events related to treatment

AE, any grade	All patients (n=95)
Any AE	5 (5.3%)
General disorders and administration site conditions	4 (4.2%)
Pyrexia	2 (2.1%)
Fatigue	1 (1.1%)
Hyperthermia	1 (1.1%)
Infections and infestations	1 (1.1%)
Urinary tract infection	1 (1.1%)
Nervous system disorders	1 (1.1%)
Intracranial mass	1 (1.1%)

Table 43: PCD4989g adverse events of special interest

AE, any grade	All patients (n=95)
Any AE	35 (36.8%)
Rash	12 (12.6%)
Eczema	2 (2.1%)
Rash maculo-papular	2 (2.1%)
Lichen planus	1 (1.1%)
Psoriasis	1 (1.1%)
Rash erythematous	1 (1.1%)
Rash pruritic	1 (1.1%)
Aspartate aminotransferase increased	10 (10.5%)
Alanine aminotransferase increased	7 (7.4%)
Blood bilirubin increased	3 (3.2%)
Amylase increased	1 (1.1%)
Lipase increased	1 (1.1%)
Transaminase increased	1 (1.1%)
Neuropathy peripheral	8 (8.4%)
Hypothyroidism	4 (4.2%)
Pneumonitis	1 (1.1%)

Table 44: PCD4989g adverse events leading to atezolizumab withdrawal

AE, any grade	All patients (n=95)
Any AE	4 (4.2%)
Blood bilirubin increased	1 (1.1%)
Gamma-glutamyltransferase increased	1 (1.1%)
Sepsis	1 (1.1%)
Intracranial mass	1 (1.1%)

A44. Please explain what "N/A" means in Table 29 and why these data on prior radical treatment (cystectomy or nephroureterectomy) and haemoglobin level are not provided for cohort 1 of the IMvigor210 study.

N/A stands for 'not available'. For Cohort 1, cystectomy or nephroureterectomy and haemoglobin level were unfortunately omitted in error:

- Cystectomy or nephroureterectomy, 80 (67.2%)
- Haemoglobulin ≤ 10 g/dl, 19 (16.0%)

B1. Priority question. Tables 50, 51 and 71 state that a generalised gamma distribution was used for progression-free survival for both the first-line and second-line populations, but the economic models for both populations use gamma distributions. Please clarify which distribution was used.

Generalised gamma was used for progression-free-survival in both the first-line and second-line. The term 'gamma' was used in the economic model for brevity, but should in fact read 'generalized gamma'. (please also refer to response to question B7).

B2. Priority question. Table 69 states that the source of the health home visit cost is Curtis 2016 but the Curtis 2016 publication does not report this. Please provide the source of this data.

The listed citation of 'Curtis 2016' is a typographical error.

The reference for the health home visit cost in Table 69 of the company submission is the manufacturer submission for vinflunine NICE appraisal. This value can be found in Table B39 of the manufacturer company submission for TA272, January 2013.

B3. Priority question. Table 69 provides references for costs of a community nurse visit, dietician, oncologist consultation and hospice care. However, these references are not included in the company submission reference list, and the ERG have been unable to locate these costs. Please provide the sources of these costs.

Costs for community nurse visit, dietician and oncologist consultation are referenced to the 'Reference Cost Collection: National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts' (https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016). A copy of the National Schedule of Reference Costs is included in the reference file within NICE Docs as part of this response.

Community nurse visit and dietician are categorised under the index 'community health services' (CHS) - district nurse Service code NO2AF, and dietitian Service code A03.

Oncologist consultation (Consultant) is under index 'consultant lead': Medical oncology (service code 370, currency code WF01A, Non-Admitted Face to Face Attendance, Follow-Up).

Oncologist consultation (non-consultant) is under index: 'Non-consultant Led' (service code 370 WF01A Non-Admitted Face to Face Attendance, Follow-Up)

Hospice care is referenced to Curtis 2016. The unit cost of average cost per patients (£1,119) is found in section 7.5, page 101 of Curtis 2016.

B4. Priority question. Table 70 provides references for costs of adverse events for alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increased, diarrhoea, electrolyte abnormalities, hypophosphataemia, infection, peripheral neuropathy (sensory or motor) and renal failure. However, these references are not included in the company submission reference list, and the ERG have been unable to locate these costs. Please provide the sources of these costs.

These costs are referenced to the 'Reference Cost Collection: National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts' (https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016). A copy of the National Schedule of Reference Costs is included in the reference file within NICE Docs as part of this response.

Treatment for grade ≥3 alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increased, electrolyte abnormalities, hypophosphataemia and infection are assumed to require an additional clinic visit to the patients' Medical oncology consultant. This is classified as a non-admitted face to face attendance, follow-up (service code 370, currency code WF01A).

Treatment for grade ≥3 diarrhoea is costed as a non-admitted face to face attendance, first with a non-consultant gastroenterologist (currency code WF01B, service code 301).

Treatment for grade ≥3 peripheral neuropathy (sensory or motor) is costed as an outpatient attendance for pain management, service code 191.

Renal failure is costed under Acute Kidney Injury with Interventions, with CC Score 0-5, Currency code LA07k, day case.

B5. Priority question. In table 70, the source of the adverse event costs is given as the nivolumab NSCLC appraisal (for adverse events such as fatigue and leucopenia) but the values in the table are slightly higher than those in the source appraisal. The company submission does not state whether these costs were increased. Please clarify this difference.

These costs have been inflated from the 2013/14 costs used in the ninvolumab NSCLC appraisal, to 2015/16 costs. Details of the original values and applied inflation rate are shown in Table 45 below.

The cost of thrombocytopenia was assumed consistent with the cost of leucopenia and neutropenia

Table 45: Inflation of adverse event costs from 2013/14 to 2015/16

	Nivolumab company submission NICE ID900, ID811	HRG 2015-16 (Department of Health)	**Unit cost used in the atezolizumab model**	Source
NHS ref costs used in submission	2013/14		**2015/16**	
PSSRU HCHS Pay & prices index	290.5	297	**297**	
Unit used to inflate to 2015-2016 using PSSRU	1.02238	1	**1**	Curtis and Burns (2016)
Fatigue	3015.13	NA	**£3082.59**	Nivolumab company submission NICE ID900, ID811
Leucopenia	354.72	NA	**£362.66**	Nivolumab company submission NICE ID900, ID811
Neutropenia	354.72	NA	**£362.66**	Nivolumab company submission ID900, ID811

B6. Priority question. Please clarify the pathway of care for patients who stop atezolizumab treatment, either at first-line or second-line.

The pathway of care for patients who stop atezolizumab treatment will differ between those receiving it first or second line. Expert physicians experienced in the treatment of mUC

confirmed patients are unlikely to receive subsequent anti-cancer therapy after failure of atezolizumab 2L. These patients will go onto receive palliative care, including palliative chemotherapy and radiotherapy, with the intention of relieving symptoms and pain from disease.

Patients who are cisplatin ineligible, and receive atezolizumab in the first line, are likely to go onto to receive subsequent active anti-cancer therapy. NICE clinical guidelines recommend either carboplatin + paclitaxel or gemcitabine + paclitaxel for cisplatin ineligible patients who fail gemcitabine + carboplatin in the 1L. It can therefore be assumed, should patients receive atezolizumab 1L, they will subsequently receive either carboplatin + paclitaxel or gemcitabine + paclitaxel.

B7. Priority question. For time to treatment discontinuation the company submission states that a generalised gamma distribution provides the best fit for both first-line and second-line cohorts for the atezolizumab arm. However, Tables 66 and 67 of the company submission report gamma distributions instead of generalised gamma distributions for both cohorts. This is inconsistent with the stated generalised gamma distribution for time to treatment discontinuation of atezolizumab reported in Table 71. The economic models for both first and second-line populations use a gamma distribution. Please clarify which distribution is used.

Generalised gamma was used for time-to-treatment discontinuation in both the first-line and second-line. The term ‘gamma’ was used in Table 66, Table 67, and the economic model for brevity, but should in fact read ‘generalized gamma’ (please also refer to response to question B1).

B8. Priority question. Please provide a scenario analysis of an unadjusted (naive) comparison between atezolizumab and its comparators for the first-line and second-line populations using the observed study data (i.e. based on the unadjusted meta-analysis requested in clarification question A14 (a)).

As described in the response to questions A15(a) (which we believe this question is referencing), a naïve comparison between atezolizumab and the comparators was not deemed appropriate, as it is not recommended within indirect treatment comparison best practise guides.

B9. Please provide the references for the 7 cost-effectiveness studies identified in the company's systematic review of cost-effectiveness studies.

These files have been submitted to NICE Docs as part of this response (Guglieri-Lopez et al. 2015; Yagudina et al. 2015; Ramamohan et al. 2014; Robinson et al.2004; NICE TA272. 2010; PBAC Javlor public summary report 2011; PBAC Javlor public summary report 2015) .

B10. A mixed cure rate model with a 0% cure rate fraction based on a gamma distribution would be expected to give the same results as a standard gamma distribution. However, the results reported in the company submission for these two methods are different. Please explain this difference.

As described in section 5.3.5 of the company submission, the mixed-cure rate incorporates background mortality. As such, even at 0% cure rate, a gamma distribution mixed cure rate model differs to a standard gamma distribution.

Standard gamma distribution is denoted as:

1. $S(t)= S\_gamma(t)$

In the cured case the survival function becomes

1. $S(t)= S^*(t)[\pi+(1-\pi) S\_u (t)]$, with $\pi = 0$ this leads to
2. $S(t)= S^*(t)[S\_u (t)]$

S* is background mortality. S_u differs from S_gamma due to estimation issues captured in the hazard:

1. $h(t)=h^* (t)+ ((1-\pi) f\_u (t))/(\pi+(1-\pi) S\_u (t))$

Note that if $\pi = 0$, the expression becomes

1. $h(t)=h^* (t)+ f\_u (t)/ S\_u (t) = h^* (t) + h\_u (t)$

Upon assuming a cure 0, there is a different baseline estimation for the "uncured" survival function since background hazard h* is incorporated in the estimation. In the prediction we use background mortality S* as a multiplicative factor.

C1. Please explain the meaning of the missing footnotes a. and b. for Figure 18.

[a]No progressed disease or death only

[b]Patient is deceased (timing not implied)

C2. The PCD4989g study is not marked as confidential in section 4.11.11, but it is marked as academic in confidence in section 4.12.3.1. Please clarify which is correct.

The most recent efficacy and safety results of PCD4989g study are academic in confidence (AIC) as they will be presented at an upcoming congress. The study design and patient baseline characteristics are not AIC. As such, section 4.11.11.3 is marked as AIC, along with section 4.12.3.1. Section 4.11.11.1 and 4.11.11.2 are not AIC.

References

Agarwal N, Bellmunt J, Maughan BL, Boucher KM, Choueiri TK, Qu AQ, et al. Six-month progression-free survival as the primary endpoint to evaluate the activity of new agents as second-line therapy for advanced urothelial carcinoma. Clinical genitourinary cancer. 2014;12(2):130-7.

Balar, A. et al. 2016. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): Primary analysis of IMvigor210 cohort 1. J Clin Oncol,ASCO Meeting Abstracts, 34, LBA4500.

Bellmunt J, Thedore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454-61.

Bellmunt J, Choueiri TK, Fougeray R, Schutz FA, Salhi Y, Winquist E, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. Journal of clinical oncology. 2010;28(11):1850-5.

Chen, TT, "Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors," *Journal of the National Cancer Institute* 107, no. 9 (September 2015): djv156, doi:10.1093/jnci/djv156.

Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol 2012;30:507-12.

Cisplatin SmPC available at: https://www.medicines.org.uk/emc/medicine/623, date accessed 23rd February 2017

Culine S, Theodore C, De Santis M, et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. Br J Cancer 2006;94:1395–401.

CURTIS, L. 2016. PSSRU Unit Costs of Health & Social Care.

DEPARTMENT OF HEALTH. 2016. NHS reference costs [Online]. Available: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [Accessed 23rd February 2017].

Dreicer et al. IMvigor 210 cohort 2 Primary analysis of IMvigor210 cohort 1. J Clin Oncol 34, 2016 (suppl; abstr 4515)

F. HOFFMANN-LA ROCHE LTD 2014. Protocol GO29293: A phase II, multicenter, single-arm study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer.

F. HOFFMANN-LA ROCHE LTD 2015a. Clinical Study Protocol PCD4989g – A phase I, open label, dose escalation study of the safety and pharmacokinetics of atezolizumab (MPDL3280a) administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies.

F. HOFFMANN-LA ROCHE LTD 2015b. Clinical Study Report GO29293 – A phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer (Data cut-off: 14-Sep-2015).

Guglieri-Lopez B, Perez-Pitarch A, Porta-Oltra B, Ferriols-Lisart F, Climente-Marti M, Alos-Alminana M. Effectiveness, toxicity, and economic evaluation of vinflunine for the treatment of patients with transitional cell carcinoma in the Spanish outpatient setting. Anti-Cancer Drugs. 2015;26(8):860-5.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944−51.

Hoos A, Ibrahim R, Korman A, et al. Development of ipilimumab: contribution to a new paradigm for cancer immunotherapy. Semin Oncol 2010;37:533−46.

Jansen et al., "Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1," *Value in Health* 14, no. 4 (June 2011): 417–28, doi:10.1016/j.jval.2011.04.002.

Jansen et al., "Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report," *Value in Health* 17, no. 2 (March 2014): 157–73, doi:10.1016/j.jval.2014.01.004.

Javlor European Medicines Agency. CHMP Assessment Report . Doc.-Ref. EMEA/CHMP/370293/20092009. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000983/WC500039919.pdf. (Accessed 23rd February 2017)

LIDA, K., 2016. 1151 Gemcitabine plus paclitaxel as third-line chemotherapy: A feasible option for metastatic urothelial carcinoma patients.European Urology Supplements, 15, e1151

Logothetis CJ and Millikan R. Docetaxel in the management of advanced or metastatic urothelial tract cancer. Oncology 2002;16:107-11. (available: http://www.cancernetwork.com/oncology-journal/docetaxel-management-advanced-or-metastatic-urothelial-tract-cancer accessed 24th February 2017)

McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 1997;15:1853–7.

National Institute for Health and Care Excellence. Vinflunine for the treatment of transitional cell carcinoma of the urothelial tract: Single Technology Appraisal . TA272

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2017a. *Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900]* [Online]. Available: https://www.nice.org.uk/guidance/indevelopment/gid-tag524 [Accessed 23rd February 2017].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2017b. *Lung cancer (non-small-cell, squamous, metastatic) - nivolumab (after chemotherapy) [ID811]* [Online]. Available: https://www.nice.org.uk/guidance/indevelopment/gid-tag506 [Accessed 23rd February 2017].

NAIKI, T. 2016. MP06-17 Gemcitabine Plus Paclitaxel As Third Line Chemotherapy: A Feasible Option For Metastatic Urothelial Carcinoma Patients. The Journal of Urology, 195, e74.

Pennock GK, Waterfield W, Wolchok JD. Patient responses to ipilimumab, a novel immunopotentiator for metastatic melanoma: how different are these from conventional treatment responses? Am J Clin Oncol 2012;35:606−11.

Petrylak DP, Tagawa ST, Kohli M, et al. Docetaxel as monotherapy or combined with ramucirumab or icrucumab in second-line treatment for locally advanced or metastatic urotherlial carcinoma: an open-label, three-arm, randomized controlled Phase II trial. J Clin Oncol 2016;34:1500-9.

Pharmaceutical Benefits Advisory Committee. Vinflunine, solution concentration for I.V. infusion, 50 mg in 2 mL and 250 mg in 10 mL (as ditartrate), Javlor®. Public Summary Document. 2011.

Pharmaceutical Benefits Advisory Committee. Vinflunine solution concentration for IV infusion, 50 mg in 2 mL and 250mg in 10 mL (as ditartrate) Javlor®, Pierre Fabre Medicament Australia: resubmission. Public Summary Document. 2015.

Pond GR, Agarwal N, Bellmunt J, Choueiri TK, Qu A, Fougeray R, et al. A nomogram including baseline prognostic factors to estimate the activity of second-line therapy for advanced urothelial carcinoma. BJU international. 2014;113(5b):E137-E43.

Ramamohan V, Mladsi DM, Boey W, Pozzi R, Kaye JA. An outcomes model for high-risk non-muscle-invasive bladder cancer treatment options. Value in Health. 2014;17 (3):A87.

Robinson P, Maase H, Bhalla S, Kielhorn A, Aristides M, Brown A, et al. Cost-utility analysis of the GC versus MVAC regimens for the treatment of locally advanced or metastatic bladder cancer. Expert Rev. 2004;4(1):27-38.

Sharma et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trialhttp://dx.doi.org/10.1016/S1470-2045(17)30065-7

Song F, Altman DG, Glenny A, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003;326:472

Turner et al .2015. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med, 34, 984–98.

Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 2002;20:937-40.

Welton et al., *Evidence Synthesis for Decision Making in Healthcare*, Auflage: 1. Auflage (Chichester, West Sussex: John Wiley & Sons, 2012). Page 126

Witjes JA, Comperat E, Cowan NC, De Santis M, Gakis G, Lebret T, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol. 2014 Apr;65(4):778-92. PubMed PMID: 24373477.]

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412−20

Yagudina et al. Pharmacoeconomic analysis of urothelial transitional cell cancer treatment with vinflunine in patients resistant to the platinum-based treatment regimes. Value in Health. 2015;18 (7):A443-A4.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Action Bladder Cancer UK

Your position in the organisation: [redacted]

Brief description of the organisation: UK Bladder Cancer charity.

We have three main strands to our work:

- Improving outcomes for bladder cancer patients
- Improving research into bladder cancer
- Improving patient support

We are working to improve outcomes for bladder cancer patients by:

- Raising awareness of the signs and symptoms among the public so they seek advice sooner
- Improving awareness and investigation techniques among health professionals to improve early diagnosis
- Improving the treatment and management of bladder cancer to increase patient survival rates in line with that achieved for other common cancers

We are working to improve research into bladder cancer by:

- Identifying the key research priorities
- Encouraging, contributing to and funding research
- Improving research data and statistics

We are working to improve patient support through:

- Our high quality information materials and resources library
- Actively increasing the number of bladder cancer patient support groups across the UK
- Providing advice and support to both new and existing groups and helping to bring groups together
- Helping to give bladder cancer patients a voice

Funded by donations, fundraising events and by corporate donations. Our corporate donors include Roche and are bound by our corporate statement as follows:

CORPORATE STATEMENT Action Bladder Cancer UK is a charity working to support those with bladder cancer and to improve outcomes for patients. We are committed to working in ethical collaboration with commercial and corporate partners in the interest of people affected by bladder cancer. We will

accept funding from appropriate corporate and industry supporters. Neither our work, our campaigning nor our information materials will be influenced by accepting any corporate donations or sponsorship. We feel it is important to work with companies that manufacture drugs, treatments or devices which will treat or support bladder cancer patients. We will work in a transparent partnership with appropriate pharmaceutical companies and the medical device industry where these relationships will help promote and improve the interests of bladder cancer patients and fit within the objectives of our charity. We would not accept support from any pharmaceutical or medical industry company for work that we consider to that lie outside the agreed objectives of our charity. We are happy to accept funding, or support in kind, from appropriate corporate supporters outside the health or pharmaceutical sectors. Each corporate collaboration will be assessed and agreed on an individual basis by the charity executive. We are grateful for the support shown by our existing corporate supporters which help us in our work.

ABC UK has 8 Trustees including a healthy mix of clinicians, urology consultants, cancer nurse specialist, GP with interest in bladder cancer, researchers and patients. We have one employee and outsourced secretariat.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Awareness is so poor that initial diagnosis is invariably a shock and bc remains a difficult disease to talk about due to general lack of awareness. The fact that recurrence is so high makes it a difficult condition to live with, despite treatment for NMIBC being relatively straightforward and effective. The particular condition for this consultation is the advanced case where platinum chemotherapy has already been given and where survival rates are known to be poor. Therefore the specific condition is very difficult for both patient and carer. This new drug represents an innovative treatment and potential lifeline for patients.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Prolonging life, improved quality of life and ultimately a complete response.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Treatment of this specific condition is by platinum based chemotherapy and/or palliative care. These are readily available but response rates and quality of life are poor. Many patients with metastatic bladder cancer are not suitable for cisplatin and so there is an urgent need for alternatives.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

In its simplest form the treatment represents hope to many for whom other treatment options have been exhausted. Therefore the main benefits include:

- complete response
- prolonging life
- improved quality of life for patient, carer, family, friends

Ease of use and mental health are not primary benefits.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

This represents hope and a further treatment option. US Trial results are very encouraging and represent a complete response for a significant proportion of patients. If the treatment is licenced and similar outcomes are experienced here, there may be scope to use the treatment at other stages of the disease or as a primary treatment.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None known

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Lack of research and available treatments compared with other common cancers.

Lack of treatment effectiveness

Side effects

Please list any concerns patients or carers have about the treatment being appraised.

Since this treatment has yet to be licenced in the UK, it is difficult to say what concerns patients might have. Although the treatment has proven successful in trials, care would be needed to manage patient and carer expectations – it won't cure everyone.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Not known, however it would be highly desirable to study patient outcomes and to attempt to develop predictive tests of suitablility using, for instance, biomarkers and genomic sequencing, to enable the treatment to be used as precision medicine.

It would also be useful for patients to contribute to the 'Life and Bladder Cancer' PROMS (Patient Reported Oycome Measures Study), being run by Leeds/Sheffield.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not known

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

n/a

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

not sufficiently familiar, but see comments under Q6.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

n/a

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐X Yes ☐ No

If yes, please provide references to the relevant studies.

Life and Bladder Cancer PROMS (Patient Reported Outcome Measures) Study run by Leeds/Sheffield, Prof Jim Cato et al

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None known

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

This is a relatively small population which is more prevalent among the elderly. Significant co-morbidities will affect treatment options and suitability. Many patients with metastatic cancer have poor renal function and cannot be given platinum based chemotherapy (cisplatin),

9. Other issues

Do you consider the treatment to be innovative?

☐X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Bladder Cancer has had relatively little research and new treatment development in recent decades. Despite it being the 4th most prevalent cancer in men and 7th overall, and very expensive for the NHS to treat, mortality rates of c50% have shown NO improvement in the past 30 years.

The mechanism of this new drug is different from anything available to treat BC today, hence the treatment is highly innovative.

Are there any other issues that you would like the Appraisal Committee to consider?

ABC UK supports the licencing and use of the treatment within the NHS. Ideally more research could be commissioned to optimise the treatment regimen and to better understand the mechanism of treatment, ultimately leading to biomarkers to identify patients for whom the treatment would be effective/ineffective.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- ABC UK supports the licencing and use of the treatment within the NHS
- The treatment is highly innovative
- The treatment gives hope to many for whom other treatment options have been exhausted
- Further research/trials to optimise the treatment and develop biomarkers would be highly desirable
- Consideration should be given for research/trails for use of the treatment earlier in the disease progress and/or as a primary treatment

Submission by NHS England on atezolizumab in the systemic therapy of locally advanced or metastatic urothelial cancer

Background including the systemic treatment pathway for locally advanced or metastatic urothelial cancer

1. In terms of the TNM stage of urothelial cancer, patients with inoperable locally advanced disease have T4b any N M0 or any T N2-3 M0 stages and patients with metastatic disease have any T any N M1 stages.
2. Chemotherapy for such disease is given with palliative intent.
3. Standard 1st line systemic therapy is with cisplatin-based combination chemotherapy and results in a median duration of survival of about 15 months. The pedigree of evidence for a cisplatin-based combination in fit patients is far better than for a carboplatin-based combination, hence the preference to use a cisplatin-based combination as 1st line treatment for locally advanced/metastatic disease if possible.
4. The main clinical prognostic factors for locally advanced/metastatic disease are performance status and the presence of visceral metastases (lung, liver, bone).
5. The first key question in addressing treatment options in advanced/metastatic disease is the definition of medical fitness as many patients with locally advanced/metastatic urothelial cancer have significant comorbidities. Cisplatin-based combination chemotherapy is inappropriate if any of the following apply:
   - impaired renal function with an EDTA-assessed glomerular filtration rate (GFR) of <60mls/min
   - a performance status score of 2 or more
   - hearing loss of 25dB at 2 contiguous frequencies
   - grade 2 or more peripheral neuropathy
   - heart failure of New York Heart Association class III or more.
6. The main cisplatin-based combination used in England is the combination of cisplatin and gemcitabine as it is much less toxic than methotrexate, vinblastine, doxorubicin and cisplatin (MVAC).
7. The combination of 1st line carboplatin and gemcitabine is used in patients who are ineligible for cisplatin and gemcitabine if their GFR is between 30 and 60mls/min and/or if they have auditory/neurological/cardiac comorbidities as outlined above and/or if they have a performance status of 2. In this group of patients who are ineligible for cisplatin-based chemotherapy, the best evidence of the efficacy of 1st line carboplatin plus gemcitabine comes from a RCT reported by De Santis in which patients in the carboplatin plus gemcitabine arm were found to have a response rate of 41% and a median overall survival of 9.3 months. The combination of carboplatin plus gemcitabine is thus the comparator for atezolizumab in the cisplatin-ineligible group of patients in this appraisal (cohort 1).
8. If patients are unfit for carboplatin plus gemcitabine, it is unlikely that they will be fit for any chemotherapy or checkpoint inhibitor.

9. The administration of any chemotherapy to patients with urothelial cancer and of performance status 3 is inappropriate.
10. The role of chemotherapy as 2nd line treatment is limited. Re-treatment with a 1st line regimen is sometimes used if there has been a durable response to 1st line therapy but this is rare. It is therefore not an appropriate comparator for atezolizumab in this appraisal. The use of single agent treatment with paclitaxel and docetaxel is sometimes used in highly selected patients ie in those that are fit and highly motivated. Response rates are low, responses to treatment short and side-effects are considerable, more so with docetaxel. Vinflunine is not commissioned in NHS England (previously not recommended by NICE). The appropriate comparators for 2nd line treatment of urothelial cancer in this appraisal are the taxanes and best supportive care, the latter being applicable as some patients are fit for treatment but decline a taxane on account of poor efficacy and significant toxicity.
11. Cisplatin-based combination chemotherapy is also given in other places in the urothelial pathway. It is sometimes given as adjuvant treatment after radical surgery. It is more often used as neoadjuvant treatment prior to radical surgery or radiotherapy. Single agent cisplatin is used in fit patients having radical radiotherapy when cisplatin is given concurrently with radiotherapy. The atezolizumab 210 study allowed patients to enter the study if they had previously received such adjuvant/neoadjuvant cisplatin-based combination treatment and further cisplatin-based chemotherapy was inappropriate: into cohort 1 if patients relapsed >12 months after completing chemotherapy and into cohort 2 if patients had relapsed within 12 months of completing chemotherapy.
12. Checkpoint inhibitors represent the first significant new drug advance in the systemic therapy of locally advanced/metastatic disease urothelial cancer for 15+ years.
13. In addition to atezolizumab, other checkpoint inhibitors have emerging evidence bases in urothelial cancer: pembrolizumab, nivolumab, durvalumab and avelumab. In the 2nd line setting, there is a RCT of pembrolizumab versus single agent treatment of physician's choice (paclitaxel, docetaxel or vinflunine). The response rates were 21% vs 11%, median progression free survival 2.1 vs 3.3 months, median overall survival 10.3 vs 7.4 months and 1 year survival 21% vs 11%, respectively. There were fewer serious treatment-related events in the pembrolizumab arm. Pembrolizumab is being appraised by NICE in urothelial cancer next month.

<u>Atezolizumab in the treatment of advanced/metastatic urothelial cancer</u>

14. The wording of the marketing authorisation has not yet been set by the EMA although Roche has given the following likely wording [redacted]

15. In terms of the TNM stage of urothelial cancer, patients entered into the 210 study had inoperable locally advanced disease (ie T4b any N M0 or any T N2-3 M0 stages) or metastatic disease (any T any N M1 stages). Patients were assumed to be in the second line cohort if they had relapsed less than 12 months after completing chemotherapy given with adjuvant or neoadjuvant intent or within 12 months of completing chemo-radiotherapy as long as there was disease progression outside the radiotherapy treatment field.
16. Fixed doses of atezolizumab were used in the 210 study and were given every 3 weeks to disease progression.
17. The definition of cisplatin ineligibility of cohort 1 in the 210 trial is as outlined above in paragraph 5. This definition is important in view of the comorbidities that affect patients with urothelial cancer. It is unclear as to why these patients did not or could not receive the combination of carboplatin and gemcitabine. If atezolizumab is recommended by NICE, then NHS England would only commission use in patients previously untreated for locally advanced or metastatic urothelial cancer who satisfy the same conditions for cisplatin ineligibility as in the 210 study. This is a very important issue given the type of toxicity that occurs with drugs such as atezolizumab, the fact that the NHS has to cope with treating a wide range of uncommon, unusual and potentially severe toxicities from checkpoint inhibitors and that toxicities of treatment with checkpoint inhibitors increase with increasing comorbidities.
18. NHS England notes that 43% of cohort 2 had received 2 or more prior chemotherapy treatments for metastatic disease, an indication of their high degree of previous treatment but also their good performance status as all patients in cohort 2 either has a performance status of 0 (38%) or 1 (62%).
19. NHS England notes that the 211 study is a RCT of atezolizumab vs active treatment of physicians' choice (a taxane or vinflunine) which will provide much greater certainty as to the degree of benefit of atezolizumab over 2nd line chemotherapy ie for outcomes for cohort 2-type patients in this appraisal. However, the 211 study will not offer direct evidence of the benefit of atezolizumab over best supportive care.
20. NHS England notes that the 130 trial is randomising previously untreated patients with urothelial cancer to receive single agent atezolizumab vs gemcitabine plus cisplatin/carboplatin vs atezolizumab plus gemcitabine plus cisplatin/carboplatin. This trial will offer a clear idea as to what the contribution of atezolizumab will make to 1st line chemotherapy for locally advanced/metastatic urothelial cancer. The 130 study will not provide direct evidence to reduce any uncertainty as regards cohort 1 of the 210 study as the inclusion criteria are very different: 210 excluded patients who were eligible for cisplatin whereas 130 only allows entry of patients eligible to receive platinum-based chemotherapy.

21. NHS England agrees with the ERG that the outputs of the network meta-analysis are very uncertain, one of the main reasons for this being the great heterogeneity of the studies in the meta-analysis and another is the capping of the hazard ratios.
22. The economic model appears to assume that the combination of carboplatin and gemcitabine is given for 6 cycles. Whilst a maximum of 6 cycles is correct, many patients will discontinue this treatment after 2 -3 cycles on account of failing to respond or suffering significant toxicity.
23. Atezolizumab is a drug available via the EAMS process for inoperable locally advanced or metastatic urothelial cancer previously treated with a single chemotherapy regimen.
24. If NICE recommends atezolizumab for use in cohort 1, the NHS England treatment criteria (all of which have to be satisfied) are potentially likely to be (and subject to any considerations by the NICE TA committee):
    - Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
    - The prescribing clinician is fully aware of the management of and the treatment modifications that may be required for the immune-related adverse reactions due to anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis
    - Histologically or cytologically documented transitional cell carcinoma of the urothelial tract that is either locally advanced (ie T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease)
    - No previous chemotherapy for inoperable locally advanced or metastatic urothelial cancer
    - Patients treated with adjuvant or neoadjuvant intent or with chemo-radiotherapy AND who have relapsed more than 12 months since completing platinum-based chemotherapy are eligible to be considered as treatment naïve but must satisfy all other criteria
    - ECOG performance status of 0 to 2
    - Ineligible for cisplatin based chemotherapy due to one or more of the following: impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60mls/min), hearing loss of 25dB as assessed by formal audiometry or grade 2 or worse peripheral neuropathy or ECOG performance status of 2
    - Patient has never received any previous immune checkpoint blockade therapies
    - To be treated until disease progression or excessive toxicity whichever is the sooner
    - No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (unless solely to allow immune toxicities to settle)
    - Atezolizumab to be otherwise used as set out in its Summary of Product Characteristics

25. If NICE recommends atezolizumab for use in cohort 2, the NHS England treatment criteria (all of which have to be satisfied) are potentially likely to be (subject to any considerations of the NICE TA committee):
    - Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
    - The prescribing clinician is fully aware of the management of and the treatment modifications that may be required for the immune-related adverse reactions due to anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis
    - Histologically or cytologically documented transitional cell carcinoma of the urothelial tract that is either locally advanced (ie T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease)
    - There has been disease progression during or following previous platinum-based combination chemotherapy for inoperable locally advanced or metastatic urothelial cancer
    - Patients treated with adjuvant or neoadjuvant intent or with chemo-radiotherapy AND who have relapsed less than 12 months since completing platinum-based chemotherapy are eligible but must satisfy all other criteria
    - ECOG performance status score of 0 or 1
    - To be treated until disease progression or excessive toxicity whichever is the sooner
    - No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (unless solely to allow immune toxicities to settle)
    - Atezolizumab to be otherwise used as set out in its Summary of Product Characteristics

Prof Peter Clark

NHS England Chair Chemotherapy Clinical Reference Group and National Clinical Lead for cancer Drugs Fund

20 April 2017

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Single Technology Appraisal (STA)

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation University of Liverpool, Clatterbridge Cancer Centre and Royal Liverpool University hospital.
Member- [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Not applicable
- other? (please specify) Not applicable

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Nil

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Patients with relapse following primary treatment, or with advanced disease at presentation, confer a significant challenge, and even among those fit for optimal platinum-based combination chemotherapy the median overall survival does not exceed the range of 12-15 months (Loehrer, 1992, von der Maase, 2000, von der Maase, 2005). The recommended first line chemotherapy for these patients are cisplatin based combinations and either MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or GC (gemcitabine and cisplatin) (Loehrer, 1992, von der Maase, 2000, von der Maase, 2005) although the GC regimen is often preferred due to a milder toxicity profile (von der Maase, 2000). For patients with acceptable performance status and preserved organ functions, and where the relapse occurs later than 12 months following neoadjuvant/adjuvant cisplatinum-based combination chemotherapy, re-challange of platinum based regimen may be a feasible option (Necchi, 2015). In selected cases the addition of paclitaxel to gemcitabine and cisplatin may be considered (Bellmunt, 2012). For patients unfit for cisplatin combinations alternative although potentially less efficient combination regimens have been proposed with median survivals in the range of 6-9 months, either with alternative platinum agents (oxaliplatin [Carles, 2007] or carboplatin [de Santis, 2012]) or a platinum-free combination of paclitaxel and gemcitabine (Calabro, 2009). In patients deemed ineligible for standard cispltin based treatment, combination treatment with Split dose cisplatin and Gemcitabine has reported encouraging results. (Hussain, 2004)

Following failure of first line chemotherapy, be it early relapse following platinum based neoadjuvant/adjuvant chemotherapy, or progressive disease during palliative first-line chemotherapy, treatment options have so far been limited. Studies, mostly phase II and retrospective series, have reported activity with taxanes and pemetrexed

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(Bambury et al, The Oncologist 2015; Ko et al, Lancet Oncol 2014). Vinflunine, a microtubule inhibitor of the vinca-alkaloid family of anticancer agents (Bennouna, 2008), was the first drug to obtain European Medicines Agency (EMA) approval for use in Transitional cell cancer of urothelium (2009) due to evidence of efficacy from Phase II (Culine, 2006, Vaughn, 2009) and Phase III trials (Bellmunt, 2009, Bellmunt, 2013). Considering the multiple challenges in the second-line setting, with declining performance status due to progressive disease, persistent side effects or complications from earlier treatments, and primary or acquired chemoresistance after primary chemotherapy, the safety profile and efficacy data from the vinflunine publications are encouraging. In the phase III trial (Bellmunt, 2009, Bellmunt, 2013) median overall survival was 6.9 months in the vinflunine plus best supportive care compared to 4.3 months in the best supportive care only population.
Further empirical studies in real life settings have confirmed vinflunine to be a safe and effective second line approach in Spain (n=66, Castellano, 2014), France (n=134, Medioni, 2013) and Germany (n=77, Hegele, 2013) , UK (n=49, Hussain 2015) with reported overall survival of 7.7 – 10.4 months. Based on the accumulating evidence, the ESMO guidelines suggest vinflunine as the recommended second-line therapy in advanced bladder cancer (Bellmunt, 2014). Vinflunine is currently not recommended by NICE for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy (NICE technology appraisal 272).
This technology under consideration has the potential to change the lnadscape in the management of advanced mestastatic bladder cancer. Within the clinical trials data set we are seeing long term survivors within this group of patients. Atezolizumab has been used in clinical trial setting in United Kingdom.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

This technology has the potential to significantly alter the course of the disease for a group of patients. The toxicity data has been extremely favourable compared to systemic chemotherapy. In a small percentage of patients (2-3%) immune mediated toxicity is reported and requires educational training of clinicians and nurse practitioners. Industry has been providing robust clinical programmes and guidelines to sites using these drugs within clinical trials and are keen to provide support if and when the availability of these drugs to wider population becomes a reality. Further data on biomarkers to assess the impact of PDL-1 positivity in these disease settings on response rates, durability of response and over-all survival will help to refine the recommendations.

Atezolizumab is innovative and its potential impact on health related benefits with improved efficacy in terms of response rate and durability of response while maintaining an excellent quality of life is key to highlight. This technology is likely to provide a step change in the management of urothelial cancer. Large single arm large Phase II trial data from GO29293 has been presented and published with an encouraging efficacy and toxicity profile. Phase III (GO29294) trial data comparing Atezolizumab versus standard of care chemotherapy (Vinflunine or Docetaxel or paclitaxel) in patients progressing post platinum based therapy is awaited.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Patients in 2nd line settings post cisplatin based chemotherapy can receive this treatment. Treatment can be discontinued if there is clinical deterioration or there is evidence of progression.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

United Kingdom sites recruited a number of patients in the single arm phase II and the randomised phase III trial. Strong evidence base seen for this drug had robust representation of UK patient population. Overall survival and durability of responses

are key end points and were assessed in these trials. PDL-1 negative and positive patient groups will need to be carefully evaluated in terms of long term outcome and survival data. Phase III GO29294 trial will provide further robust data within these sub groups and correlation with clinical outcome, durability of response and overall survival.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side effect profile of this drug has been favourable. This translates into significant improvement in quality of life when compared to chemotherapy treatment that leads to a number of patients suffering from neutropenic fever, nausea and vomiting and diarrhoea that requires hospitalisation and in-patient bed days for symptom support. The immune mediated toxicity has only been in 2-3 % of patients and have generally been well managed in specialist sites.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

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- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

These drugs are offered to patients based on their performance status and meeting specific criteria stipulated within treatment protocols. They are not likely to lead to any exclusion of patients on any other grounds and therefore equality legislation is unlikely to be applicable in this treatment setting.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Single arm large Phase II trial data from GO29293 has been presented and published with an encouraging efficacy and toxicity profile. In May 2016 FDA has approved the drug in USA in 2nd line setting. This single-arm clinical trial involving 310 patients with locally advanced or metastatic urothelial carcinoma measured the objective response rate. The durability of responses seen in a sub group of patients has been encouraging. The study also looked at the difference in response rate in based on "positive" versus "negative" expression of the PD-L1 protein on patients' tumor-infiltrating immune cells. Overall 14.8 percent of patients experienced at least a partial response, and the duration of response ranged from more than 2.1 to more than 13.8 months at the time of the response analysis. In patients who were "positive" for PD-L1 expression, 26 percent of patients experienced a tumor response (compared to 9.5 percent who were classified as "negative" for PD-L1 expression). As overall survival is limited in this group of patients there is an urgency from patient and clinician perspective of this proposed appraisal to NHS so that patients meeting the criteria to access this drug are not denied this treatment while waiting for phase III trial data. The large phase III international trial data GO29294 comparing Atezolizumab versus standard of care chemotherapy of choice (Vinflunine or Doecetaxel, or weekly paclitaxel) has completed recruitment and will be reported in due course of time and if that meets its primary end point of improvement in overall survival this will change the landscape in management of advanced and or metastatic

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Single Technology Appraisal (STA)

bladder cancer in 2nd line setting. Bladder cancer is given a Cinderella status. The myth that 2nd line palliative chemotherapy has limited role needs changing. The landscape in bladder cancer management is changing and we need to ensure that best available treatment on the basis of clinical trials are available for our patients. Hoffman-Censits JH, Grivas P, Van Der Heijden MS, Dreicer R, Loriot Y, Retz M, Vogelzang NJ, Perez-Gracia JL, Rezazadeh A, Bracarda S, Yu EY, Hoimes CJ, Bellmunt J, Quinn DI, Petrylak DP, Hussain SA, Cui N, Mariathasan S, Abidoye OO and Rosenberg JE (2016). IMvigor 210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). Genitourinary Cancer Meeting: 2016 Genitourinary Cancers Symposium. Welcome and General Session 4: Immunotherapy for Urothelial Carcinoma. J Clin Oncol 34, 2016 (suppl 2S; abstr 355)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

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How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Patients with advanced metastatic bladder cancer who are fit and well for 2nd line chemotherapy can significantly benefit from this technology when this is made available. The delivery of care with the input of NHS and industry in partnership providing education and training will have far reaching impact in delivering this drug safely and improving the outcome for this group of patients where survival and clinical outcome has remained poor over the last decade.

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Single Technology Appraisal (STA)

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation St Bartholomew Hospital NHS Trust / Barts Cancer Institute – Centre of Experimental Cancer Medicine

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

NICE guidelines recommend sequencing chemotherapy in this setting. Platinum based therapy is recommended first line. There is no consensus on subsequent therapies. Benefits are modest. Some patients are unfit for appropriate front line chemotherapy. This is also an area of unmet need.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There is no personalised therapy in bladder cancer.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This technology should be used instead of chemotherapy in relapsed disease. Data also exists for previously untreated patients not fit for chemotherapy. It is attractive here too.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

This is the first new agent for metastatic bladder cancer for a generation.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE guidelines recommend sequencing chemotherapy in this setting. Platinum based therapy is recommended first line. There is no subsequent therapies.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

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Atezolizumab is associated with long term durable remissions in both the PD-L1 positive and negative populations. There is enrichment in the PD-L1 positive subgroup. These durable responses do not occur with chemotherapy, especially in refractory bladder cancer. This is attractive to patients.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Atezolizumab has an attractive adverse event profile. There is not quality of life data. This is particularly true in view of the tolerability of chemotherapy.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

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Single Technology Appraisal (STA)

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Impact on NHS. This would be replacing chemotherapy which is administered an almost identical manner. Education on immune therapy is on-going in view of its approvals in renal, melanoma and lung cancer.

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Single Technology Appraisal (STA)

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Action Bladder Cancer UK and consequently I will not be submitting a personal statement.

Name: ...[redacted].....

Signed: .....

Date: ....10 APRIL 2017.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotheray

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: Fight Bladder Cancer

Do you know if your nominating organisation has submitted a statement?

☐ No

(Nomination Statement only submitted)

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes

- a carer of a patient with the condition?

☐ No

- a patient organisation employee or volunteer?

☐ Yes

Do you have experience of the treatment being appraised?

☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I sm a Bladder cancer patient. I was diagnosed May 2016 (St2 G3), I received I cycle of chemo treatment. I had a bad reaction to this and following a weeks stay in hospital treatment was stopped. I had a radical cystectomy (RC) September 2016. My recent 6 month check was clear.

In the 6 months since my RC, I have been focussing on building up my strength and fitness and my confidence in living life with a urostomy bag. I am having to make a number of adjustments in my day life eg when caring for my horses, sleeping and travelling. My energy levels are not as pre-treatment and I also have tinnitus following the chemotherapy.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

At the macro level, that the Cancer is eradicated.

Underlying outcomes from the treatment that I consider important to me:

Quality of life, aligned to this are limited (or ideally no) side effects.

Remission, or at least keeping progression at bay.

Increased Survival period.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Treatment to date has been for stage 2 g3 bladder cancer ….so not directly comparable with current Atezolizumab trial.

What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Initial trials appear to indicate that:

- Increase the life expectancy for those with Stage 4 Bladder Cancer

- Its relatively well tolersted, Have less side effects thereby improving the quality of life for those undergoing treatment and consequently less impact on family/carers

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Offers an improved response rate than current treatment, with less side effects.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not aware of any

4. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Metastatic urothelial bladder cancer has a poor prognosis, and survival rates have not changed in past 30 years. Treatment that is available is relatively ineffective and carries a relatively high risk of significant side effects.

Please list any concerns you have about the treatment being appraised.

None specific at present.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

n/a

5. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Not aware of any within the trial population

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Not aware of any within the trial population

6. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes (limited)

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

No experience of using this treatment

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, Appear to be. Not aware of any limitations to date.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

n/a

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ No

If yes, please provide references to the relevant studies.

7. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

None apparent

8. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Atezolizumab is one o

Is there anything else that you would like the Appraisal Committee to consider?

No

9. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
-

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma

Produced by Southampton Health Technology Assessments Centre

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Keith Cooper (Senior Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. Neelam Kalita (Research Fellow) critically appraised the health economic systematic review, critically

appraised the economic evaluation and drafted the report. Jill Colquitt critically appraised the clinical effectiveness systematic review and drafted the report. Emma Loveman critically appraised the clinical effectiveness systematic review and drafted the report. Olu Onyimadu (Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. Geoff Frampton (Senior Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor.

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LIST OF ABBREVIATIONS

1L	First-line
2L	Second-line
AE	Adverse event
ALT	Alanine aminotransferase
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BSC	Best supportive care
CAR	Carboplatin
CD	Could not be determined
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
DIC	Deviance information criterion
DOC	Docetaxel
DOR	Duration of response
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
eMit	Pharmaceutical electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence review group
FDA	Food and Drug Administration
GEM	Gemcitabine
GFR	Glomerular filtration rate
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IRF	Independent review facility

K-M	Kaplan Meier
LYG	Life years gained
MAA	marketing authorisation application
MAIC	Matching-adjusted indirect comparison
M-CAVI	Methotrexate, carboplatin, vinblastine
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
mUC	Metastatic urothelial carcinoma
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
Nab-PTX	Nanoparticle albumin bound paclitaxel
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NIHR	National Institute of Health Research
NMA	Network meta-analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PPV	Personalised peptide vaccine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSS	Personal social services
PTX	Paclitaxel
QALY	Quality-adjusted life year
QLQ	Quality of Life Questionnaire
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumors
SE	Standard error
SEER	Surveillance, epidemiology and end results program

SmPC	Summary of product characteristics
STC	Simulated treatment comparison
TTD	Time to discontinuation
TTP	Time to progression
UK	United kingdom
VFL	VInflunine

SUMMARY

Scope of the company submission

The company's submission (CS) generally reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). This is to appraise the clinical effectiveness and cost-effectiveness of atezolizumab (an intravenous immunotherapy) within its marketing authorisation for treating locally advanced or metastatic urothelial carcinoma in people whose disease has progressed after prior chemotherapy or for whom cisplatin-based chemotherapy is unsuitable. The comparators specified in the scope are:

- Cisplatin-ineligible people (first-line therapy): gemcitabine + carboplatin; or best supportive care.
- People whose disease has progressed after platinum-based therapy: re-treatment with first-line platinum therapy (adequate responders only); docetaxel; paclitaxel; or best supportive care.
- People who are cisplatin-ineligible and whose disease has progressed after platinum-based therapy: re-treatment with first-line platinum therapy (adequate responders only); docetaxel; paclitaxel; or best supportive care.

The company's decision problem differs from the NICE scope in three respects: best supportive care is not considered as a comparator for cisplatin-ineligible people receiving first-line therapy; a distinction is not made between cisplatin-eligible and cisplatin-ineligible people who have progressed after previous platinum-based therapy; and re-treatment with first-line platinum therapy is not considered in the second-line setting. Justifications for these differences are provided, mainly reflecting lack of available evidence.

The current submission is based on immature clinical effectiveness data (single-arm studies only) and lacks data on health-related quality of life. These data are expected to become available when phase III ongoing randomised controlled trials comparing atezolizumab against chemotherapy are completed in November 2017 (second-line setting) and June 2020 (first-line setting). For the present technology appraisal the company has requested that their submission is considered by NICE for the Cancer Drugs Fund.

Summary of submitted clinical effectiveness evidence

The CS includes:

- A systematic review of clinical effectiveness studies for atezolizumab and a systematic search for studies on a wide range of comparators;
- A network meta-analysis comparing atezolizumab to comparators in the NICE scope, based on a simulated treatment comparison.

A systematic search was conducted by the company to identify studies on atezolizumab and any comparator chemotherapy drugs that could be relevant in first-line or second-line treatment settings. The search identified only one study on atezolizumab. This was an ongoing single-arm phase II study (Imvigor 210) which included chemotherapy-naive cisplatin-ineligible patients receiving first-line treatment (cohort 1) and platinum chemotherapy pre-treated patients receiving second-line treatment (cohort 2). The search identified 41 studies of comparators that were deemed eligible for inclusion in a feasibility assessment for network meta-analysis, of which seven comparator studies were finally included in meta-analyses. Assessment of the atezolizumab study followed a systematic review process but the review of comparators was more superficial, with few details of the studies provided.

At the last available data-cut, and based on independent review facility assessment using RECIST v1.1 tumour assessment criteria, first-line patients in Imvigor 210 had a median overall survival of 15.9 months, median progression-free survival 2.7 months, an objective response rate of 22.7%, and the median duration of response had not yet been achieved (median follow-up was 17.2 months and median treatment duration 15 weeks [range 0 to 102 weeks]). Second-line patients had a median overall survival of 7.9 months, progression-free survival of 2.1 months, an objective response rate of 15.8%, and the median duration of response had not yet been achieved (maximum duration of response at the latest data cut was 22.6 months). Median follow-up was 21.1 months and median treatment duration 12 weeks [range 0 to 104 weeks)].

Comparison of the clinical effectiveness of atezolizumab against comparator chemotherapy drugs was limited by a lack of primary evidence, as the relevant comparators were either single-arm studies or single arms within controlled trials. To enable a network to be formed for a network meta-analysis, the company employed a simulated treatment comparison to ‘predict’ a matching atezolizumab arm for each comparator study. The resulting comparisons of atezolizumab against each comparator were then included in a network meta-analysis. The

company selected a fractional polynomial model approach for the network meta-analysis since higher-order fractional polynomial models do not require the assumption of proportional hazards. This approach to network meta-analysis is relatively new but is well-suited to the data format available to the company, which consisted of individual patient data for atezolizumab and aggregate population data for the comparators.

The CS presents network meta-analyses on overall survival and progression-free survival and appropriately acknowledges that these have limitations and their results are uncertain, producing clinically implausible results when used directly without adjustment in the economic model. None of the meta-analysis results are discussed in support of the clinical effectiveness of atezolizumab.

In addition, the ERG has identified a number of methodological issues with how the company has conducted the simulated treatment comparison and network meta-analysis which cast further doubt on the validity of the results of these analyses (see 'Commentary on the robustness of the submitted evidence' below).

Summary of submitted cost effectiveness evidence

The CS includes:

- A review of published economic evaluations of treatments for patients with metastatic or locally advanced urothelial carcinoma,
- An economic evaluation undertaken for the NICE STA process to assess atezolizumab for patients with locally advanced or metastatic urothelial carcinoma. The cost effectiveness of atezolizumab is compared with gemcitabine + carboplatin for patients for whom cisplatin-based chemotherapy is unsuitable as a first-line treatment and compared with docetaxel, paclitaxel and best supportive care for patients whose disease has progressed after prior chemotherapy.

A systematic review was conducted by the company to identify economic evaluations of treatments for patients with metastatic or locally advanced urothelial carcinoma. The review identified seven studies but reported that none of these were relevant to the current submission.

The company constructed two partitioned survival models in Microsoft Excel with identical model structure. The models compared first-line atezolizumab with gemcitabine + carboplatin; and second-line atezolizumab with docetaxel, paclitaxel and best supportive care. The models have a lifetime time horizon of 20 years, with discounting of 3.5% per annum for costs and health benefits, a weekly cycle length and a half-cycle correction. The perspective of the analysis is for the NHS and Personal Social Services. The models have three health states: 'progression-free survival', 'progressed disease' and 'death'.

The models use clinical trial data for atezolizumab from IMvigor 210, a single-arm phase II study. Clinical trial data for the comparators are derived from studies found through a systematic search of the clinical literature. The model uses parametric survival modelling to fit survival curves to the observed data for progression-free survival and overall survival for atezolizumab. The company assumes that progression-free survival for atezolizumab is equivalent to its comparators. For the comparators' overall survival, the overall survival curves for atezolizumab are adjusted using the results of the company's fractional polynomial model. The model derives the proportion of patients in the progressed disease state as the difference between the progression-free survival and overall survival curves. The generalised gamma distribution was used for progression-free survival and overall survival for first-line and second-line comparisons.

Utility estimates were taken from the Australian Pharmaceutical Benefits Advisory Committee (PBAC) cost-utility analysis for vinflunine, in which quality of life values from the EORTC QLQ Q30 questionnaire for patients with advanced urothelial carcinoma who had received vinflunine were mapped to EQ-5D values. Atezolizumab is administered intravenously every three weeks and the recommended dose is 1200mg at a proposed list price of £3807.69 per dose. The cost of comparator treatments are taken from the pharmaceutical electronic market information tool (eMit) and their doses are as recommended by their Summaries of Product Characteristics. Health state costs are based on those used in the NICE technology appraisal for vinflunine (TA272).

The results of the economic model are presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per quality-adjusted life-year (QALY). For the base case the incremental cost per QALY gained is £44,158 for first-line atezolizumab compared to gemcitabine + paclitaxel (Table 1). The ICERs for second-line atezolizumab compared to

docetaxel, paclitaxel and best supportive care are £131,579, £104,850, £98,208 per QALY gained respectively (Table 2).

Table 1 First-line base case cost effectiveness results

Intervention / comparator	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Atezolizumab	£77,211	2.69			
Gemcitabine + carboplatin	£18,106	1.35	£59,106	1.34	£44,158

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Table 2 Second-line base case cost effectiveness results

Intervention / comparator	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Atezolizumab	£71,868	1.23			
Docetaxel	£9,439	0.76	£62,430	0.47	£131,579
Paclitaxel	£16,606	0.71	£55,262	0.53	£104,850
Best supportive care	£4,836	0.55	£67,032	0.68	£98,208

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

In probabilistic sensitivity analyses, the probability of first-line atezolizumab being cost-effective is 10.9% and 53.9% at willingness to pay thresholds of £30,000 and £50,000 per QALY respectively. The probability of second-line atezolizumab being cost-effective is 0% and 0% at willingness to pay thresholds of £30,000 and £50,000 per QALY respectively

The company conducted sensitivity analyses and scenario analyses and concluded that the key drivers to the cost-effectiveness results were the price of atezolizumab and the utility of patients in the progressed disease health state. However, the company did not include sensitivity analyses for overall survival or time to treatment discontinuation

Commentary on the robustness of submitted evidence

Strengths

The company has conducted thorough searches and, despite some inconsistencies in application and reporting of the eligibility screening process appears to have identified all of the key studies on atezolizumab and the scoped comparators.

The model structure is representative of the clinical pathway for patients with advanced or metastatic urothelial carcinoma. The company conducted a systematic review to identify cost-effectiveness, HRQoL and cost studies and values from this review were utilised in the model. The models are intuitive and user-friendly.

Weaknesses and areas of uncertainty

Weaknesses

The ERG has the following concerns regarding the simulated treatment comparison:

- It is based on a very small set of covariates.
- Some aspects of the analysis are unclear, including how the company accounted for missing covariate values.
- The cumulative impact of small errors and inconsistencies in the data is unclear.

The ERG has the following concerns regarding the network meta-analysis:

- The company suggests that the proportional hazards assumption is unlikely to hold for comparisons of atezolizumab against standard chemotherapy drugs; however, they based their network meta-analysis for first-line comparisons on a zero-order version of the fractional polynomial model which assumes proportional hazards. The company does not discuss the plausibility of this model.
- Hazard ratios for overall survival were not used to inform clinical effectiveness of atezolizumab and were considered to be clinically implausible when applied in the economic analysis without adjustment.
- Hazard ratios for progression-free survival were considered to be clinically implausible and were not used to inform the clinical effectiveness or cost-effectiveness evaluation of atezolizumab.

Areas of uncertainty

The company has not provided any 'reality checks' to gauge whether their network meta-analysis analysis results might be reasonable or subject to bias. Uncertainties arising at different steps of the simulated treatment comparison and meta-analysis are not discussed or propagated through to the final results so the cumulative impact of small errors and inconsistencies identified by the ERG is unclear.

The fractional polynomial network meta-analysis approach is a relatively complex method that involves numerous computational steps, and it is important that the analysis approach is reported clearly and as fully as possible for the method to be adequately understood. The company's description of the methods is rather limited and several key aspects of the methodology not reported in the CS were revealed indirectly by the company in responses to clarifications. Due to the limited reporting it is possible that some methodological issues might have gone undetected by the ERG.

There is considerable uncertainty regarding the extent to which the clinical benefits of atezolizumab exceed those of comparator treatments. The uncertainty is due to the immaturity of the evidence base for atezolizumab and because there are no direct randomised controlled trials between atezolizumab and its comparators.

The company has not fully explored uncertainty around the model results through sensitivity and scenario analyses. In particular, they have not included sensitivity analyses varying the treatment effect of atezolizumab or varying parametric survival distribution for overall survival and time to treatment discontinuation.

Summary of additional work undertaken by the ERG

In order to address the issues identified above we undertook a series of sensitivity analyses that varied the treatment effect of atezolizumab, the parametric survival distributions used for overall survival and time to treatment discontinuation, and the utility values used for model health states.

Our base case contained the following elements: changes to utility values and parametric survival distributions used for overall survival and time to treatment discontinuation.

The first-line and second-line results are shown in Table 3 and Table 4. The ERG base case ICER for first-line atezolizunab compared to gemcitabine + carboplatin is £93,948 per QALY gained. The ERG base case ICERs for second-line atezolizumab compared to docetaxel, paclitaxel and best supportive care are £288,247, £180,901 and £166,805 per QALY gained respectively. The ERG cautions that there is considerable uncertainty in the model results.

Table 3 ERG first-line base case analysis results

Intervention / comparator	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
Atezolizumab	£60,650		1.32		
Gemcitabine + carboplatin	£12,469	£48,181	0.81	0.51	£93,948

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Table 4 ERG second-line base case analysis results

Intervention / comparator	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
Atezolizumab	£66,254		0.84		
Docetaxel	£8,196	£58,059	0.64	0.20	£288,247
Paclitaxel	£13,615	£52,640	0.55	0.29	£180,901
Best supportive care	£4,090	£62,164	0.47	0.37	£166,805

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

1 INTRODUCTION TO THE ERG REPORT

This report is a critique of the company's submission (CS) to NICE from Roche on the clinical effectiveness and cost effectiveness of atezolizumab for treating locally advanced or metastatic urothelial carcinoma. It identifies the strengths and weaknesses of the CS. A clinical expert was consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG and NICE on 8th February 2017. A response from the company via NICE was received by the ERG on 27th February 2017 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Summary and critique of the company's description of the underlying health problem

The company has provided an accurate overview of urothelial carcinoma (CS section 3), including a very brief overview of the condition (CS section 3.1), information on the course of disease and prognosis (CS section 3.2), the burden of illness (CS section 3.3), and an explanation of the unmet clinical need (CS section 3.4).

The CS refers both to 'bladder cancer' and 'urothelial carcinoma', although the condition defined in the scope of the current technology appraisal is, strictly, urothelial carcinoma. The majority of bladder cancers (~90%) in the UK are attributable to urothelial carcinoma,[1] and the majority of urothelial carcinomas (90-95%) develop in the bladder.[2] The remaining urothelial carcinomas (10-15%) develop in the renal pelvis and the ureters (referred to as upper tract urothelial carcinomas) and also in the urethra. Although not mentioned in the CS, occurrence of urothelial carcinomas at these different sites is not independent: in 17% of cases of upper tract urothelial carcinoma there will be concurrent bladder cancer present, and 22-47% of the upper tract urothelial carcinomas which develop will recur in the bladder.[2]

Note that the term 'bladder cancer' as used in the scientific literature and clinical guidance documents can have several meanings: it may refer to any cancer of the urinary bladder; or urothelial carcinoma; or both.

Development and classification of urothelial carcinoma

Urothelial carcinoma (also commonly referred to as transitional cell carcinoma) begins in transitional cells (also called urothelial cells), which are flexible cells forming the inner lining (urothelium) of the bladder and upper urinary tract. The CS points out that patients are classified according to the stage of development of the carcinoma, as having either early non-muscle-invasive bladder cancer, muscle-invasive bladder cancer, or metastatic cancer (CS section 3.1).

The CS does not describe the staging or grading of urothelial carcinoma, although this information is readily available from organisations such as Cancer Research UK, Macmillan Cancer Support, and the European Association of Urology.[1-5] The stage of bladder cancer is commonly represented using the Tumour-Node-Metastasis classification (TNM).[5] CS Table 7 shows how non-muscle invasive disease, muscle-invasive disease and metastatic disease relate to the different stages of cancer on the TNM classification.

In non-muscle-invasive bladder cancer the tumour remains confined to the lining of the bladder wall, i.e. it remains within the urothelium (stage Tis or Ta) or has invaded the adjacent connective tissue layer (stage T1) but has not penetrated into the underlying muscle layer. Tumours that have penetrated into the muscle layer (stages T2-T4) are referred to as muscle-invasive bladder cancer. These may spread locally or regionally, or metastasise to distant parts of the body, and are then referred to as metastatic bladder cancer.

The CS does not explicitly define 'locally advanced' urothelial carcinoma. However, it is specified (using the TNM classification) in the inclusion criteria for the company's pivotal atezolizumab study (Imvigor 210) as '*T4b and any N; or any T and N2-3'* (CS Table 25). According to Cancer Research UK, 'locally advanced bladder cancer' refers to cancer that has grown through the bladder wall or has spread only to lymph nodes.[6]

Risk factors for urothelial carcinoma

The CS correctly points out that well-known risk factors for bladder cancer are advanced age, smoking, and exposure to some industrial chemicals. Cancer Research UK lists a wider range of risk factors, including (among others) exposure to ionizing radiation, exposure to chlorinated water, use of certain drugs (e.g. pioglitazone, cyclophosphamide), and a history of bladder infections or inflammation.[7, 8] However, according to the European Association of Urology, there is consensus that the most important modifiable risk factor for urothelial carcinoma is smoking.[9]

Cancer Research UK estimates that 42% of bladder cancer cases in the UK could be preventable due to their link to lifestyle factors.[8]

Incidence rates

The CS reports that bladder cancer is the 10th most common cancer in the UK, although Cancer Research UK state that it is the 7th most common.[8] The latest data cited are from 2014, when there were 10,063 new cases (CS section 3.1). These figures are consistent with the current incidence data available from Cancer Research UK,[8] although it is not clear which type(s) of bladder cancer the data refer to. The incidence of bladder cancer is higher in males (around 7,300 cases in 2014) than in females (around 2,800 cases in 2014), and is more common in White than Asian or Black people, and in people living in deprived areas.[8] From 2012 to 2014, more than half of bladder cancers (55%) were diagnosed in people aged 75 years and over.[8] As mentioned in the CS, the incidence of bladder cancer has decreased by 27% in the UK since the late 1970s and has also decreased in other European countries, and this trend is thought to reflect changing smoking habits and stricter controls on exposure to industrial chemicals.[10]

Course and prognosis

The CS provides an accurate description of the symptoms, course and prognosis of bladder cancer (CS section 3.2). Haematuria (blood in the urine) is the most frequent presenting symptom of bladder cancer, occurring in approximately 80% of cases. Patients may also experience increased frequency and urgency of urination and pain when passing urine. These symptoms mean that bladder cancer is often diagnosed at an early stage, with 75-85% of urothelial carcinomas of the bladder being classed as not invasive at diagnosis (although only 40% of urothelial carcinomas of the upper urinary tract are classed as non-invasive at diagnosis).[2]

The CS points out that non-muscle-invasive bladder cancer is highly treatable but has a high risk of recurrence. The high recurrence rate means that follow-up is a crucial component in effective management.[11] Literature cited by the CS suggests that up to 45% of patients with non-muscle-invasive bladder cancer will eventually progress to muscle-invasive bladder cancer, and that 20-50% of those with muscle-invasive bladder cancer will progress further to metastatic disease.

The CS reports survival rates from the SEER (Surveillance, Epidemiology, and End Results Program) of the US National Cancer Institute (Howlader et al.[12]), which cover the period 1975-2008. According to the SEER data, the 5-year survival rate for localised non-muscle-invasive bladder cancer was 69%, dropping to 34% for those with regional spread, and 6% for metastatic disease. Cancer Research UK provides overall mortality rates[13] and survival rates[8] for bladder cancer, but not specifically for non-muscle-invasive, muscle-invasive, or metastatic disease. Age-specific bladder cancer mortality rates in the UK rise steeply from around age 55-59, with the highest rates being in the 90+ age group.[13] According to Cancer Research UK, males have better survival than females,[14] yet mortality rates are considerably (2.1 times) higher for males,[13] reflecting the higher prevalence of bladder cancer in males.

Section 3.5.3 of the CS presents a table showing bladder cancer 5-year survival rates and the probabilities of recurrence separately for different cancer stages at diagnosis (CS Table 7). The CS credits these data to Howlader et al. 2011,[12] Kaufman et al. 2009,[11] National Collaborating Centre for Cancer 2015 (which reflects NICE guideline NG2[15]), Sharma et al. 2009,[16] de Vos & de Wit 2010,[17] and the American Cancer Society 2015.[18] The data in CS Table 7 appear to be from the SEER program; however, we could not find the source data for CS Table 7 in any of these cited references. The American Cancer Society[18] reported that 5-year survival rates from the SEER program for bladder cancer stages 0, 1, 2 and 3 were about 98%, 88%, 63% and 46% respectively.

2.2 Summary and critique of the company's overview of current service provision

The CS provides a description of the current first line treatment for people with locally advanced or metastatic urothelial bladder cancer (CS section 3.5.1). This is in line with the NICE recommendations.[15] For patients who are otherwise physically fit (performance status 0 or 1) and have adequate renal function, a cisplatin-based chemotherapy such as cisplatin with gemcitabine or accelerated MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) with granulocyte-colony stimulating factor is recommended. For those in whom cisplatin is unsuitable (e.g. if performance status is poor, or they have inadequate renal function), NICE recommends carboplatin with gemcitabine. The company cites evidence from a randomised controlled trial by De Santis et al. (2009)[19] which they say estimates that carboplatin with gemcitabine are used in up to 50% of patients in the first line setting. However, this is a secondary reference which cites

four studies which were published between 2000 and 2006. We note that the 2014 European Society for Medical Oncology practice guidelines[20] concur with this figure, although no source is cited. It is therefore unclear if the estimate of 50% is still valid. The CS concludes in Section 3.5.2 that a significant proportion of patients therefore do not receive the most effective first-line therapy (cisplatin with gemcitabine) and in these patients alternatives are needed.

The CS mentions that most patients will experience disease progression and may require second-line therapy, citing Bellmunt et al. 2013[21] which is a randomised controlled trial (CS section 3.5.1). There is no reference for this statement in the Bellmunt 2013 paper; however, on the basis of evidence presented on the course and prognosis of bladder cancer (CS section 3.2), the ERG agrees that most patients will experience disease progression. The CS correctly states that there is only one treatment (vinflunine) with a licensed indication for second line treatment for urothelial cancer but that it is not recommended by NICE.[22] The CS states there is therefore a wide variety of practice in the choice of second line treatment for these patients citing two sources (the 2014 European Society for Medical Oncology practice guidelines[20] and a UK survey by Lamb et al.[23]) and the view of their clinical experts (CS section 3.5.1). The variety of practice is not discussed in the guideline document; the UK survey shows variability in practice, but the survey was conducted in 2011. The CS concludes (CS section 3.5.2) that no treatment has been shown to improve survival in the second-line setting, and the ERG concurs.

2.3 Summary and critique of the company's definition of the decision problem

Population

The population defined in the company's decision problem is adults with locally advanced or metastatic urothelial carcinoma:

- for whom cisplatin-based chemotherapy is unsuitable
- whose disease has progressed after prior chemotherapy

This corresponds with the final scope issued by NICE and the draft Summary of Product Characteristics (SmPC) for atezolizumab.

The CS refers to first-line (1L) and second-line (2L) treatment, which correspond to two treatment cohorts of the company's key clinical effectiveness study for atezolizumab (Imvigor 210). The populations specified in Imvigor 210 were defined as patients with advanced urothelial cancer:

- who were cisplatin-ineligible (medically ineligible to receive cisplatin chemotherapy), and were either previously untreated or had disease progression at least 12 months after their last dose of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen (cohort 1, 1L);
- who had disease progression following treatment with a platinum-based chemotherapy regimen (cohort 2, 2L).

The ERG considers that the population described in the decision problem is appropriate for the NHS, although notes that the final wording of the indication may change when the Medicinal Products for Human Use (CHMP) opinion is released.

The ERG notes that atezolizumab has FDA approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.[24]

Intervention

The intervention specified by the NICE scope and the company's decision problem is atezolizumab (Tecentriq), a monoclonal antibody that binds to programmed death ligand 1 (PD-L1). Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated [redacted] and regulatory approval is expected in [redacted]. The recommended dose is 1200 mg administered intravenously every three weeks until loss of clinical benefit or unmanageable toxicity (CS Table 6 and draft SmPC). This is the same dose as used in the Imvigor 210 study, although treatment in the study was continued until disease progression per RECIST (Response Evaluation Criteria for Solid Tumours) v1.1 in first-line patients, or until lack of clinical benefit in second-line patients. The ERG considers that the intervention in the decision problem reflects its anticipated use in the UK and is appropriate for the NHS.

Comparators

The comparators are listed in the final scope issued by NICE according to the patient population.

For first-line patients for whom cisplatin-based chemotherapy is unsuitable, the comparators specified in the NICE scope are gemcitabine + carboplatin, or best supportive care. However,

the company's decision problem includes only gemcitabine + carboplatin. The company states that according to their expert clinical advisor panel, all patients willing and able to receive therapy would receive a first-line treatment option and that those receiving best supportive care would be unable or unwilling to receive any active treatment, including atezolizumab. The company states that these patients would represent a small minority, and also notes that best supportive care has not been assessed in a clinical trial in the first line setting, so that a comparison with atezolizumab would not be possible. However, the company does not provide evidence of the numbers of patients receiving best supportive care as a first-line treatment. The ERG's clinical advisor suggested that as atezolizumab is an immunotherapy, which would have a better safety profile than chemotherapy, then patients unable or unwilling to receive chemotherapy might be able and willing to receive atezolizumab.

For people whose disease has progressed after prior chemotherapy (i.e. second-line), the NICE scope refers specifically to platinum-based prior chemotherapy. The NICE scope separates second-line patients into those who are suitable and unsuitable for cisplatin-based chemotherapy, and for both groups the following comparators are specified:

- Retreatment with first-line platinum-based chemotherapy (only for people whose disease has had an adequate response); for cisplatin-ineligible patients retreatment would be with gemcitabine +carboplatin
- Docetaxel
- Paclitaxel
- Best supportive care

The CS decision problem for the comparators differs from the NICE scope in that the company has removed retreatment with first-line platinum-based chemotherapy as a comparator. The company's justification is that their expert clinical advice was that retreatment with first-line therapy is an option for only a very small proportion of people, is not considered standard of care within England, and '*has not been the subject of a systematic clinical evaluation'*. The ERG notes that the company does not provide any evidence regarding the proportion of people undergoing retreatment with first-line therapy to justify the exclusion. However, the ERG's clinical advisor suggested that the company's approach seems reasonable, given the limited evidence base.

As a result of having removed retreatment as a comparator, the CS decision problem for the comparators differs from the NICE scope as the company does not distinguish between the second-line cisplatin-eligible and cisplatin-ineligible groups. The company's justification for combining the groups is that treatment patterns and response rates for patients receiving second-line treatment with docetaxel, paclitaxel or best supportive care are '*not anticipated to be different based on their eligibility for cisplatin and receiving 2L treatment*' (CS section 1.1). The ERG's clinical advisor suggested that it is difficult to know whether cisplatin-eligible and ineligible patients would fare differently on second-line treatment, given the limited evidence base; and the ERG notes that the studies on relevant second-line comparators did not report whether any of their patients were cisplatin-ineligible (see section 3.1.3 below).

The CS does not define best supportive care, for patients in either the first-line or second-line settings. In response to a clarification request from the ERG and NICE (clarification response A2), the company stated that: '*Patients will receive best supportive care when they are not suitable for active second-line treatment due to clinical considerations of their disease, co-morbidities, or performance status. For these patients, the aim of treatment is to relieve symptoms of their disease, and would include support from oncology and palliative care teams including consultants and specialist nurses, palliative radiotherapy for the relief of symptoms, analgesia, support in the community, and hospice admission*.'

In their clarification of best supportive care (clarification response A2) the company also provided an explanation of their definition of second-line treatment, as follows:
"For clarity, the second line (2L) population includes the following:

- *Patients whose disease has progressed after platinum-based chemotherapy*
- *Patients for whom cisplatin-based chemotherapy is unsuitable and whose disease has progressed after* ***non-****platinum-based therapy"* (ERG bold)

As we note above, this is inconsistent with the NICE scope which specifically refers to patients whose disease has progressed after platinum-based chemotherapy. However, the CS does not refer to non-platinum first-line therapy, so the extent of any deviation from the scope is unclear.

Outcomes

The outcomes listed in the company's decision problem are the same as those specified by the NICE final scope: overall survival, progression-free survival, response rates, adverse effects

and health-related quality of life. However, the CS does not actually report health-related quality of life; therefore, the company's decision problem is misleading. The outcomes are appropriate and clinically meaningful to patients, and the ERG considers that all important outcomes, other than quality of life, have been included in the decision problem.

Economic analysis

The economic analysis described in the decision problem conforms with the NICE reference case and is appropriate for the NHS. The company conducted a cost-utility analysis with a 20-year time horizon, which is considered sufficiently long to reflect any differences in costs or outcomes. Costs are considered from the NHS and Personal Social Services perspective

Other relevant factors

The NICE scope does not specify any subgroups that should be considered, and in line with this none are considered in the company's cost-effectiveness analysis, although clinical effectiveness evidence is presented according to PD-L1 expression subgroups.

No issues related to equity or equality have been identified by the NICE scope, the company decision problem, or the ERG.

3 CLINICAL EFFECTIVENESS

3.1 Summary and critique of the company's approach to systematic review

3.1.1 Description of the company's search strategy

The CS states that a wide search was conducted for clinical effectiveness evidence, although the search strategy is not provided (CS section 4.1). Upon request from the ERG and NICE, the company provided a detailed search strategy for each of their information sources (clarification response A4) and these appear to be appropriate and fit for purpose. Overall, the systematic search process is well described, and the information sources and search dates are clearly reported (CS Table 9). The sources included MEDLINE, EMBASE, and the Cochrane Library (searched in June 2016), study registries and conference abstracts (searched in July 2016), and HTA and drug regulatory agencies (searched in August 2016). The CS states that no time limits were applied to the bibliographic searches, except for conference abstracts which were restricted to 2015-2016 (CS section 4.1.3.1). The eligibility criteria (CS Table 10) indicate that reviews (systematic and non-systematic) and meta-analyses were excluded, but the CS does not report whether any were used as a source of references. The CS does, however, report that reference lists of the included primary studies were checked by two reviewers to identify any trials directly comparing atezolizumab versus any comparator (CS section 4.1.5).

The CS states that the goal of the clinical effectiveness search was '*to capture current and upcoming treatments for all relevant markets in the relevant indications for atezolizumab*' (CS section 4.1.1). As such, the search is likely to have been considerably wider than the scope of the current technology appraisal.

The clinical effectiveness search was 5-7 months out of date when the ERG received the CS. We therefore ran a search for the period 2016-2017 on MEDLINE, EMBASE, and the Cochrane Library, covering the condition (bladder or urothelial carcinoma) linked to the following comparators (alone or in combination): paclitaxel, docetaxel, gemcitabine, carboplatin, vinflunine, MVAC (methotrexate + vinblastine + doxorubicin + cisplatin), and best supportive care. We also checked clinicaltrials.gov and the UK Clinical Trials Gateway for potentially relevant studies of atezolizumab or comparators. We identified five systematic reviews or meta-analyses covering possible comparators[25-30] that are not cited in the CS and which appear to

have been published after the company's searches were conducted. We did not find any additional completed or ongoing studies of atezolizumab.

In addition to the update searches, the ERG checked the reference lists of key guidance documents,[5, 9, 15] an evidence review for NICE,[31] recent review articles[32, 33] and a meta-analysis[30] for any potentially relevant studies. We identified 18 studies on comparators (published from 1997 to 2017) which are not cited or listed in the CS but appear, based on their titles and abstracts, to be potentially relevant according to the company's eligibility criteria (CS Table 10). Upon request from the ERG and NICE (clarification question A11), the company confirmed that 16 of these references had been identified and screened for eligibility, and were subsequently excluded, whilst two had not been identified as they had been published after the company's searches were conducted. The potential relevance of these references, and whether they were excluded appropriately, are discussed below in section 3.1.3.

The searches for economic evaluations and utilities (HRQoL) were conducted in September 2016 and resource-use searches were conducted in December 2016. Well-documented and comprehensive search strategies are provided for these searches in CS Appendices 8.7, 8.9 and 8.10. In summary, the ERG considers that the searches and methodology employed by the company to support the systematic reviews of economic evaluations (section 4.1 below), HRQoL (section 4.3.6 below) and resources (section 4.3.7 below) were comprehensive and fit for purpose.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The CS reports eligibility criteria for the population, intervention, comparators, outcomes, and study design in CS Table 10. The company confirmed (clarification question A6) that all of the eligibility criteria were specified a priori.

Eligible population

The population eligibility criteria (but not the scope or decision problem), specifically exclude adjuvant and neoadjuvant stages of the treatment pathway, although the ERG notes that the studies which were ultimately included by the company differed in whether they reported adjuvant and neoadjuvant therapy (section 3.1.3). The eligibility criteria report PD-L1 expression subgroups ("2/3") but no subgroups are specified in the scope and decision problem; the CS

does not explain the rationale for these subgroups, although we understand that efficacy of atezolizumab is likely to vary according to PD-L1 expression status.

Eligible intervention and comparators

The eligibility criteria for the comparators are not fully clear in the CS, since CS Table 10 lists two different sets of eligible comparators, under both the 'Intervention' eligibility criteria domain and the 'Comparators' eligibility criteria domain:

- The 'Intervention' domain in CS Table 10 lists (in addition to atezolizumab) examples of 38 eligible comparators. These include platinum-based, taxane-based and other non-platinum chemotherapies, and monoclonal antibody therapies. The CS also states that '*any other applicable chemotherapies, immunotherapies, antineoplastic agents, antineoplastic protocols, molecular-targeted therapies, cancer vaccines, protein kinase inhibitors, angiogenesis inhibitors, taxanes, taxoids, etc*.' would be eligible.
- The 'Comparators' domain in CS Table 10 specifies '*any pharmacological intervention used*', placebo, and best supportive care.

These two lists of eligible comparators in CS Table 10 are both considerably broader than the comparators specified in the scope and decision problem. However, the CS implies (CS Figure 3; CS section 4.1.4) that the eligibility criteria in CS Table 10 were those used for initial screening of titles and abstracts, and that different, smaller, sets of comparators were subsequently considered eligible:

- CS section 4.1.4 (Search results) states that studies were prioritised in terms of the importance of the comparators, based on clinical guidelines and standards of care in the UK, France, Australia, Canada, and Sweden, with studies on the following comparators being eligible: '*best supportive care, carboplatin + paclitaxel, docetaxel, paclitaxel, nab-paclitaxel, vinflunine, gemcitabine, gemcitabine + paclitaxel, MVAC, carboplatin, cisplatin, oxaliplatin (platinum-based re-challenge if >12 months since last dose), pembrolizumab, nivolumab, and gemcitabine + cisplatin for 2nd line as well as gemcitabine + carboplatin, gemcitabine + paclitaxel and best supportive care for the first-line cisplatin-ineligible population*.' According to CS Figure 3, this prioritisation took place at the full-text screening step. This list of comparators is still broader than the list in the decision problem.
- CS section 4.10.3 (Comparators of interest), which refers to the assessment of studies for the network meta-analysis, lists the eligible comparators as being gemcitabine +

- carboplatin for first-line treatment, and paclitaxel, docetaxel or best supportive care for second-line treatment. The CS does not explain why this list of comparators is different to the "priority" comparators specified in CS section 4.1.4, and no reasons are given in CS Figure 3 as to why studies were excluded at these screening steps.

Eligible outcomes

The CS lists 12 eligible outcomes (CS Table 10), and these are reflective of the NICE scope and the company's decision problem. However, the CS states that only four of these outcomes were considered for the network meta-analysis: overall survival, 12-month survival, progression-free survival and objective response rate (CS section 4.10.5). No reason is given in the CS for focusing on these outcomes, although the ERG agrees that overall survival and progression-free survival are important outcomes for the evaluation of urothelial cancer treatments.

Eligible study designs

Randomised controlled trials (RCTs), non-randomised trials, and single-arm studies were eligible, and this seems appropriate. Phase I studies were excluded.

Summary of the screening process

CS section 4.1.3.2 (Review strategy) briefly describes the eligibility screening process, and provides a PRISMA flow chart (CS Figure 3). In CS Figure 3 the numbers of excluded publications is incomplete (373 of 631 recorded only). The company clarified that the remaining 258 records were excluded because no outcomes of interest were reported (clarification response A7).

The CS does not state how many reviewers conducted the eligibility screening process but the company confirmed (clarification question A6) that titles/abstracts and full texts were assessed by two reviewers. The CS does not report whether any types of bias may have arisen during the eligibility screening.

According to the CS, the literature was initially screened on titles and abstracts using the eligibility criteria listed in CS Table 10. The remaining publications and internet search results were then assessed based on the full-text versions, yielding a data set of n=233 publications for inclusion in a 'qualitative synthesis' to ascertain feasibility of a network meta-analysis.

Network meta-analysis feasibility assessment

The CS reports that a two-stage process was then used to identify potential bridging studies which might enable indirect linking between relevant comparators in the network meta-analysis (CS section 4.10.5):

In stage 1, 233 studies were assessed and excluded if they did not report one or more of the four outcomes of interest. After this step 74 publications reporting 43 studies remained (i.e. 159 were excluded). There is a discrepancy in that CS section 4.10.5 implies the 159 publications had been excluded due to ineligible outcomes whilst CS Figure 3 and the company's clarification response A8 state that the reason for exclusion was '*interventions not first priority*'.

In stage 2, studies were selected according to their feasibility for inclusion in the network meta-analysis, based on '*building the study networks and their connectivity*', '*assessing the availability of baseline factors associated with the clinical outcomes of interest*', and, for the overall survival and progression-free survival analyses, '*assessing the presence of Kaplan-Meier curves in the corresponding publications*' (CS section 4.10.5). However, the CS does not provide explicit objective criteria for how eligibility decisions were made at stage 2. At this stage 27 publications were excluded, leaving 47 publications for inclusion in the analysis, and these reported on 28 individual studies. The reasons for exclusion are listed in CS Appendix 8.2, but the descriptions are inconsistent and imprecise. The company provided clarification upon request from the ERG and NICE (clarification response A9). The remaining 28 studies which were included after the network meta-analysis feasibility assessment are listed in CS Table 13 (2 studies on first-line therapies) and CS Table 14 (26 studies on second-line therapies).

One of the studies listed as being excluded is the single-arm atezolizumab study Imvigor 210, although the company has included Imvigor 210 in their network meta-analysis. Imvigor 210 has both first-line (1L) and second-line (2L) cohorts and is therefore listed twice in CS Appendix 8.2, meaning that the actual number of excluded studies of comparators was 14 (6 on first-line therapies, 8 on second-line). The ERG has checked and concurs with the company's reasons for excluding these 14 studies, with the exception of a study by Meluch et al. (2001).[34] Appendix 8.2 of the CS states that the Meluch study was excluded due to having no predictors; however, age (median and range), sex, and ECOG performance status were reported (the study contained a mix of first-line and second-line patients so we believe it would not meet the eligibility criteria).

The CS states that for time-to-event analyses (i.e. overall survival and progression-free survival), Kaplan-Meier curves were required, and any studies listed in CS Table 13 and CS Table 14 which were not included in network meta-analysis had been excluded due to unavailability of Kaplan-Meier curves (CS section 4.10.5 and clarification response A10). By comparing these tables in the CS it can be deduced that 21 studies (all on second-line therapies) had been excluded due to 'unavailability of Kaplan-Meier curves'. The ERG checked these 21 studies (listed in Appendix 1) and we found that 13 of them did report Kaplan-Meier curves and, therefore, appear to have been inappropriately excluded from the network meta-analysis. However, these studies were on second-line comparators which do not appear to meet the company's final criteria for inclusion (gemcitabine, MVAC, gemcitabine + paclitaxel, carboplatin + paclitaxel, vinflunine). A possible exception is a study by Ko et al. 2013[35] which was on nab-paclitaxel. This study appears to meet the inclusion criteria, since paclitaxel is a relevant comparator (Appendix 1); however, the ERG's clinical expert advisor suggested that the nab (nanoparticle albumin bound) formulation of paclitaxel is rarely, if ever, used for urothelial carcinoma and as such it would be reasonable to exclude it as a comparator.

A further discrepancy in the screening process is that the company's network meta-analyses of overall survival and progression-free survival included different comparators, despite data being available for both outcomes in several studies. As shown in Table 5 below, the overall survival analysis included docetaxel, paclitaxel, and best supportive care, which is consistent with the NICE scope and the company's decision problem. However, in addition to these comparators the company's progression-free survival analysis included gemcitabine, carboplatin + paclitaxel, and vinflunine which are not NICE scoped comparators. Inconsistently, the company's progression-free survival analysis did not include studies by Vaishampayan et al. 2005[36] on carboplatin + paclitaxel or Vaughn et al. 2009[37] on vinflunine (Appendix 1).

As noted above (section 3.1.1), the ERG identified 18 further publications (each describing a single study) which appeared, on title and abstract, to be potentially eligible for inclusion but which are not cited or referenced anywhere in the CS. The company explained (clarification request A11) that 16 of these publications had been identified and screened, then were subsequently excluded; and two were not published at the time of the company's searches in June 2016. The company's clarification response explains the reasons for exclusion; after consulting the full publications the ERG agrees that these studies would be excluded, although in some cases for different reasons to those stated by the company.

The ERG notes that two studies on second-line paclitaxel are available. One by Ko et al. 2013,[35] was on nab-paclitaxel and (as mentioned above) was excluded from the company's overall survival analysis. The other, by Lee et al. 2012,[38, 39] was on a polymeric micelle formulation of paclitaxel and was included in the overall survival analysis. The CS does not discuss the relevance to current clinical practice of any of the chemotherapy formulations in the studies that they included, and we are unclear whether the polymeric micelle formulation of paclitaxel would have similar effectiveness and tolerability compared to standard paclitaxel chemotherapy.

ERG conclusion on the company's screening process

The eligibility screening process is poorly reported and has been applied inconsistently, with: 16 of the screened studies not being referenced in the CS; 13 studies apparently being excluded for reasons other than those stated in the CS; and inconsistent inclusion/exclusion of studies according to the outcome being analysed.

The bottom line for the overall survival analysis appears to be that no key studies have been missed. It is unclear, however, whether the only included paclitaxel study, which used a polymeric micelle formulation, is representative of standard paclitaxel chemotherapy.

For the progression-free survival analysis, the company included comparators which are not specified in the NICE scope or the company's decision problem. The ERG believes this is not a major concern for the current technology appraisal, since the progression-free survival analysis is not used by the company to support the clinical effectiveness of atezolizumab or to inform the economic analysis.

3.1.3 Identified studies

Following the eligibility screening process reported above (section 3.1.2), the company included one single-arm atezolizumab study (Imvigor 210) and 10 comparator studies in their network meta-analysis (Table 5). No RCTs of atezolizumab were identified. As well as being used in the network meta-analysis, Imvigor 210 is reported separately in the CS as being the primary source of efficacy and safety data for atezolizumab (CS section 4.11).

Some RCTs with one or more relevant comparator arms were identified but the majority of the comparator studies which met the eligibility criteria were single-arm studies. As described above

(section 3.1.2), the progression-free survival analysis included studies on comparators which are not specified in the NICE scope or company's decision problem.

Table 5 Comparator study arms included in network meta-analysis

Outcome	Position in the treatment pathway	
	First-line (cohort 1 in atezolizumab study Imvigor 210 [40])	**Second-line (cohort 2 in atezolizumab study Imvigor 210 [41])**
OS (informs company's economic model)	GEM + CAR (Bamias et al.[42]) GEM + CAR [a] (De santis et al.[19, 43, 44])	BSC [a] (Bellmunt et al.[21, 45]) BSC [a] (Noguchi et al.[46, 47]) DOC (Kim et al.[48, 49]) DOC + PBO [a] (Choueiri et al.[50]) PTX (Lee et al.[38, 39])
PFS (does not inform company's economic model)	GEM + CAR (Bamias et al.[42])	BSC [a] (Bellmunt et al.[21, 45]) BSC [a] (Noguchi et al.[46, 47]) DOC (Kim et al.[48, 49]) DOC + PBO a (Choueiri et al.[50]) GEM (Albers et al.[51]) [b] PTX (Lee et al.[38, 39]) Nab-PTX (Ko et al.[35]) [b] CAR + PTX (Kouno et al.[52]) [b] VFL [a] (Bellmunt et al.[21, 45])

BSC: best supportive care; DOC: docetaxel; CAR: carboplatin; GEM: gemcitabine; Nab: nanoparticle albumin bound; PBO: placebo; OS: overall survival; PFS: progression-free survival; PTX: paclitaxel; STC: simulated treatment comparison

[a] single arm from a randomised controlled trial

[b] reports both OS and PFS curves but included only in the PFS analysis (CS Appendix 8.5)

The CS additionally reports a single-arm phase Ia study of atezolizumab (PCD49089g) which the company has cited as a source of some supporting information on atezolizumab efficacy and safety. We note that since PCD49089g is a phase I study it does not meet the company's eligibility criteria (as listed in CS Table 10) and also the cohort was heavily pre-treated and most patients did not receive the licensed dose of atezolizumab (as indicated by the company in clarification response A41). We have summarised the characteristics and effectiveness results of study PCD4989g in Appendix 2.

Only those studies which met the eligibility criteria for network meta-analysis according to the NICE scope and company's decision problem are summarised here.

3.1.3.1 Atezolizumab study: Imvigor 210

Design characteristics of the Imvigor 210 study are given in CS Table 27, which we have summarised below in Table 6.

Eligibility criteria

The CS provides an extensive list of the inclusion and exclusion criteria for the first-line and second-line cohorts of Imvigor 210 (CS Table 28). Due to the large number of criteria provided these are not reproduced fully here, but key criteria are summarised in Table 7 and Table 8.

Participant flow

Section 4.11.5 of the CS (Participant flow) does not provide the flow of the study participants (i.e. the numbers of participants who were screened, enrolled, treated and analysed) in Imvigor 210. However, diagrams showing the participant flow are provided in the study publications for the first-line cohort[40] and the second-line cohort.[41] Due to copyright restrictions these flow diagrams are not reproduced here.

Of 167 participants screened for eligibility for the first-line (cisplatin-ineligible) cohort, 44 were ineligible and were excluded before enrolment. Ineligibility reasons were clearly reported and appear appropriate for 24 of these people, but were reported only as 'all other reasons' for the remaining 20.[40] A total of 123 participants were enrolled in the first-line cohort, but four participants were excluded after enrolment, with reasons reported. One of these exclusions was due to disease progression before cycle 1, although this does not appear to be one of the pre-specified exclusion criteria (as listed in CS Table 28). The remaining 119 participants received at least one dose of atezolizumab. Of these, 102 subsequently discontinued treatment. Reasons for discontinuation were disease progression (n=77), patient withdrawal (n=12), adverse events (n=11) and unspecified other reasons (n=2). The number of participants remaining on-treatment at the July 2016 data-cut (median follow-up 17.2 months; clarification response A34) was n=17.[40]

Table 6 Key design characteristics of the IMvigor 210 study

Location	Patients were recruited from 70 centres in North America and Europe, including 3 sites in the UK.
Design	Single-arm open-label phase II study
Eligibility criteria for participants	Patients with locally advanced or metastatic urothelial carcinoma were enrolled regardless of their PD-L1 expression, or number of prior therapies (from first-line cisplatin-ineligible patients to heavily-treated patients with exposure to multiple prior regimens). Patients were enrolled into one of two cohorts: **Cohort 1:** chemotherapy-naïve patients who are cisplatin-ineligible (N=119) **Cohort 2:** patients who have progressed during or after at least one platinum chemotherapy regimen (N=310)
PD-L1 subgroups	Baseline PD-L1 expression in tumour specimens was centrally evaluated using the VENTANA PD-L1 (SP142) immunohistochemistry assay (Ventana Medical Systems, Mountain View, California, US). PD-L1 expression on IC was evaluated based on three scoring levels: • IC2/3, ≥5% PD-L1 expression in immune cells • IC1, ≥1% and <5% PD-L1 expression in immune cells • IC0, <1% PD-L1 expression in immune cells
Trial drugs, permitted and disallowed concomitant medication	Single-agent atezolizumab 1200 mg administered by intravenous infusion on day 1 of each 21-day cycle until disease progression according to RECIST v1.1 criteria (Cohort 1 only) or until lack of clinical benefit (Cohort 2)
Patient monitoring	Patients had tumour assessments at baseline, every 9 weeks for 12 months, and every 12 weeks thereafter. Patients who discontinued treatment continued follow-up assessments for survival and subsequent anti-cancer therapy every ≈3 months until death, loss to follow-up, withdrawal of consent, or study termination, whichever occurred first.
Primacy outcomes	Co-primary endpoint: [a] • Independent review facility-assessed ORR (confirmed) according to RECIST v1.1 criteria (central independent review; Cohort 1 & 2), and; • Investigator-assessed ORR (according to modified RECIST criteria; immune-related response criteria [Cohort 2 only]).
Secondary outcomes	DOR and PFS assessed by the independent review facility and investigator according to RECIST v1.1 criteria, OS, and 1-year OS. DOR and PFS according to modified RECIST criteria will be additional secondary endpoints. The efficacy endpoints as assessed by modified RECIST criteria are applicable only to Cohort 2.

DOR: duration of response; ORR: objective response rate; OS: overall survival; PD-L1: programmed death ligand 1; PFS: progression-free survival; RECIST: response evaluation criteria in solid tumours

[a] Reference for the primary outcome was a 10% historical control rate (see section 3.1.6)

Table 7 Key inclusion criteria for the Imvigor 210 atezolizumab study

First-line (1L) cohort	Second-line (2L) cohort
● ECOG performance status 0, 1 or 2. ● No prior chemotherapy for inoperable locally advanced or metastatic or recurrent urothelial carcinoma. ● For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, > 12 months treatment free between the last treatment administration and the date of recurrence was required in order for participants to be considered treatment naive in the metastatic setting. ● Ineligible ('unfit') for cisplatin, as per specified criteria in CS Table 28.	● ECOG performance status of 0 or 1. ● Disease progression during or following treatment with at least one platinum containing regimen (e.g., GEM, MVAC, GEM + CAR) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence. A regimen is defined as patients receiving ≥2 cycles of a platinum containing regimen. Patients who received one cycle of a platinum-containing regimen but discontinued due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity may also be eligible ● Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/ neo-adjuvant regimen will be considered as 2L patients. Patients with progression after chemo-radiotherapy must demonstrate progression outside the prior radiotherapy port.
● Historically or cytologically documented advanced or metastatic urothelial carcinoma of the bladder, renal pelvis, ureters or urethra; locally advanced bladder cancer must be inoperable. ● Availability of viable tumour specimens as defined in CS Table 28. ● Life expectancy ≥12 weeks. ● Measurable disease as defined by RECIST v.1.1. ● Adequate haematologic and end-organ function (not defined).	

CAR: carboplatin; ECOG: Eastern Cooperative Oncology Group; GEM: gemcitabine; MVAC: methotrexate, vinblastine, doxorubicin & cisplatin combination; RECIST: response evaluation criteria in solid tumours

Of 486 participants screened for eligibility for the 2L (platinum-treated) cohort, 170 were excluded before enrolment. Ineligibility reasons are clearly reported for 134 of these and appear appropriate, but are reported as 'other reason' with no further detail for the remaining 36.[41] A total of 316 participants were enrolled in the 2L cohort, of which 311 received atezolizumab treatment. The five who did not receive atezolizumab were stated not to have met the eligibility criteria, but no reasons are given). One participant was excluded after receiving atezolizumab, due to being not evaluable because of incorrect cohort assignment, although results are reported in the CS for all 311 patients. Of the remaining participants, 248 subsequently discontinued treatment, due to disease progression (n=211), adverse events (n=13), patient withdrawal (n=9) and unspecified other reasons (n=15). The number of participants remaining on-treatment at the September 2015 data-cut (median follow-up 11.7 months; clarification response A34) was n=62.[41]

According to the publications,[40, 41] one first-line cohort participant was re-assigned to the second-line cohort and two second-line participants were re-assigned to the first-line cohort between the May 2015 and September 2015 data cuts.

Table 8 Key exclusion criteria for the Imvigor 210 atezolizumab study

1L and 2L cohorts
● Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment (exceptions: palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging; hormone-replacement therapy or oral contraceptives). ● Active or untreated CNS metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments (patients with treated asymptomatic CNS metastases are eligible, provided they meet all of the criteria specified in CS Table 28). ● Uncontrolled tumour-related pain. ● Comorbidities as specified in CS Table 28, including: leptomeningeal disease; uncontrolled pleural effusion; pericardial effusion; ascites requiring recurrent drainage procedures (≥1 per month); active tuberculosis; active hepatitis B or C; positive test for HIV; severe infections within 4 weeks of starting atezolizumab, or infection signs and symptoms within 2 weeks; history of autoimmune disease; history of specified respiratory diseases including idiopathic pulmonary fibrosis, pneumonia, pneumonitis. ● Allergic hypersensitivity to specified antibodies or biopharmaceuticals. ● Uncontrolled hypercalcaemia, or symptomatic hypercalcaemia requiring specified therapies. ● Low serum albumin as defined in CS Table 28. ● Any other evidence of or suspicion of diseases or metabolic dysfunction that would contraindicate use of an investigational drug, affect the interpretation of the results, or render the patient at high risk from treatment complications. ● Medication-related exclusion criteria as specified in CS Table 28 for stated time periods prior to the initiation of atezolizumab treatment (or anticipated need for): CD137 agonists or immune checkpoint blockade therapies; systemic immune-stimulatory agents (e.g. interferons); systemic corticosteroids or other systemic immunosuppressive medications; antibiotics. ● Prior allogeneic stem cell or solid organ transplant. ● Significant cardiovascular disease as specified in CS Table 28. ● Major surgical procedure other than for diagnosis within 4 weeks of starting atezolizumab, or anticipated need for such procedure during the study. ● Receipt of live attenuated vaccine within 4 weeks of starting atezolizumab, or anticipated need for vaccine during the study.

Baseline characteristics

Baseline characteristics of the participants in Imvigor 210 are reported in CS Table 29 and reproduced here in Table 9, including additional information reported in the publications.[40, 41]

Imvigor 210 was a multinational study conducted in the USA, Canada, France, Germany, Italy, Spain, The Netherlands, and the UK. Five of the participants in the first-line cohort (4.2%) and 17 of the participants in the second-line cohort (5.5%) were in the UK. The CS gives a brief overview of the participants' characteristics (CS section 4.11.5) and concludes that the demographic profiles of each of the first-line and second-line cohort populations are consistent with those observed in the general urothelial carcinoma population in clinical practice, and consistent with patient populations in other recent clinical trials. The ERG's clinical expert advisor agreed that the two populations in Imvigor 210 are generalisable to those with advanced or metastatic bladder cancer in England. Median age was 73 years for participants in the first-line cisplatin-ineligible cohort and 66 years in the second-line platinum-treated cohort, with the youngest patients in each cohort being aged 51 years and 32 years respectively. In both cohorts the majority of the participants were male, and in the second-line cohort the majority were of white ethnicity, although ethnicity is not reported for the first-line cohort.

The CS points out that in the first-line cohort the most common reason for patients being cisplatin ineligible was impaired renal function (69.7% of participants had GFR <60 mL/min), and that the baseline characteristics are representative of patients with poor prognostic factors, including ECOG performance status =2 (20.2%), visceral metastasis (65.5%), liver metastasis (21.0%) and creatinine clearance < 60 mL/min (70.6%).

As shown in Table 9, 15.1% of the patients in cohort 1 (cisplatin-ineligible) had received prior cisplatin therapy. The CS states that this is likely to be due to treatment with cisplatin in the neoadjuvant setting, and following progression patients are subsequently deemed cisplatin ineligible at the time of selecting first-line treatments in the metastatic setting.

In the 2L cohort the majority of participants had visceral metastases (78.4%), with approximately one third having liver metastases (31.0%) and two thirds having ECOG performance status of 1. The CS points out that approximately 40% of participants in the 2L cohort had received ≥2 regimens in the metastatic setting, indicative of a heavily pre-treated population. A prior cisplatin-based regimen had been received by 73% of participants, whilst 26% had received carboplatin alone. The CS states, and the ERG's clinical expert advisor agreed, that this is broadly representative of UK clinical practice in metastatic urothelial carcinoma.

We note that a relatively high proportion of the participants in Imvigor 210 had upper tract urothelial carcinoma, i.e. the primary tumour site was the renal pelvis or ureters: 27.7% in the first-line cohort and 22.2% in the 2L cohort. This is higher than the expected 'real world' proportion of upper tract urothelial carcinomas which is usually given as being around 5-10%.[2] Upper tract carcinomas are more likely to be invasive at diagnosis and have a worse prognosis than those which arise in the bladder.[2]

Table 9 Baseline characteristics of participants in the Imvigor 210 study

	Cohort 1 (1L) Cisplatin-ineligible n=119	**Cohort 2 (2L) platinum-treated n=310**
Age, years, median (range)	73.0 (51–92)	66.0 (32–91)
Age ≥ 80 years, n (%)	25 (21.0)	24 [a] (7.7)
Sex, male, n (%)	96 (80.7)	241 (77.7)
Primary tumour site, n (%) [b]		
Bladder or urethra	85 (71.4)	239 [a] (76.8)
Renal pelvis or ureter	33 (27.7)	69 [a] (22.2)
Metastatic disease, n (%)	110 (92.4)	291 [a] (93.9)
Visceral sites [c]	78 (65.5)	243 (78.4)
Liver only	25 (21.0)	96 (31.0)
Lymph node only	31 (26.1)	43 (13.9)
Prior therapy, n (%)		
Radiotherapy	12 (10.1)	99 [a] (31.9)
Perioperative chemotherapy [d]	22 (18) [e]	56 [a] (18.0)
Cisplatin-based	18 [a] (15.1)	227 (72.9)
Carboplatin-based	1 [a] (0.8)	80 (26.1)
Number of prior regimens (metastatic setting)	n=0, 98.3% n=1, 1.7%	n=0, 18.1% n=1, 39.0% n=2, 21.3% n≥3, 21.6%
Prior cystectomy or nephroureterectomy	80 (67.2) [f]	228 [a] (73.5)
Haemoglobulin ≤ 10 g/dl	19 (16.0) [f]	69 [a] (22.3)
PD-L1 expression immunohistochemistry subgroups (%)		
IC0 (PD-L1 expression <1%)	32.8	33.2%
IC1 (PD-L1 expression ≥1 but <5%)	40.3	34.5

IC2/3 (PD-L1 expression ≥5%)	26.9	32.2
IC1/2/3 (PD-L1 expression ≥1%)	67.2	66.8

Table 9 continued	**Cohort 1 (1L) Cisplatin-ineligible n=119**	**Cohort 2 (2L) platinum-treated n=310**
ECOG PS 0	45 [a] (37.8)	117 (37.7)
ECOG PS 1	50 [a] (42.0)	193 (62.3)
ECOG PS 2	24 (20.2)	1 [a] (0.3)
Renal impairment, GFR <60 and >30 mL/min	83 (69.7)	108 or 109 [a] (35)
Hearing loss, 25 dB[f]	17 (14.3)	Not reported
Peripheral neuropathy, ≥Grade 2	7 (5.9)	Not reported
Renal impairment and ECOG PS 2	8 (6.7)	Not reported

ECOG: Eastern Cooperative Oncology Group; GFR: glomerular filtration rate; PS: performance status
[a] number not reported in CS or publication; estimated from percentage by ERG
[b] excluding 1 participant with primary tumour site prostatic urethra
[c] liver, lung, bone, any non-lymph node or soft tissue metastasis
[d] adjuvant or neoadjuvant treatment with first disease progression beyond 12 months (except for 1 participant who received targeted therapy)
[e] as reported in the publication[40] (CS reports percentage = 20.2)
[f] provided by the company in clarification response A44

3.1.3.2 Comparator studies

The CS does not provide the baseline characteristics of the comparator studies, except in relation to whether the studies reported four prognostic variables (proportion with age > 65 years, proportion male, proportion with liver metastases, and proportion with ECOG performance status ≥1) (CS Table 17). In response to a clarification request by the ERG and NICE (clarification response A25), the company provided tables summarising the characteristics of the comparator studies. However, the tables focus mainly on methodological aspects of the studies and they report very little information on the participants' characteristics. Whilst this partly reflects a paucity of information reported by the primary studies, there is more information available in the study publications that could have been provided. The ERG has consulted the study publications and we have summarised the available information on the participants' characteristics for the first-line studies in Table 10 and for the second-line studies in Table 11.

Table 10 Baseline characteristics of participants in the first-line comparator studies

Baseline characteristic	Bamias et al.[42]	De Santis et al.[19, 43, 44]
Study design	Single arm	RCT
Regimen (number of participants) Data are reported for **bold** arms	**GEM + CAR (n=34)**	**GEM + CAR (n=119)** M-CAVI (n=119)
Age, years, median (range)	75.5 (57–84)	70 (36–87)
Age, proportion >65 years	-	-
Sex, male, n (%)	28 (82)	90 (75.6)
Primary tumour site, n (%): bladder	30 (88)	90 (75.6)
renal pelvis	3 (9)	12 (10.1)
ureter	1 (3)	12 (10.1)
urethra	0 (0)	3 (2.5)
other (unspecified)	0 (0)	2 (1.7)
ECOG PS 0, n (%)	11 (32)	20 (16.8) [a]
ECOG PS 1, n (%)		46 (38.7) [a]
ECOG PS 2, n (%)	-	53 (44.5) [a]
ECOG PS ≥2, n (%)	23 (68)	-
With comorbidities, n (%)	22 (65) [b]	59 (49.6) [c]
Haemoglobin <10 mg/dl, n (%)	5 (15)	-
Any metastases, n (%)	-	-
Visceral metastases, n (%)	15 (44)	55 (46.2)
Liver metastases, n (%)	-	20 (16.8)
Median follow up, months	8	54
Adjuvant or neoadjuvant therapy, n (%)	6 (17.6)	0 (0)

- (dash) indicates data not reported; CAR: carboplatin; GEM: gemcitabine; ECOG: Eastern Cooperative Oncology Group; MCAVI: methotrexate + carboplatin + vinblastine; PS: performance status; WHO: World Health Organisation

[a] reported as WHO PS score (which is the same as ECOG PS score)

[b] described as comorbidities precluding cisplatin therapy

[c] described as associated chronic disease

As can be seen in Table 10, it is difficult to determine whether the two studies of first-line gemcitabine + carboplatin were homogeneous because the studies used different criteria for describing the participants' characteristics, or did not report some key characteristics. Both studies enrolled predominantly men (75.6% to 82%); most primary tumours (75.6% to 88%) were in the bladder; and just under half the participants in each study (44% to 46.2%) had

visceral metastases. Participants in the Bamias et al. study[42] were older than those in the De Santis et al. study[44] (median age 75.5 versus 70 years) and a higher proportion had comorbidities (65% versus 49.6%), although the proportion of patients with ECOG performance status 0 or 1 was lower in the Bamias et al. study (32% versus 55.5%). However, the definitions of comorbidities were not identical in the studies. Only Bamias et al. permitted prior adjuvant or neoadjuvant therapy (received by 17.6% of patients). We note that the study by Bamias et al. had a relatively small sample size (n=34) compared to that of De Santis et al. (n=119).

The summary of participant characteristics for the five studies of second-line comparators (Table 11) shows that it is difficult to compare these studies in detail, as different criteria were used to describe the participant populations, and some studies did not report key information. For age, the studies either reported the proportion of participants aged ≥65 years (three studies; range 45.8 to 49 years), or the median age (three studies; range 57 to 65 years) (one study reported both measures). Four studies reported that the participants were predominantly male (68.1% to 80%) whilst Bellmunt et al.[21] did not report this. Only the studies by Kim et al.[49] and Lee et al. [39] reported the primary sites of the carcinoma, which was most frequently in the bladder (58% to 70%), though in both these studies nearly a quarter (23% to 24%) of the tumours originated in the ureters. The studies all included patients with ECOG performance score 0 or 1, apart from Lee et al.[39] which included 14% of patents with performance score 2. Four studies (except Lee et al.[39]) reported the proportion with haemoglobin concentration <10 mg/dl, and this ranged from 8.5% to 22%. Four studies (except Noguchi et al.[47]) reported the proportion with visceral metastases, which ranged from 61% to 74%, whilst three studies (excluding Bellmunt et al.[21] and Noguchi et al.[47]) reported liver metastases, which ranged from 30% to 37.5%. The median follow-up in the second-line comparator studies varied considerably, from 3.2 to 45 months. Sample sizes were relatively small in three studies by Kim et al., Lee et al. and Noguchi et al. (31 to 41 participants) but larger in the studies by Choueiri et al. (n=75) and Bellmunt et al. (n=117).

The bottom half of Table 11 contains sparse information because several characteristics of the study populations (e.g. the composition, duration and frequency of previous chemotherapy and radiotherapy treatment regimens, and patients' responses to these), which might have a bearing on patients' tolerance of or response to subsequent therapy, were not reported in the primary studies. Although the NICE scope mentions cisplatin-ineligible patients in the second-line setting, the CS and the company's clarification response A25 do not state whether any of the

patients in the included second-line studies were cisplatin-ineligible. Upon checking the publications we found that none of the five included studies provided this information, and only two of the studies reported the proportion of patients who had received prior cisplatin.

By comparing Tables 9, 10 and 11 it can be seen that the first-line atezolizumab cohort had a greater percentage of patients with ECOG PS = 0-1 compared to the first-line gemcitabine + carboplatin studies (79.8% versus 32.0 % in Bamias and 55.5% in De Santis) and a greater percentage with visceral metastases (65.5% versus 44.0% in Bamias and 46.2 in De Santis). The second-line atezolizumab cohort had a greater percentage of patients with visceral metastases than the four comparator studies where this outcome was reported (78.4% versus a range of 61% to 74% in the comparators) but the percentage with liver metastases was within the range of the four comparator studies which reported this (31% versus a range of 15% to 37.5%).

Of the two second-line studies that included best supportive care arms, Bellmunt et al.[21, 45] did not provide a definition of best supportive care, whilst Noguchi et al.[46, 47] stated '*BSC was including palliative radiotherapy, antibiotics, analgesics, corticosteroids, and transfusion*.'

Overall, due to the paucity and inconsistency of the available information on participants' baseline characteristics, it is difficult to be certain whether the second-line studies were adequately homogeneous to be eligible for the company's network meta-analysis; or whether any individual studies had particularly better or worse prognostic characteristics that might suggest a need for further exploration in sensitivity analyses.

Table 11 Baseline characteristics of participants in the second-line comparator studies

	Bellmunt et al.[21, 45]	**Choueiri et al.[50]**	**Kim et al.[48, 49]**	**Lee et al.[38, 39]**	**Noguchi et al.[46, 47]**
Study design	RCT	RCT	Single arm	Single arm	RCT
Regimen (number of participants) *Data in this table are for the arms shown in* ***bold***	VFL + BSC (n=253) **BSC (n=117)**	DOC + vandetanib (n=74) **DOC + PBO (n=75)**	**DOC (n=31)**	**PTX (n=37)**	PPV + BSC (n=39) **BSC (N=41)**
Age, years, median (range)	-	-	64 (40-79)	57 (44-78)	65 (46-81)
Age, proportion ≥65 years	57 (49)	33 (45.8)	15 (48)	-	-
Sex, male, n (%)	-	49 (68.1)	24 (77)	29 (78)	33 (80)
Primary site, n (%): bladder	-	-	18 (58)	26 (70)	-
renal pelvis	-	-	6 (19)	2 (5)	-
Ureter	-	-	7 (23)	9 (24)	-
Urethra	-	-	0 (0)	0 (0)	-
other (unspecified)	-	-	0 (0)	0 (0)	-
ECOG PS 0, n (%)	45 (38)	37 (47.2) [a]	0 (0)	14 (38)	33 (80)
ECOG PS 1, n (%)	72 (62)	38 (52.8)	31 (100)	18 (48)	8 (20)
ECOG PS 2, n (%)	0 (0)	0 (0)	0 (0)	5 (14)	0 (0)
Haemoglobin <10 mg/dl, n (%)	14 (12)	6 (8.5)	7 (23)	-	9 (22)
Any metastases, n (%)	-	-	-	-	41 (100)
Visceral metastases, n (%)	87 (74)	46 (63.9)	19 (61)	23 (62)	-
Liver metastases, n (%)	-	27 (37.5)	10 (32)	11 (30)	Liver/bone 6 (15)
Median follow up, months	45	7.1	37.6	16.6	3.2
1L setting, n (%): metastatic	-	-	29 (94)	30 (81)	15 (37) [b]
perioperative (neo/adjuvant)	-	-	2 (6)	17 (46) [c]	14 (34) [b]
1L response: complete or Partial	-	-	17 (55)	11 (30)	-

stable disease	-	-	9 (29)	5 (14)	-
progressive disease	-	-	3 (10)	6 (16)	-
not evaluable	-	-	2 (6)	15 (41) [d]	-
Cisplatin-ineligible	-	-	-	-	-
Prior cisplatin, %	72.6 [e]	-	94 [f]	- [g]	-
Prior taxane	-	Only PTX (11.1%)	-	None permitted	-
Prior palliative chemotherapy	-	-	-	31 (84)	-
Prior radiotherapy, %	-	20.8	-	-	12
Platinum-free interval	-	-	< 3 months: 36%	< 3 months: 43% ≥6 months: 27%	-
Treatment sequence information	-	Prior therapies: >1: 28 (38.9) >2: 10 (13.9)	Setting: 2L: 26 (84) 3L: 5 (16)	-	Prior therapies: [h] 1: 10 (35) ≥2: 5 (17)

- (dash) indicates data not reported; BSC: best supportive care; DOC: docetaxel; ECOG: Eastern Cooperative Oncology Group; PBO: placebo; PPV: personalised peptide vaccination; PS: performance score; PTX: paclitaxel; VFL: vinflunine

[a] deduced by ERG from eligibility criteria

[b] publication reports prior chemotherapy setting for only 29 of the 41 patients; % values calculated by ERG

[c] publication reports 2 values; ERG believes this one is correct

[d] not evaluable or no evidence of disease

[e] 72.6% received cisplatin and no other platinum; 19.7% carboplatin; 7.7% other (unspecified) platinum combination

[f] of which 87% had received GEM + CIS

[g] 11.1% had received salvage MVAC (methotrexate + vinblastine + doxorubicin + cisplatin) after prior failure of GEM + CIS

[h] prior chemotherapy for advanced bladder cancer

Ongoing trials

The CS reports that there are two ongoing phase III studies, one planned phase III study and one ongoing phase Ib/2 study which have relevance to the current appraisal (CS section 4.14).

- IMvigor 211 (phase III, ongoing) is comparing atezolizumab against investigator's choice of chemotherapy (vinflunine, docetaxel or paclitaxel) in metastatic urothelial carcinoma in a second and third line setting. Completion is expected in November 2017.
- IMvigor 130 (phase III, planned) will evaluate the safety and efficacy of atezolizumab ± gemcitabine/carboplatin compared against gemcitabine/carboplatin in cisplatin-ineligible patients with metastatic urothelial carcinoma in a first-line setting. Completion is expected in June 2020.
- WO29635 (phase Ib/2, ongoing) is a study in non-muscle-invasive bladder cancer of the safety, pharmacokinetics, immunogenicity, patient reported outcomes, and preliminary anti-tumour activity of atezolizumab administered as a single agent and in combination with Bacille Calmette-Guérin vaccine (BCG) in patients with BCG-unresponsive non-muscle-invasive bladder cancer, and in combination with BCG in patients with BCG relapsing, and very high risk, BCG-naive non-muscle-invasive bladder cancer.
- IMvigor 010 (WO29636) (phase III, ongoing) is a study in muscle-invasive bladder cancer on patients selected according to their PD-L1 status which is comparing atezolizumab as an adjuvant therapy against observation alone.

The ERG's update searches (section 3.1.1) did not identify any further ongoing studies.

3.1.4 Description and critique of the approach to validity assessment

Section 4.11.6 of the CS is titled 'Quality assessment of non-randomised evidence' but does not report quality assessment. Section 4.11.7 of the CS is titled 'Methods for assessing risk of bias' but states only that the risk of bias was not assessed for Imvigor 210 as it was a single-arm study. However, an earlier section describing the methods of the network meta-analysis (CS section 4.10.6) describes a method for quality assessment, referring to CS Appendix 8.3 where a quality assessment for the Imvigor 210 study is reported. This was undertaken separately for the two publications for each cohort in the study and also for the clinical study report, and was adapted from a National Institutes for Health (NIH) tool for case series studies.[53] There is no discussion of why this was adapted, or the appropriateness of using a case series study quality

tool when the NIH has tools available for all types of observational studies. One question from the tool that was not applied by the company was 'were the cases consecutive?'.

The CS provides several summary tables of quality assessment in CS Appendix 8.3. Several of the tables are un-numbered and no explanation of the different tables is provided. The CS conducted quality assessments of the studies used in their network-meta analysis, using three approaches:

- The adapted NIH questions for case series studies, applied to the single-arm studies;
- NICE risk of bias questions for RCTs (also applied to the single-arm studies if an individual question was appropriate);
- Cochrane risk of bias questions for RCTs (also applied to the single-arm studies if an individual question was appropriate).

Given that the CS states that no RCT evidence was identified (CS section 4.11.9) it is unclear why so much emphasis was placed on tools for assessing RCTs, and why both the NICE and Cochrane tools for RCTs were considered necessary. The CS presents the results of the three approaches for assessing study quality separately, which makes it difficult to identify the 'bottom' line key issues about study quality. An overall summary of the quality assessments is provided in CS Figure 4 but this arbitrarily classifies studies as having 'high', 'moderate to high'. 'moderate', 'low to moderate' or 'low' quality. These categories are not explained and do not indicate whether there are threats to validity (i.e. risks of systematic errors or lack of generalisability). The ERG and NICE requested explanation of the quality assessment process (clarification question A26) but the company's response does not define their decision criteria for the different study quality classes.

The company has not used their quality assessment to inform other aspects of the submission, and there is no discussion provided as to whether study quality would affect the eligibility of studies for inclusion in the network meta-analysis. According to the company's summary in CS Figure 4 there was 'moderate to high' heterogeneity within studies which were subsequently included in their meta-analysis. The company stated (clarification response A24) that it was necessary to include studies of heterogeneous populations due to the lack of alternative data.

The ERG has assessed the relevant arm of each included study using the NIH tool because the studies are used as single-arm studies in the company's analysis and the questions regarding

risk of bias for RCTs are therefore redundant. The ERG considers that three questions from an NIH appraisal tool for before-and-after studies[54] are also relevant (enrolment of all eligible participants, blinding of outcome assessors, and sample size) as these address potential threats to validity or reliability. These additional three questions have therefore been assessed by the ERG for each study.

The ERG's detailed quality assessment of the atezolizumab studies, first-line comparator studies and second-line comparator studies is tabulated in Appendix 3 (Table 54 to Table 56). For Imvigor 210 the ERG has checked the criteria for the study as a whole, not the individual publications as assessed by the company. Quality assessment of the phase I study PCD4989g is not reported in the CS and the company explained that this was because the study only provides descriptive supporting information (clarification response A27).

As shown in Appendix 3, the ERG generally agrees with the company's assessment (where reported) of these studies, although our assessment differs on the question of whether all subjects were comparable. This is because the NIH tool gives no guidance on what this question is assessing; for this question we have assessed studies on how comparable the populations are to the NICE scope.

For the additional ERG questions, it is unclear whether sample sizes in the Bamias et al. and Noguchi et al. studies would be adequate to provide confidence in the findings since they were determined on response rates rather than survival outcomes. If based on sample sizes, confidence in the findings would be highest for the studies by De Santis et al., Bellmunt et al. and Chouieri et al., which had 75-119 participants, than the remaining studies which had only 31-41 participants. None of the studies reported using blinded outcome assessors. Three studies (De Santis 2012, Choueiri 2012, Noguchi 2014) were assessed as enrolling all eligible participants that met the pre-specified entry criteria into the study. The remaining studies did not present enough information to assess this question.

In summary, the ERG believes that the main validity issue for the included studies is the lack of direct head-to-head randomised studies comparing atezolizumab to relevant comparators and uncertainty as to how similar the baseline characteristics of the studies are, given the limited available information.

3.1.5 Description and critique of the company's outcome selection

The NICE scoped outcomes of overall survival, progression-free survival, response rates and adverse effects of treatment were measured in IMvigor201 and PCD4989g. The NICE scoped outcome of HRQoL was not reported in any of the primary studies making up the evidence base, although this is not made clear in the company's decision problem.

Efficacy results are presented in the CS for various data-cuts (which we have summarised in section 3.3). In the Imvigor 210 study, objective response rate was the primary outcome. This was assessed by an independent review facility (IRF) using the RECIST (Response Evaluation Criteria In Solid Tumours) v1.1 criteria which is a standard approach for determining tumour size.[55] In cohort 2 investigator-assessed modified RECIST immune response criteria were also used which quantify only the viable portions of the tumour (references are provided[56, 57]). The CS states that the modified criteria are not yet used in standard practice (CS section 4.13.2). In clarification response A35 the company stated that the rationale for using the modified RECIST criteria was to account for the possibility of 'pseudoprogression' (i.e. where tumour size reflects immune cell infiltration rather than active cancer), and the potential for delayed anti-tumour activity.

The ERG has focused on reporting outcomes for the most recent data-cut and, where reported, we present results obtained using both RECIST methods. We have focused on the assessments by the independent review facility because these should be at lower risk of bias than investigator assessments. However, the CS does not report whether the independent review facility was blinded to any aspects of the Imvigor 210 study design, and does not explain whether the independent review facility was related to an independent data monitoring committee which is described in CS section 4.11.6. The CS states that there was a high concordance rate between independent review facility and investigator assessments (94%; CS section 4.11.10.3), but does not report results from both assessment approaches for the latest data-cut (20-month follow-up).

Secondary outcomes were the duration of response and progression-free survival assessed using RECIST v1.1 criteria by the independent review facility and investigator; overall survival; and 1-year survival; and these are appropriate endpoints.

Safety outcomes reported in the CS include treatment-emergent adverse events (no definition is provided in the CS or the clinical study report), serious adverse events, and adverse events of special interest. Those of special interest were immune-mediated adverse events and renal function events which are anticipated effects of using a monoclonal antibody therapy. Another possible adverse event of special interest could be infusion related reactions. Rates of these are presented for both cohorts of the Imvigor 210 study, although the CS does not list them as specific events of special interest. Overall, the safety outcomes reported are those that the ERG would expect to be provided for a monoclonal antibody anticancer therapy.

In summary, the ERG considers that the selected outcomes are appropriate to the NICE scope, with the exception that no data on HRQoL were available.

3.1.6 Description and critique of the company's approach to trial statistics

The CS states that effectiveness analyses in IMVigor 210 were performed on the intention-to-treat (ITT) population. This is not defined in the CS but the company explained (clarification response A37) that it refers to enrolled patients who received any amount of study drug. The company also stated in the clarification response that an exception to this involves objective response rate analyses, which were performed on the objective response-evaluable population, defined as ITT patients who have measureable disease per RECIST v1.1 criteria at baseline. The ERG notes that the CS does not present the numbers for the response-evaluable population in cohorts 1 and 2.

The CS reports using a hierarchical fixed-sequence testing procedure to compare the primary endpoint, objective response rate, between atezolizumab and a historical response rate of 10%. Hypothesis testing was carried out on three pre-defined populations (based on decreasing proportion of PD-L1 expression) sequentially on the basis of independent review-assessed objective response rate according to RECIST v1.1 followed by investigator assessed objective response rate according to modified RECIST criteria. If no statistical significance was detected at a particular level in the hierarchy, no further hypothesis testing was done. The ERG agrees that this is an appropriate statistical approach and is consistent with statistical recommendations of the EMEA.[58]

The source and justification of the selected 10% historical control response rate is not specified in the CS or the associated publications. In response to a clarification question from the ERG and NICE (clarification A36), the company provided a justification for using this response rate as a reference and noted that a recent study of nivolumab in metastatic urothelial carcinoma also used a 10% historical control rate to assess effectiveness.[59] The ERG's clinical expert advisor agreed that the company's justification for using a historical control response rate of 10% is reasonable.

The CS reports the statistical power of Imvigor 210 in section 4.11.4, although this appears to relate to the study as a whole, rather than to the individual cohorts on which the analyses are based.

According to the study protocol, [redacted]

A number of data-cuts were conducted for both cohorts in IMVigor 210, which included interim analyses, primary analyses, updated analyses and follow-up analyses (CS Table 26). The CS clearly states which data-cuts are presented throughout the results section.

For cohort 1, primary analyses were undertaken when the last patient enrolled had a minimum of 6 months follow-up (median follow-up 8.5 months, range 0.2 to 14.3 months) and follow-up analyses were undertaken at 15 months (the company stated in clarification response A34 that median follow-up was 17.2 months, range 0.2 to 23.5 months). Response rates at the primary analysis and 15-month follow-up are presented in the CS; overall survival, progression-free survival and adverse events are presented at the 15-month follow-up only. Interim analyses of cohort 1 were also undertaken but results are not presented in the CS.

For cohort 2, primary analyses were undertaken when the last patient enrolled had a minimum of 6 months follow-up (the company stated in clarification response A34 that median follow-up

was 7.1 months, range 0.23 to 10.61 months) and follow-up analyses were undertaken at 20 months (median 21.1 months, range 0.2 (censored) to 24.5 months). Response rates at the primary analysis and 20-month follow-up are presented in the CS; overall survival, progression-free survival and adverse events are presented at the 15-month follow-up only. 'Updated analyses' of cohort 2 (median follow-up 11.7 months) were also undertaken (CS section 4.11.1) but results are not presented in the CS.

In summary, the company's approach to trial statistics in Imvigor 210 appears appropriate.

Limited details on study PCD4986g are provided in the CS; the company provided the study protocol in response to clarification request A42. Similar methods to IMVigor 210 were used for calculation of overall survival, progression free survival and duration of response.

3.1.7 Description and critique of the company's approach to the evidence synthesis

3.1.7.1 Simulated treatment comparison

In the absence of direct head-to-head comparisons of atezolizumab with the scoped comparators, the company conducted a simulated treatment comparison (STC), also referred to as a 'prediction model' by the CS. An STC can be used to carry out 'unanchored' indirect comparisons, where there is a disconnected treatment network or single-arm studies, and allows adjustment for differences across trials.[60] It is a form of outcome regression and is appropriate for the current evidence base, i.e. where individual patient data are available in one (atezolizumab) population and only aggregate data are available for the comparator populations. The company briefly justifies why they chose to use STC rather than unadjusted (naive) comparisons or a matching-adjusted indirect comparison (MAIC) (CS section 4.10.7). The ERG agrees that STC is the most suitable approach for the available data structure, although, as noted below, the method is strongly dependent on assumptions.[60]

In an STC, a statistical model describing the outcomes in terms of the covariates is fitted to the individual patient data for a treatment of interest (in this case, the intervention, atezolizumab), and used to predict the outcomes that would have been observed in the aggregate target population.[60] This effectively creates an atezolizumab arm within each comparator study, and

the resulting 'predicted controlled trials' can then be incorporated into a network meta-analysis, with atezolizumab as the common link.

The company's approach to the STC prediction model is described briefly in CS section 4.10.8. The first step in the STC analysis approach is to identify the covariates (i.e. the prognostic factors and effect modifiers for survival) that will be used in the prediction model. We note that the assumption of an unanchored STC is that all effect modifiers and prognostic factors are accounted for, which is considered 'largely impossible' to meet, leading to an unknown amount of bias in the unanchored estimate.[60] It is important therefore that as many of the key covariates as possible can be identified and included in the analysis to reduce the bias.

STC prediction covariates

The CS specifies four covariates which they used in their prediction model: the proportions of patients who: were aged > 65 years; were male; had liver metastases; and had ECOG performance status ≥1 (equivalent to Karnofsky performance status ≤90%[61]) (CS Table 17). No justification is given in the CS for any of these covariates being prognostic factors or effect modifiers. The CS states that due to the limited amount of data available in metastatic urothelial cancer, studies were included when ≥1 out of the four predictors were reported, although included studies for comparators of interest all reported a minimum of three of the four factors (CS section 4.10.4).

The CS states (section 4.10.13) that where trials did not report baseline values for the covariates of interest, the missing values were imputed by generating random values from a uniform distribution, with boundaries defined by the range of reported values across the studies included in the analysis. As the company acknowledges in the CS (and also in clarification response A31) this approach has limitations. The ERG believes that a multiple imputation approach would have been more appropriate. Multiple imputation aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them.[62]

In response to a clarification request from the ERG and NICE, the company explained that the age cut-off of ≥65 years was selected as this was considered a clinically important age cut-off, but they did not give any empirical evidence for this (clarification response A17). The company also provided a description of a targeted literature search, not reported in the CS, which they

had conducted to identify relevant prognostic factors (clarification response A16). This search identified liver involvement, ECOG performance status and haemoglobin concentration (<10g/dL) as being relevant prognostic factors based on the literature, and age and sex were thought to be relevant prognostic factors according to the opinion of one Roche internal clinical expert.

The company stated in clarification response A16 that haemoglobin concentration <10g/dL was identified as a prognostic factor but excluded from analysis since trials typically excluded all patients with low baseline haemoglobin. The ERG notes that four out of the five second-line studies that were included by the company for their network meta-analysis did report the proportion of patients with haemoglobin <10g/dL, which ranged from 8.5% to 23% (Table 11).

The ERG's clinical advisor agreed that performance status and age are important prognostic factors; however, they are correlated and the impact of this is unclear. The advisor also suggested that re-treatment interval could be considered as a prognostic factor, if reported.

The company stated in clarification response A18 that IMVigor10 included patients at second and later lines of treatment. Therefore a cut-off of two or more prior chemotherapies was used to assess the impact of having a larger or lower proportion of patients being third-line or more, in contrast to only second-line. This prognostic factor was not selected in the base-case model as it did not improve predictive performance.

The ERG noticed some discrepancies in the proportions of patients with each covariate that are reported in CS Table 17 and we queried these with the company (clarification question A22):

- Data for the proportion with liver metastases in a randomised controlled trial conducted by Bellmunt et al.[21, 45] are available in an abstract but excluded from the analysis. The company stated that this was because the abstract did not meet the inclusion criteria, and they suggested that this omission would not affect the overall results. Liver metastasis data were also omitted for a study conducted by Lee et al.;[38, 39] the company stated this was due to a typographical error but would not affect the overall results.
- The company did not use ECOG performance scores which are reported in a publication for the best supportive care and vinflunine arms of the Bellmunt et al. RCT. The company stated, without providing a rationale, that this was because they instead calculated the weighted mean of covariates across both treatment arms – to adjust for

the study rather than each arm separately, as the prediction model aimed at imputing a hypothetical missing atezolizumab arm for the study as a whole. The ERG notes that this calculation increased the proportion of patients in the best supportive care arm with poorer prognosis (ECOG performance status ≥1) from 0.62 to 0.69, i.e. a slight worsening of the population's prognostic characteristics.

- The ERG queried why the age data for the Bellmunt et al. RCT differ in CS Table 17 from those reported in the publication. The company explained that they imputed the proportion of patients aged >65 years for those studies where only the mean or median were reported (clarification response A21), but exceptionally, for the Bellmunt et al. RCT, the imputed data for age >65 were used as the data available in the paper were unfortunately overlooked.

The CS does not discuss whether the extent of systematic error due to imbalance in unaccounted for covariates is acceptable and no estimates are presented for the degree of likely bias. The CS does, however, note caveats around the estimates and that the outcomes of the network meta-analysis are uncertain, producing 'clinically implausible' results when applied in their economic model without correction.

There is imbalance between the study populations in the four prognostic factors listed in CS Table 17 and this is noted in the CS (CS section 4.10.6). The resulting potential bias reduction that STC would provide compared with an unadjusted (naive) comparison is not reported.

STC prediction models

The CS focuses on the STC for overall survival and progression-free survival outcomes. The company also analysed other endpoints that were not of relevance to the economic model, to more broadly assess the comparative effectiveness of atezolizumab versus other interventions (clarification response A12 and A20). However, the analyses of objective response rate and 12-month survival rate were not used to inform the company's assessment of clinical effectiveness, they did not provide parameters for the economic analysis, and no results for these binary outcomes are provided in the CS. Therefore, only overall survival and progression-free survival analyses are described here.

Cox regression models based on the selected covariates were used to simulate an atrezolizumab arm for each comparator study. The models were fitted to bootstrap samples

from the individual patient data from the atezolizumab Imvigor 210 study. The company tested the fit of nine competing models which included different combinations of the covariates and their interaction terms (CS Table 18). Model selection was based on the best predictive performance as judged using the concordance index (indicating the probability that a patient with longer survival time will have a lower risk score). Model parameters and concordance indices for the overall survival outcome are given in CS Table 20 for first-line treatment comparisons and in CS Table 22 for second-line comparisons. For both the first-line and second-line treatment comparisons the company chose the four-covariate model (age, sex, liver metastasis, performance status) without interactions, as adding interactions did not improve fit. For second-line comparisons the company tested including the number of prior chemotherapies (proportion of patients receiving ≥2 prior chemotherapies) as a fifth covariate but this did not improve fit. The ERG notes that, both for first-line and second-line comparisons, the model fit based on the concordance index did not differ tangibly between the four-covariate model and a model which included only liver metastases and performance status, although this is not discussed in the CS.

The Cox models generated predicted log-hazards over time with their associated standard errors and these were used as predicted atezolizumab data points in the network meta-analysis.

Summary of the ERG's appraisal of the STC

The NICE Decision Support Unit provides recommendations on the methods of simulated treatment comparison analysis.[60] A table showing the ERG's appraisal of the company's approach compared against these recommendations is provided in Appendix 4.

In summary, the ERG has the following concerns about the company's approach to the STC:

- Relatively few covariates were used in the prediction model;
- The selection of the covariates in the prediction model is not well justified and is subject to a number of uncertainties.
- The company used a single data calculation method for imputing missing data; multiple imputation would have been preferable to clarify uncertainty around the plausibility of imputed data values.
- The cumulative impact of small errors and inconsistencies in the data is unclear.

3.1.7.2 Network meta-analysis

Analysis of survival data depends on the assumption of proportional hazards being satisfied, and violations of the assumption can lead to severely biased estimates of expected survival.[63] The validity of the proportional hazards assumption has not been ascertained for comparison of atezolizumab against traditional chemotherapy in urothelial carcinoma. Based on appraisals of immunotherapies in melanoma and non-small cell lung cancer, the company reasons, appropriately, that the proportional hazards assumption is unlikely to hold for comparisons involving atezolizumab (CS section 4.10.9).

Fractional polynomial models

Given the possible violation of the proportional hazards assumption, the company developed fractional polynomial models for their network meta-analysis. Whereas traditional survival analysis represents the treatment by a single parameter, i.e. the hazard ratio, the fractional polynomial approach models the hazard over time and represents the treatment effect with multiple parameters. As such, fractional polynomial models can be an appropriate way to model survival data where the proportional hazards assumption is violated, and are suitable for comparisons where both individual patient data and aggregate patient data are available.[63]

The company conducted their network meta-analysis using a Bayesian framework. The time-to-event data for the comparators were obtained by digitising Kaplan-Meier curves for overall survival and progression-free survival reported in the included studies. The survival proportions for each monthly time interval were extracted and used to calculate the number of patients at risk at the start of each interval and the incident number of deaths. The CS briefly reports that the event probability for each time interval was obtained from a binomial likelihood distribution based on the underlying hazard function modelled by the fractional polynomial analysis. The predicted log-hazard for each comparison with atezolizumab at multiple time points was fitted with a normal distribution. The approach described by the company is broadly consistent with an approach for using fractional polynomial models in network meta-analysis as outlined by Jansen (2011),[63] except that fewer details of the analysis are provided in the CS. The CS does not provide any data on the number of events and patients at risk that they obtained from the included studies, but this information was provided by the company in clarification response A32.

Three orders of fractional polynomial models were considered: zero-order, which corresponds to an exponential model and assumes proportional hazards; first-order, which corresponds to the Weibull model (where exponent P1=0) or the Gompertz model (where exponent P1=1); and second-order with exponents P1 and P2 (giving possible combinations of P1=P2=0, P1=0, P2=1, and P1=P2=1). According to the CS and the company's response to clarification question A13, the zero-order fractional polynomial model was included to allow assessment of the proportional hazards assumption ('*e.g. through the deviance information criterion (DIC)), which was possible as the model was fitted to the same data as the more complex models'*.

Study heterogeneity assumptions

The company states that there was a 'limited evidence base' with which to estimate the between-study standard deviation and they therefore used informative prior distributions for the fixed-effects model parameters, taken from Turner et al.,[64] to account for between-study heterogeneity (CS Table 19). The ERG agrees that this is an appropriate approach. However, whilst the CS states that three priors (informative, weakly informative and vague) were compared in sensitivity analyses, no sensitivity analysis results are reported. These were subsequently provided by the company, for second-line comparisons only (clarification response A30).

The CS states that fixed-effects models were first fit, with random-effects models subsequently fit if the data allowed. It is important to consider the plausibility of model assumptions rather than basing decisions solely on model fit,[65] but the choice of fixed or random effect models was justified only on model fit (in clarification response A28 the company stated that random-effects models were included to allow for between-study heterogeneity; however, fixed-effects were subsequently chosen based on model fit). The process of assessing model fit is not clearly explained in the CS, which mentions that, in addition to the deviance information criterion, 'additional criteria' were used, but these are not specified (CS Section 4.10.10).

According to the CS, a fixed-effects model was used for the first-line treatment comparisons. The ERG requested an explanation from the company via NICE as to why a random-effects model was not used (clarification response A29). The company provided DIC values for comparisons of the fixed-effects and random-effects models for each of the three between-study heterogeneity priors and explained that the choice of fixed-effects model was based on the DIC. For the second-line treatment comparisons, the CS states that a random-effects model was

explored in sensitivity analysis (CS section 4.10.11.12); however, no sensitivity analysis is reported (this, together with sensitivity analysis of the heterogeneity priors was subsequently provided by the company in clarification response A30).

Model selection for first-line comparisons

For first-line treatment comparisons of overall survival the company selected the zero-order fractional polynomial model, as this had the lowest DIC among three fixed-effects models that were compared (CS Table 21), indicating that the more complex first-order fractional polynomial models did not perform better. The CS states that second-order fractional polynomial models were not considered due to the limited evidence base. Given the fit of the zero-order model it might be assumed that hazards were proportional in the comparison of atezolizumab to gemcitabine + carboplatin, although this is not stated in the CS. Visual inspection of overall survival curves (CS Figures 8 and 9) suggests that hazards may not have been proportional (in one study the curves cross) but the CS does not comment on this. The network meta-analysis section of the CS does not provide any information about time-dependency of the hazard ratio. However, in reporting the economic analysis (CS section 5.3.6) the CS states that the hazard ratio increased linearly over time and required capping to avoid clinically implausible values (see section 4.3.5).

Model selection for second-line comparisons

For second-line treatment comparisons of overall survival the company selected the Gompertz (i.e. first-order) fractional polynomial model, as this had the lowest DIC among three fixed-effects models that were compared (CS Table 23). Second-order models were considered, and had lower DIC values indicating better fit, but the CS states these exhibited large posterior correlations (>0.9) indicative of over-fitting and so were not used. Posterior correlations were also relatively large (>0.8) for the selected Gompertz model but the CS does not discuss this. Hazard ratio time curves are presented for comparisons of atezoluzumab against best supportive care, paclitaxel and docetaxel (CS Figures 15-17) with the corresponding parameter estimates (CS Table 24), and these indicate that the hazard ratio for the atezolizumab-docetaxel comparison decreased with time. In reporting the economic analysis (CS section 5.3.6) the CS states that the hazard ratios for second-line comparisons increased linearly over time and required capping to avoid clinically implausible values (see section 4.3.5).

The CS states that the clinically implausible values of hazard ratios are likely to reflect the sparse nature of the evidence base and results of the network meta-analysis are therefore subject to uncertainty. Hazard ratios for overall survival were employed in the economic analysis (subject to capping). However, the CS states that hazard ratios from network meta-analysis of progression-free survival could not be used in the economic analysis due to being clinically implausible (CS section 4.10.11) and results of these analyses are provided separately in CS Appendix 8.5. Given that the analyses of progression-free survival were not used by the company to support either the clinical effectiveness or cost-effectiveness of atezolizumab, these are not considered in detail in the current report.

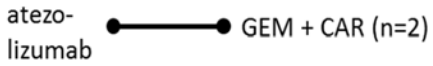
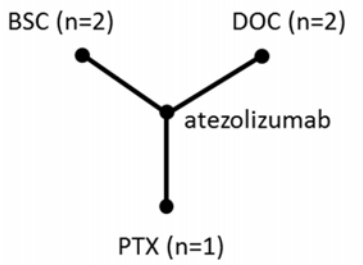
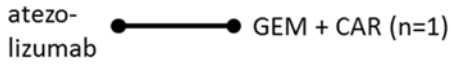
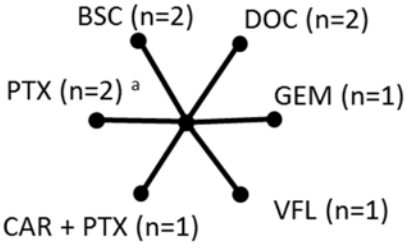
Network structure

The CS does not present network diagrams; however, the networks are simple (summarised in Table 12). As all comparisons are against atezolizumab, there are no indirect comparisons involved. Results of the network meta-analysis for each comparison would therefore be identical to those obtained by performing separate pairwise comparisons under the same statistical model (confirmed by the company for the fractional polynomial model in clarification responses A14 and A15). As noted above (section 3.1.2) the company has been inconsistent in applying their eligibility criteria such that they have included more comparators for their analysis of progression-free survival than for their analysis of overall survival.

Output of the network meta-analysis

The fractional polynomial analysis generates results which reflect the time course of the log-hazard function and as such can be expressed as log-hazard function curves and their parameters (intercept and slope). An explanation of the relationship between the log hazard function and hazard ratio is given below in section 4.3.5.2. When reporting the results of the network meta-analysis (see section 3.3.6), the company does not provide any guidance on the clinical interpretation of these parameters or any discussion of any of the clinical effectiveness results from the network meta-analysis.

Table 12 Summary of simulated treatment comparisons in the network meta-analysis

Outcome	First-line treatment (cohort 1 in atezolizumab study Imvigor 210)	Second-line treatment (cohort 2 in atezolizumab study Imvigor 210)
Overall survival (informs company's economic model)		
Progression-free survival (does not inform company's economic model)		

BSC: best supportive care; CAR: carboplatin; GEM: gemcitabine; DOC: docetaxel; PTX: paclitaxel; VFL: vinflunine
[a] nanoparticle albumin bound paclitaxel in one study

Summary of the ERG's appraisal of the network meta-analysis

The ERG has assessed the company's network meta-analysis using a critical appraisal checklist which we have based on published reporting guidelines (Jansen et al.,[65] inter alia). Our appraisal is provided in Appendix 5.

In summary, the ERG has the following concerns regarding the company's approach to the network meta-analysis:

- The simulated treatment comparison which informs the network meta-analysis has several limitations (as noted above we identified concerns around the selection of covariates and handling of missing data; see also Appendix 4);
- It is unclear whether the included studies were adequately homogeneous to permit valid meta-analysis; some aspects of prior therapies received by patients were not reported in the primary studies, and best supportive care was not adequately defined;

- A lack of sensitivity analyses to test the robustness of both the simulated treatment comparison and the network meta-analysis methods means that specific uncertainties are not propagated through to aid interpretation of the final clinical effectiveness results;
- The meta-analysis produced clinically implausible hazard ratios (which, as explained in section 4.3.5, resulted in the need for capping of the hazard ratios in the economic analysis);
- The meta-analysis is not used to provide any evidence for the clinical effectiveness of atezolizumab.

3.2 Overall summary statement of the company's approach

A summary of the ERG's appraisal of the company's approach to the evidence synthesis is given in Table 13.

The company conducted extensive searches which appear to have identified all relevant studies. The eligibility screening process is described in stages, making it somewhat difficult to follow, but the inclusion/exclusion criteria are deducible. The eligibility criteria have not been consistently applied, although this does not appear to have resulted in any major inclusion/exclusion errors. The screening process is described only briefly in the CS, but in clarification response A9 the company stated that screening was conducted by two reviewers.

Whilst the overall systematic review process appears reasonable, there are several issues with the meta-analysis methods applied by the company (simulated treatment comparison and network meta-analysis) which mean that the results of the analyses are uncertain. These are explained in detail in section 3.1.7 and summarised in section 3.4.

The submitted evidence is consistent with the decision problem

Table 13 Quality assessment (CRD criteria) of the CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	**Yes.** But these were not applied consistently, with some studies being excluded for reasons other than those stated.
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	**Yes.** The search was broad and comprehensive and a detailed search strategy was provided in a clarification request. The ERG identified 18 studies that appeared to be eligible but were not cited or referenced in the CS. The company clarified that 16 of these had been identified, screened and excluded and two were published later than the company's searches. Overall, no relevant studies appear to have been missed.
3. Is the validity of included studies adequately assessed?	**Partly.** The company used a NIH checklist for single-arm studies which does not cover some potential biases. Decisions on study quality are summarised narratively and difficult to interpret in relation to whether there are threats to internal or external validity. The quality assessment does not appear to inform any decisions about study eligibility.
4. Is sufficient detail of the individual studies presented?	**Partly.** Yes for the atezolizumab study, but no details of the comparator studies are provided in the CS. Some details of

	study drug dosing, study design, eligibility criteria and age, sex and ethnicity (but not other baseline characteristics) were provided by the company in clarification response A25.
5. Are the primary studies summarised appropriately?	**Partly.** Yes for the atezolizumab study, but no details of the comparator studies are provided in the CS. The company conducted a simulated treatment comparison but the CS does not summarise the characteristics, or specify the sample size, of the simulated study arms; limitations of the available data and the need for assumptions mean that the results may not be reliable.

3.3 Results

Results from the two cohorts of the Imvigor 210 study and the PCD4989 study are summarised in CS Sections 4.11.10 and 4.11.11. The main source of evidence is from the Imvigor 210 study, where efficacy results are presented in the CS for various data-cuts (CS Table 26). The ERG has reproduced the most recent data cut for each cohort. For cohort 1 (first-line treatment), this was at 15 months (4th July 2016 data cut with a median follow-up of 17.2 months [range 0.2 to 23.5 months]; company's clarification response A34) and with 14% of participants remaining on treatment. For cohort 2 (second-line treatment), this was at 20 months follow-up (4th July 2016 data cut with a median follow-up 21.1 months [range 0.2 to 24.5 months]; company's clarification response A34). The ERG has focused on results from the independent review facility assessment of outcomes; investigator-assessed outcomes are only reported where independent review facility assessments are unavailable. Where available, all data presented in the CS have been checked with the publications and the clinical study report.

Patients in PCD4989g received second-line treatment with atezolizumab, but not with the licensed dose, and therefore the results from this study should be interpreted with caution. A summary of study PCD4989g and its clinical effectiveness results is provided in Appendix 2.

3.3.1 Effectiveness of first-line atezolizumab

Results are reported for cohort 1 (first-line therapy) in CS section 4.11.10.2.

Survival

Overall survival and progression-free survival were secondary outcomes in the Imvigor 210 study. The median overall survival in cohort 1, assessed by independent review facility using RECIST v1.1 was 15.9 months, and 57.2% of patients had 12-month survival (Table 14). The Kaplan-Meier overall survival curve for first-line atezolizumab treatment (cohort 1) in Imvigor 210 (CS Figure 19) is shown in Figure 1.

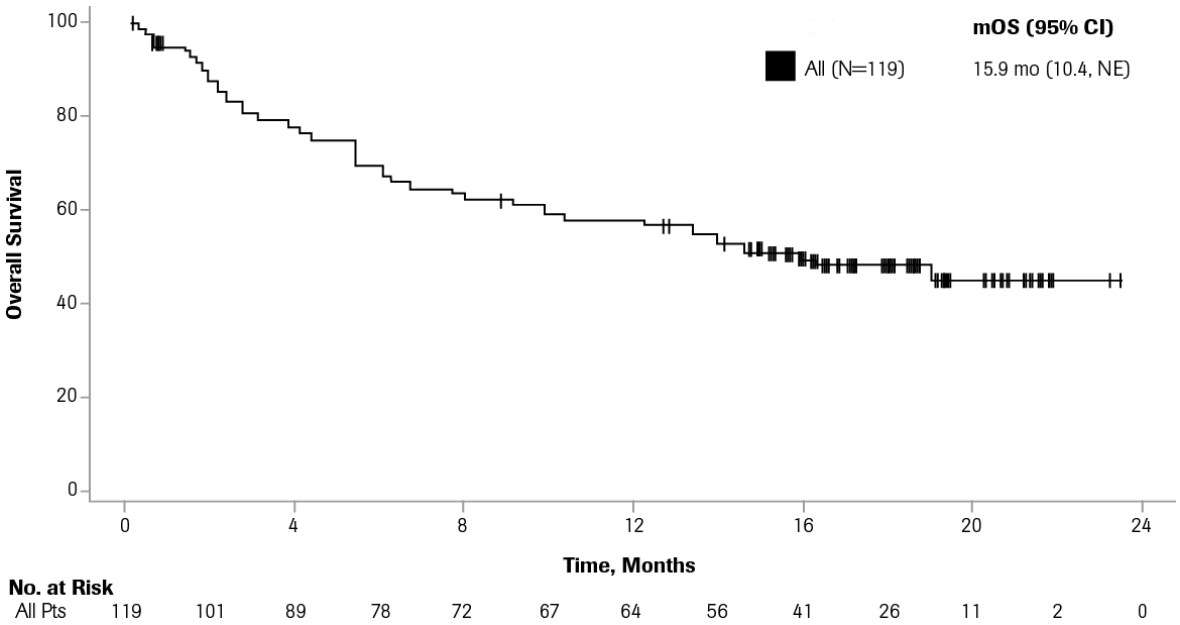


Figure 1 Kaplan-Meier overall survival curve for first-line atezolizumab (Imvigor 210 cohort 1)

Progression free survival at the 15 month analysis was 2.7 (95% CI 2.1, 4.2) months (Table 14). The CS does not report a Kaplan-Meier curve for first-line progression-free survival.

Table 14 Survival outcomes for cohort 1 of Imvigor 210

Outcome (95% CI) **(RECIST v1.1; IRF assessed)**	**Imvigor 210 cohort 1** **All patients, N = 119**
Overall survival, median, months	15.9 (10.4, NE)
12 months survival, %	57.2% (48.2%, 66.3%)
Progression-free survival, median, months	2.7 (2.1, 4.2)

CI: confidence interval; IRF: independent review facility; NE: not estimable

Response rates

Objective response rate as assessed by the independent review facility using RECIST v1.1 was the primary endpoint in cohort 1 of the Imvigor 210 study. Results are reported in CS Section 4.11.10.2. At the 15-month follow-up analysis, 22.7% achieved an objective response, and a complete response was seen in 9.2% of patients (Table 15). The CS states in Section 4.11.10.2 that the 15-month follow-up analysis confirms the findings from the primary analysis (data cut at a median follow-up of 8.5 months) that the objective response rates exceed the 10% historical control.

Median duration of response had not been reached in cohort 1 of Imvigor 210. CS Section 4.11.10.2 and CS Figure 18 show that the majority of responses were longer than one year, with many still ongoing at the 15-month data cut. The median treatment duration was 15 weeks (range 0 to 102 weeks).

Table 15 Response outcomes for cohort 1 of Imvigor 210

Outcome (95% CI) **(RECIST v1.1; IRF assessed)**	**Imvigor 210 cohort 1** **All patients, N = 119** [a]
ORR, %	22.7 (15.52, 31.27)
Complete response, %	9.2
Median time to onset of first response, months	2.1 (range 1.8 – 10.5)

CI: confidence interval; IRF: independent review facility; ORR, objective response rate
[a] Includes 20 patients with missing/unevaluable responses. All treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1.

3.3.2 Effectiveness of second-line atezolizumab

Results are presented for cohort 2 of the Imvigor 210 study in CS Section 4.11.10.3.

Survival

Overall survival and progression-free survival were secondary outcomes in cohort 2 of the Imvigor 210 study (CS Section 4.11.10.3). At the 20-month follow-up assessment in Imvigor 210 cohort 2, the overall survival was 7.9 months as assessed by the independent review facility using RECIST v1.1 (Table 16). The Kaplan-Meier overall survival curve for second-line atezolizumab treatment in Imvigor 210 (CS Figure 21) is shown in Figure 2.
Twelve month survival was 36.9% and median progression free survival 2.1 months. The CS does not report a Kaplan-Meier curve for second-line progression-free survival.

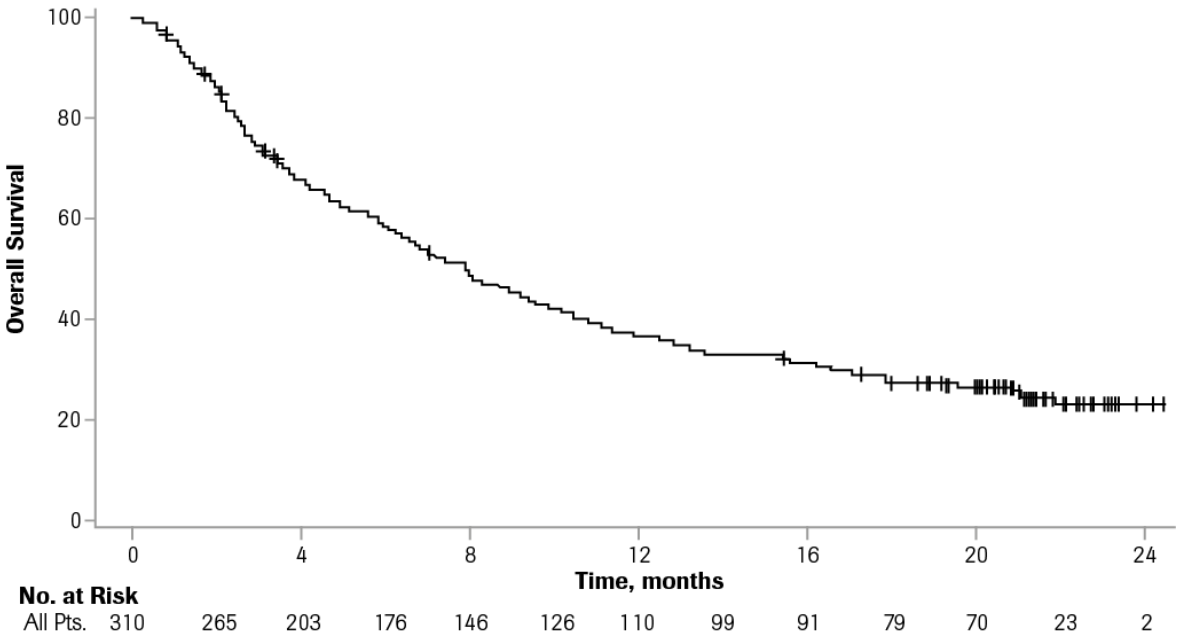


Figure 2 Kaplan-Meier overall survival curve for second-line atezolizumab (Imvigor 210 cohort 2)

Table 16 Survival outcomes for cohort 2 of Imvigor 210

Outcome (95% CI) **(RECIST v1.1; IRF assessed)**	**Imvigor 210 cohort 2: All patients, N = 310**
Overall survival, median, months	7.9 (6.7–9.3)
12 months survival, %	36.9% (31.4–42.3)
Progression-free survival, median, months	2.1 (2.1–2.1) [a]

CI: confidence interval; IRF: independent review facility; NE: not estimable
[a] ERG unclear why confidence interval as reported in the CS has zero range

Response rates

Objective response rate as assessed by the independent review facility using RECIST v1.1 was a co-primary endpoint in cohort 2 of the Imvigor 210 study, alongside objective response rate assessed by the investigator using modified RECIST criteria. Results are reported in CS Section 4.11.10.3. At the 20-month follow-up analysis, objective response rate was 15.8 months by independent review facility assessment and a complete response was seen in 6.1% of patients (Table 17). The median treatment duration was 12 weeks (range 0 to 104 weeks).

Median duration of response had not been reached in cohort 2 of Imvigor 210. The maximum duration of response at the latest follow-up analysis (which had median follow-up 21.1 months) was 22.6 months. The median time to response was 2.1 months (95% CI 2.0, 2.2). At the time of the 12-month analysis 65.3% of participants were ongoing with a response (not reported for the 20-month analysis).

Table 17 Response outcomes for cohort 2 of Imvigor 210

Outcome (95% CI) **(RECIST v1.1; IRF assessed)** [a]	**Imvigor 210 cohort 2: All patients, N = 310**
ORR, per RECIST, %	15.8 (11.9–20.4)
ORR per immune-modified RECIST, %	19.7 (15.4–24.6)
Complete response, %	6.1% (3.7–9.4)
Duration of response, maximum months	22.6

CI: confidence interval; IRF: independent review facility; ORR, objective response rate
[a] CS Table 36 implies both RECIST and modified RECIST assessments were done by the IRF; the company's response to clarification request A35 states, however, that the standard RECIST criteria were applied by the IRF whereas the modified RECIST criteria were investigator-assessed.
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3.3.3 HRQoL results

The Imvigor 210 study and the PCD4989g study did not include HRQoL outcomes.

3.3.4 Sub-group analysis results

Response rate outcomes for atezolizumab in the Imvigor 210 study are reported according to PD-L1 expression subgroups for the first-line cohort (CS section 4.11.10.2) and second-line cohort (CS section 4.11.10.3). These subgroups are not discussed here as they are not reported for survival outcomes.

The CS states (narratively only) that results for subgroups defined by demographic and baseline characteristics showed positive results on objective response rates (CS sections 4.11.10.2 and 4.11.10.3). In response to a clarification request by the ERG and NICE, the company noted that because of different data cuts the subgroup results are inconsistent with those reported in the CS (clarification response A39). The ERG agrees that the subgroup results for cohort 1 broadly agree with the narrative summary in the CS, but that there is more uncertainty in the subgroup data than in the whole-population analyses. For cohort 2 the results data provided by the company in their clarification response are not structured by baseline characteristics and the ERG has not been able to compare these with the narrative summary in the CS.

The NICE scope and company's decision problem do not specify any subgroups.

3.3.5 Effectiveness of comparators

3.3.5.1 First-line comparators

The CS does not provide effectiveness results for the two studies of first-line comparator treatments which were included in the company's network meta-analysis. The ERG has summarised these from the study publications in Table 18 (for the company's meta-analysis results see section 3.3.6 below).

Overall survival

Median overall survival on first-line gemcitabine + carboplatin was 9.3 months in the De Santis et al. study and 9.8 months in the Bamias et al. study (Table 18). The Kaplan-Meier curves for

overall survival on first-line gemcitabine + carboplatin in these studies (CS Figures 8 and 9) are included below in Figure 3 and Figure 4.

Progression-free survival

Median progression-free survival on first-line gemcitabine + carboplatin was 4.4 months in the Bamias et al. study and 5.8 months in the De Santis et al. study. A Kaplan-Meier curve for progression-free survival on first-line gemcitabine + carboplatin in the study by Bamias et al. is reported in CS Appendix 8.5 (not reproduced here).

Response rates

Objective response rates on first-line gemcitabine + carboplatin ranged from 24% to 41.2%, but the rate of complete responses was only 3% to 3.4% (Table 18)

Table 18 Survival and response rates in first-line comparator studies

Outcome (95% CI)	De Santis 2012[44] Gemcitabine + carboplatin	Bamias 2007[42] Gemcitabine + carboplatin
Overall survival, median, months	9.3 (CI not reported)	9.8 (4.7, 14.9)
Progression free survival, median, months	5.8 (CI not reported)	4.4 (1.03, 7.75)
Overall response, % [a]	41.2 (CI not reported)	24 (11 to 41)
Complete response, %	3.4 (CI not reported)	3 (0 to 15)
Partial response, %	37.8 (CI not reported)	21 (9 to 38)

[a] referred to as objective response (Bamias) or overall response (De Santis)

3.3.5.2 Second-line comparators

The CS does not provide effectiveness results for the five studies of second-line comparator treatments which were included in the company's network meta-analysis. The ERG has summarised these from the study publications in Table 19 (for the company's meta-analysis results see section 3.3.6 below).

Overall survival

Median overall survival on second-line best supportive care was reported in two studies (Bellmunt et al. and Noguchi et al.) and ranged from 4.1 months to 4.6 months (Table 19). The

Kaplan-Meier curves for overall survival on best supportive care in these studies (CS Figures 10 and 11) are included below in Figure 5 and Figure 6.

Median overall survival on second-line docetaxel was reported in two studies (Chouieri et al. and Kim et al.) and ranged from 7.03 months to 8.3 months (Table 19). Note that the docetaxel arm in the Chouieri et al. study was a combination of docetaxel + placebo. The CS does not comment on the nature of the placebo or whether incorporation of a placebo in the arm would affect interpretation. The Kaplan-Meier curves for overall survival on second-line docetaxel in these studies (CS Figures 12 and 14) are included below in Figure 7 and Figure 8.

Median overall survival on second-line paclitaxel, reported in one study (Lee et al.), was 6.5 months (Table 19). The corresponding Kaplan-Meier curve (CS Figure 13) is included below in Figure 9.

Progression-free survival

Median progression free survival on second-line best supportive care was 1.8 months in the Noguchi et al. study (not reported for the Bellmunt et al. study) (Table 19). The Kaplan-Meier curves for progression-free survival on best supportive care in these studies are reported in CS Appendix 8.5 (not reproduced here).

Median progression-free survival on second-line docetaxel in the studies by Chouieri et al. and Kim et al. ranged from 1.4 months to 1.58 months (Table 19). The Kaplan-Meier curves for progression-free survival on second-line docetaxel in these studies are reported in CS Appendix 8.5 (not reproduced here).

Median progression-free survival on second-line paclitaxel, reported in one study (Lee et al.) was 2.7 months (Table 19). The corresponding Kaplan-Meier curve is reported in CS Appendix 8.5 (not reproduced here).

Response rates

No responses were achieved in best supportive care study arms. The overall response rate on second-line docetaxel ranged from 6% to 7%, but the rates of complete responses were not

reported. Overall response rate was higher in the paclitaxel study, at 21%, but only 3% of the patients receiving paclitaxel were complete responders (Table 19).

Table 19 Survival and response rates in second-line comparator studies

Outcome (95% CI)	Noguchi 2016[47] BSC	Bellmunt 2013[21] BSC	Choueiri 2012[50] Docetaxel	Kim 2016[49] Docetaxel	Lee 2012[39] Paclitaxel
Overall survival median, months	4.1 (2.8, 6.9)	4.6 (4.1, 6.6)	7.03 (NR)	8.3 (5.9, 10.6)	6.5 (5.0, 8.0)
Progression free survival, median, months	1.8 (1.3, 2.3)	NR	1.58 (NR)	1.4 (1.3, 1.6)	2.7 (0.9, 4.6)
Overall response, % [a]	0	0	7 (NR)	6 (1 to 21)	21 (7 to 34)
Complete response, %	0	0	NR [a]	NR	3 (NR)
Partial response, %	0	0	NR	NR	18 (NR)

BSC: Best supportive care; NR: not reported
[a] referred to as objective response (Kim, Lee) or overall response (Bellmunt, Chouieri)

3.3.6 Network meta-analysis results

As explained above (section 3.1.7), the ERG is concerned that the company's approach to network meta-analysis enables violation of the proportional hazards assumption. The results of the analysis may therefore be incorrect and should be considered uncertain. However, we have reproduced the company's results here for consideration.

The company presents the results of the network meta-analysis as hazard ratios and also visually in a series of Figures, in which the survival curves for the simulated atezolizumab arm, the observed atezolizumab arm in Imvigor 210, and the comparator arm can be compared for each treatment comparison.

Hazard ratios

For first-line comparison of atezolizumab against gemcitabine + carboplatin the CS reports a hazard ratio for overall survival of 0.6 (credible interval 0.47 to 0.82), i.e. in favour of atezolizumab (CS section 4.10.11.1). However, the time point to which this hazard ratio refers is not stated.

For second-line comparisons of atezolizumab against best supportive care, docetaxel and paclitaxel, the CS provides charts showing plots of the posterior median log hazard ratio against time in CS Figures 15-17. These are for a fixed-effects analysis. The curves (not reproduced here) appear to suggest that the log hazard ratio is time-invariant for best supportive care and paclitaxel but time-dependent for docetaxel. However, the CS does not provide any interpretation of these curves. Wide credible intervals indicate that there is considerable uncertainty in the predicted log hazard ratios, especially after month 15.

Note that interpretation of time-dependent hazard ratios can lead to implausible values of the hazard ratio at given time points; for this reason the company capped the overall survival hazard ratio estimates obtained from the network meta-analysis to enable their inclusion in the economic model (see section 4.3.5.2).

The company reports the parameters of the log-hazard function (slope, intercept, and their correlation) for second-line comparisons (CS Table 24) but not for first-line comparisons. The CS does not explain how they should be interpreted in order to draw conclusions on the effectiveness of atezolizumab. Parameters of the log-hazard function are not reproduced here but those which inform the economic analysis are discussed in section 4.3.

Survival curves

Curves for overall survival are provided in CS Figures 8 to 14. Curves for progression-free survival are provided in Figures 1 to 10 in CS Appendix 8.5. The Figures for overall survival are reproduced here for consideration. Any visual comparison of the observed atezolizumab curves against the corresponding comparator curves would effectively be a naive (unadjusted) comparison since differences in the studies' characteristics are not taken into account.

Overall survival: first-line

Overall survival on first-line gemcitabine + carboplatin, compared with first-line atezolizumab (two studies), is shown in Figure 3 and Figure 4.

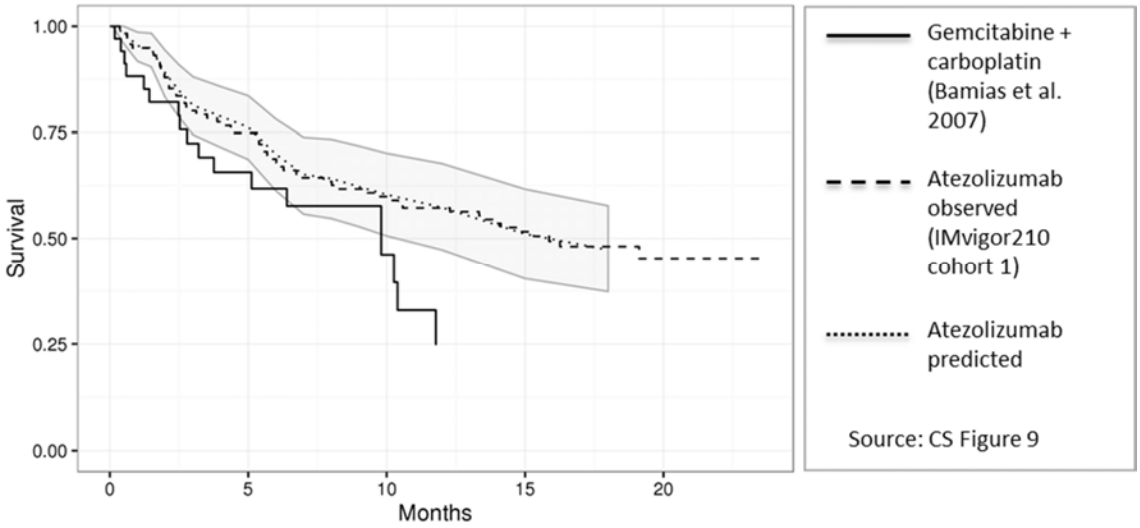

Figure 3 Overall survival curves for first-line gemcitabine + carboplatin (Bamias et al. 2007) and atezolizumab

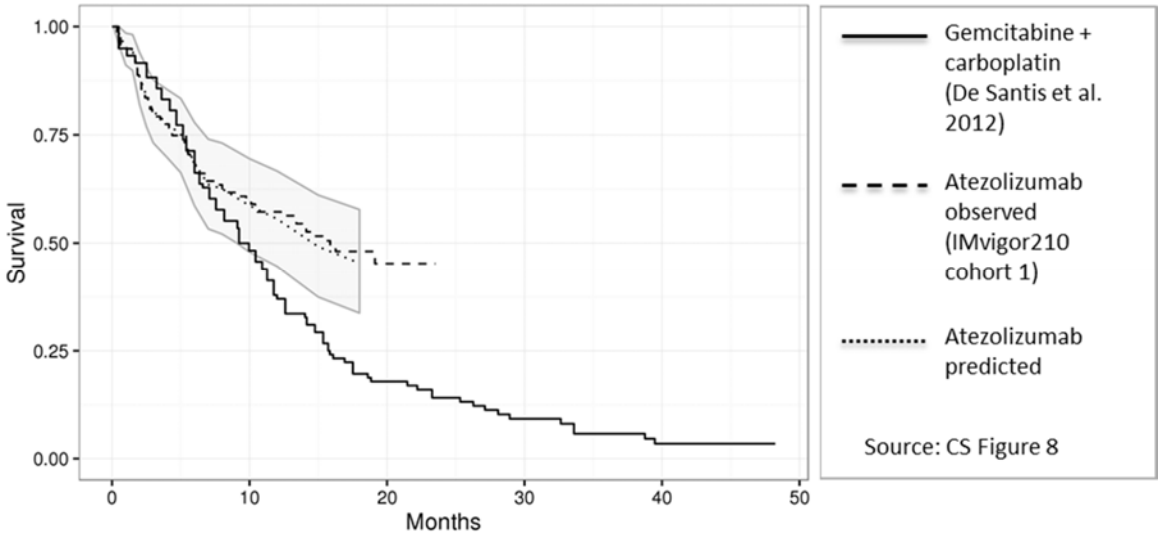

Figure 4 Overall survival curves for first-line gemcitabine + carboplatin (De Santis et al. 2012) and atezolizumab

Overall survival: second-line

Overall survival on second-line best supportive care, compared with second-line atezolizumab (two studies), is shown in Figure 5 and Figure 6.

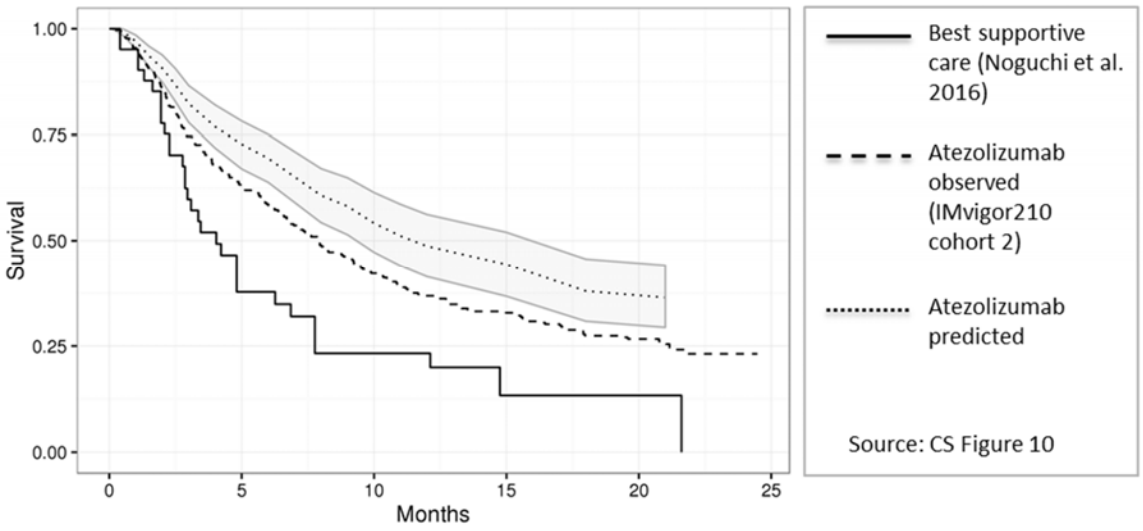

Figure 5 Overall survival curves for second-line best supportive care (Noguchi et al. 2016) and atezolizumab

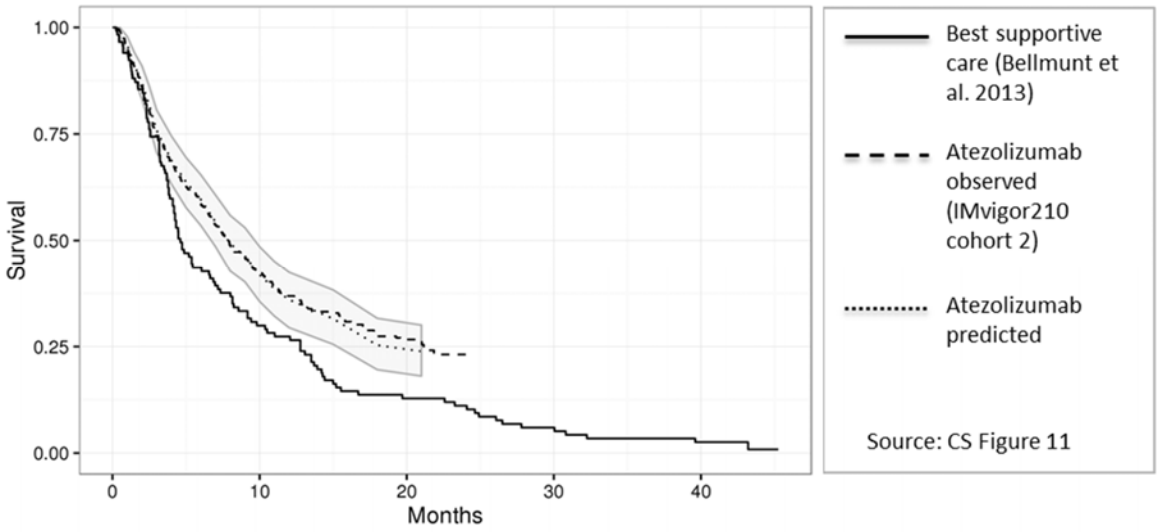

Figure 6 Overall survival curves for second-line best supportive care (Bellmunt et al. 2013) and atezolizumab

Overall survival on second-line docetaxel, compared with second-line atezolizumab (two studies), is shown in Figure 7 and Figure 8.

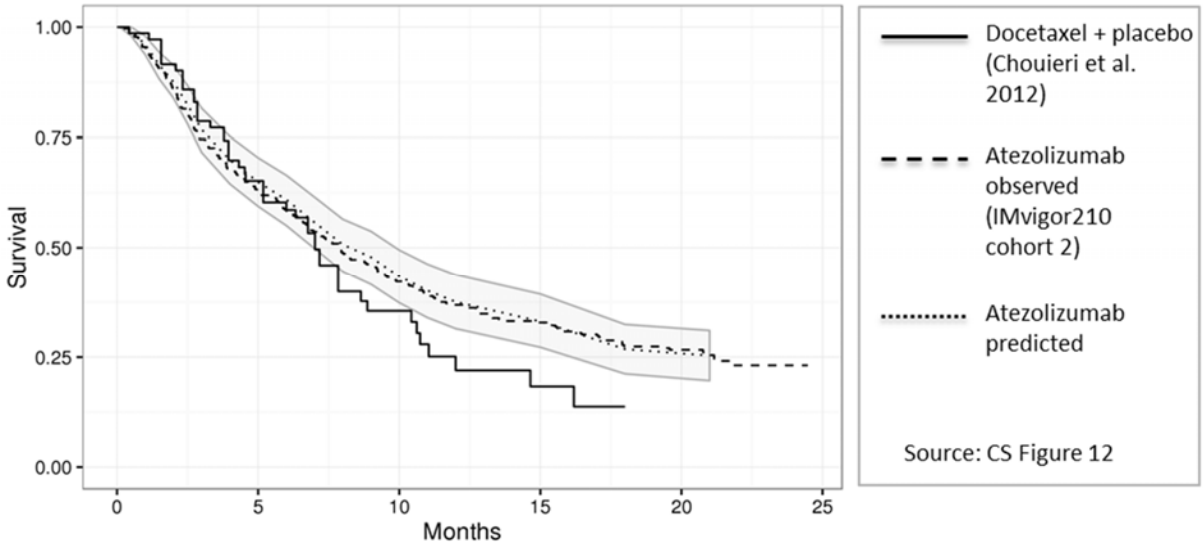

Figure 7 Overall survival curves for second-line docetaxel (Choueiri et al. 2012) and atezolizumab

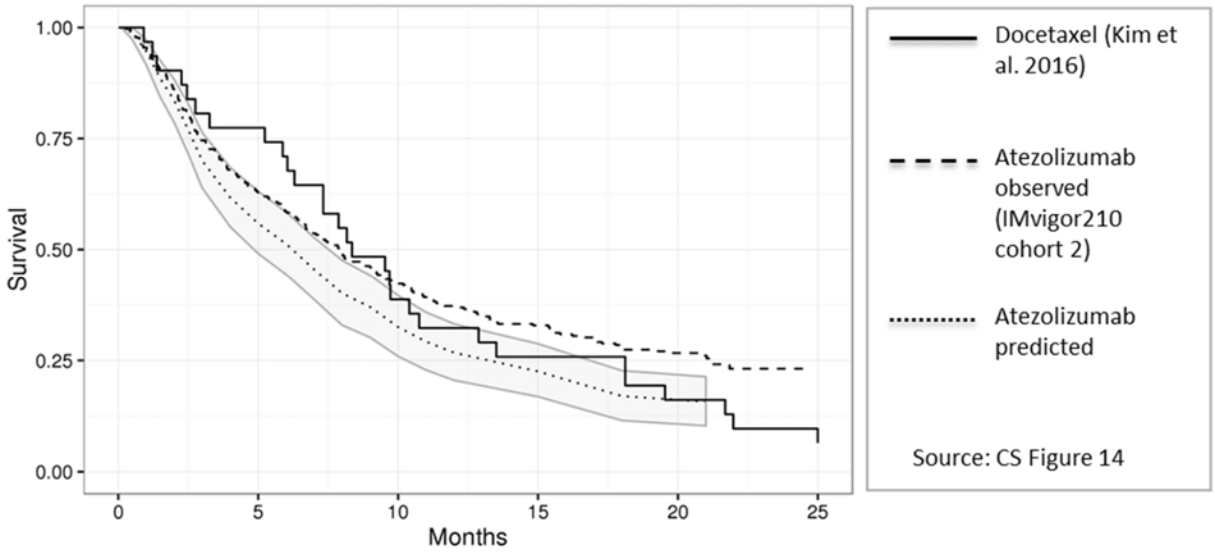

Figure 8 Overall survival curves for second-line docetaxel (Kim et al. 2016) and atezolizumab

Overall survival on second-line paclitaxel, compared with second-line atezolizumab (one study), is shown in Figure 9.

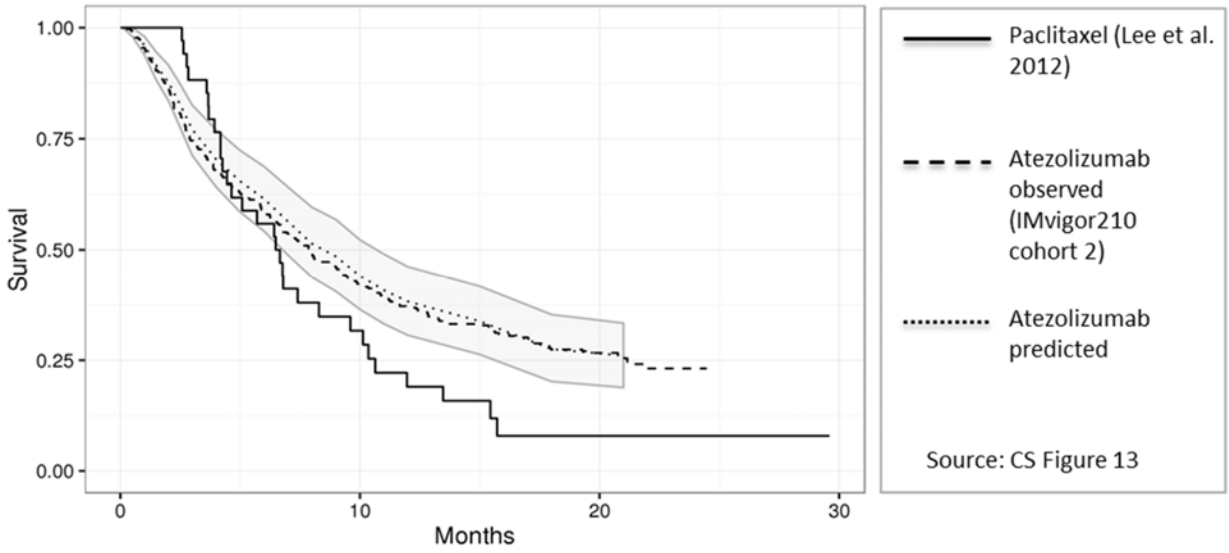

Figure 9 Overall survival curves for second-line paclitaxel (Lee et al. 2012) and atezolizumab

3.3.7 Adverse events

The CS presents safety endpoints from the two cohorts of the Imvigor 210 study and the PCD4989g study (minimal data) in CS section 4.12.3. We have summarised adverse event information from the PCD4989g study here, although the company stated that patients in PCD4989g received less than the licensed atezolizumab dose (see Appendix 2). No pooled adverse event data from the three sources of evidence are presented in the CS.

The rate of any adverse event was around 96-98% in the Imvigor 210 study (Table 20). Rates were generally similar across the two cohorts, where reported. The most frequent side effects, affecting at least 20% of the patients, were fatigue (tiredness), decreased appetite, nausea (feeling sick), and dyspnoea (shortness of breath).[66] Serious adverse events were experienced in 38% of patients in cohort 1 and 47% in cohort 2. The most commonly reported serious adverse events, reported in at least 2.5% of participants, were acute kidney injury, small intestinal obstruction, renal failure, sepsis and diarrhoea in cohort 1 (proportions are not reported in the CS). In cohort 2 the most commonly reported serious adverse events, reported in at least 3 participants, were [redacted] (data from

updated clinical study report). The CS states that these were related to underlying disease in most instances.

Grade 3-4 events were experienced in 45%-60% of participants.

Treatment-related adverse events

The CS does not specify how treatment-related was defined. The Imvigor 210 study publication by Balar et al. 2017[40] states only that this was '*deemed to be related to treatment by the investigator*'. No other information about the definition of 'treatment-related' is given in the clinical study reports.

The rate of treatment-related adverse events across the three cohorts was 66-71%.Treatment related serious adverse events were experienced in 10.1% and 12.3% of participants in the two cohorts of Imvigor 210 respectively and in 5.3% of participants in study PCD4989g (Table 20). Rates for individual treatment related serious adverse events were generally low. Most frequently reported across the three cohorts were diarrhoea (2.5% in cohort 1, 0.3% in cohort 2, 0 in PCD4989g), renal failure (1.7% in cohort 1, 0 in cohort 2 and PCD4989g) and pyrexia (0.8% in cohort 1, 0.6% in cohort 2 and 2.1% in PCD4989g) (data provided in clarification response A43). Of the Grade 3-4 adverse events, 16–18% were deemed to be treatment related.

The most commonly reported treatment-related grade 3-4 adverse events in the Imvigor 210 study were fatigue, diarrhoea, anaemia, increases in alanine aminotransferase, aspartate aminotransferase and bilirubin, and renal failure (Table 21; data for cohort 1 are from clarification response A43). In study PCD4989g 9.5% of participants experienced treatment-related grade 3-4 events (data are from clarification request A43). Across the three cohorts the rates of these individual events were low, around 2%.

Table 20 Overview of adverse events

Event, %	**Imvigor 210 Cohort 1, 15-month cutoff, n=119**	**Imvigor 210 Cohort 2, 20-month follow-up, n=310**	**PCD4989g study, n=95[a]**
Adverse event, any	95.8	97.7	97.9
Treatment-related adverse event, any	66.4	71.0	66.3
Serious adverse event, any	37.8	46.5	-
Treatment-related serious adverse event, any	10.1	12.3	5.3 [b]
Grade 3-4 event	45.4	60.0	50.5
Treatment-related grade 3-4 event	16.0	18.1	9.5
Grade 5 event (death related to adverse event)	3.4	1.0	1.1
Treatment-related grade 5 event (death related to adverse event)	0.8	0	-
Adverse event of special interest	31.1	30.0	36.8 [b]
Grade 3-4 adverse event of special interest	7.6	6.5	-
Adverse event leading to dose interruption	34.5	32.3	-
Adverse event leading to study drug withdrawal	7.6	3.9	4.2 [b]

[a] as confirmed in clarification A41, not all participants received the licensed dose, results are supportive data only.
[b] from clarification response A43

Adverse events of special interest

Adverse events of special interest (Table 22) were mostly immune-mediated adverse events and renal function events which are anticipated effects of using a monoclonal antibody therapy. They were experienced by 30-31% of patients in Imvigor 210 and 36.8% in study PCD4989g.

The most frequent adverse events of special interest in cohort 1 were: rash (10.1%), hypothyroidism (7.6%), increased alanine aminotransferase (7.6%) increased aspartate aminotransferase (6.7%), increased bilirubin (3.4%), colitis (2.5%), dermatitis (2.5%) and peripheral neuropathy (2.5%) (data provided by the company in clarification response A43). Twenty-five percent of participants received steroids for an adverse event of special interest in this cohort (Table 22). The CS states that no major decline in median estimated glomerular filtration rate was observed in cohort 1.

Table 21 Treatment related grade 3-4 adverse events

Event, %	Imvigor 210 Cohort 1, 15-month cutoff, n=119	Imvigor 210 Cohort 2, 20-month follow-up, n=310	PCD4989g n=95 [a]
Overall	16.0	18.1	9.5
Fatigue	3.4	1.6	Not reported
Diarrhoea	1.7	0.3	Not reported
Pruritus	0.8	0.3	Not reported
Decreased appetite	0.8	0.6	Not reported
Hypothyroidism	0	0.3	Not reported
Anaemia	0.8	0.6	1.1
Chills	0	0	Not reported
Nausea	0	1.9	Not reported
Pyrexia	0	0.6	Not reported
Rash	0.8	0.3	Not reported
Vomiting	0	1.3	Not reported
Rash, maculopapular	0	0	1.1
ALT increase	3.4	1.9	1.1
Arthralgia	0	1.0	Not reported
AST increase	2.5	1.6	1.1
Blood bilirubin increase	1.7	0.6	Not reported
Blood alkaline phosphatase increase	0.8	1.6	1.1
Dyspnoea	0	0	Not reported
Infusion-related reaction	0	0	Not reported
Lymphocyte count decrease	0	1.0	1.1
Renal failure	1.7	0.6	Not reported
Asthenia	0	0	2.1
Neutropenia	0	0	1.1

ALT, alanine aminotransferase; AST, Aspartate aminotransferase
[a]as confirmed in clarification response A41, not all participants received the licensed dose, results are supportive data only.

Table 22 Adverse events of special interest, immune-mediated requiring systemic corticosteroids.

	Imvigor 210 Cohort 1, 15-month cutoff, n=119		**Imvigor 210 Cohort 2, 20-month follow-up, n=310**	
Event, % (rounded)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Overall	12[a]	7[b]	13[c]	3
Rash	3	1	[redacted]	[redacted]
ALT increase	2	2	[redacted]	[redacted]
Blood bilirubin increase	2	2	[redacted]	[redacted]
Rhabdomyolysis[d]	2	1	-	-
AST increase	1	1	[redacted]	[redacted]
[redacted]	-	-	[redacted]	[redacted]
Autoimmune colitis	1	1	-	-
Colitis	1	1	[redacted]	[redacted]
Diarrhoea[d]	1	1	-	-
Liver disorder[d]	1	1	-	-
Rheumatoid arthritis	1	1	-	-
Arthralgia[d]	1	0	-	-
Arthritis[d]	1	0	-	-
Hypothyroidism	1	0	-	-
Muscle spasms[d]	1	0	-	-
Rash, maculopapular	1	0	[redacted]	[redacted]
Tenosynovitis[d]	1	0	-	-

a [redacted] b [redacted] c [redacted]
d [redacted]

ALT, alanine aminotransferase; AST, Aspartate aminotransferase
Data for cohort 2 not reported in the CS and have been taken from the updated CSR.

The most frequent adverse events of special interest in cohort 2 were: rash (11.6%), increased alanine aminotransferase (5.2%), increased aspartate aminotransferase (5.2%), hypothyroidism (3.2%), maculo-papular rash (3.2%), peripheral neuropathy (3.2%), pneumonitis (2.6%), and increased bilirubin (2.6%) (data provided by the company in clarification response A43). The CS states that in 63 patients treated with atezolizumab for ≥1 year in cohort 2, 13% experienced an immune-mediated adverse event of any grade, and 3% experienced a Grade 3–4 immune-

mediated adverse event. In these patients, rash, acute kidney injury and influenza-like illness were the most common immune-mediated adverse events of any grade (n=2 each).

In study PCD2989g adverse events of special interest were provided by the company in response to clarification question A43. The most commonly reported events were similar to those seen in the two cohorts of Imvigor 210: rash (12.6%), aspartate aminotransferase increase (10.5%), peripheral neuropathy (8.4%), and alanine aminotransferase increase (7.4%).

Across both cohorts of Imvigor 210 12-13% of patients experienced immune-mediated adverse events of special interest requiring systemic corticosteroids (Table 22).

Rates of infusion-related reactions are reported (CS Tables 43 and 46), although they were not classed by the company as adverse events of special interest. Rates of infusion-related reactions were relatively low, affecting 3% of patients in cohort 1 and 0.6% in cohort 2 (none were Grade 3-4).

Adverse events leading to atezolizumab dose interruption or withdrawal

In cohort 1, 34.5% of patients had an adverse event leading to dose interruption and 7.6% had an adverse event leading to treatment withdrawal. In cohort 2, 32.3% of patients had an adverse event leading to dose interruption and 3.9% had an adverse event leading to treatment withdrawal (CS section 4.13.1). In study PCD4989g 4.2% of patients had an adverse event leading to treatment withdrawal (reported by the company in clarification response A43).

Specific adverse events leading to atezolizumab withdrawal were specified by the company in clarification response A43. Across both cohorts of Imvigor 210 and also in study PCD4989g the reasons for withdrawal were diverse and mostly affected only one patient each. These included, among others: cohort 1: cardiac arrest, myocardial infarction, sepsis, diarrhoea, rheumatoid arthritis, respiratory failure; cohort 2: sepsis, pulmonary sepsis, colitis, fatigue, cerebral haemorrhage, pneumonitis, pruritis; study PCD4989g: increased bilirubin, sepsis, intracranial mass. The rates of withdrawals were not specified in relation to the time on treatment.

Deaths

In cohort 1, there were 59 deaths: 52 were due to progressive disease, five due to grade 5 adverse events (four within 30 days of the last atezolizumab dose; one more than 30 days after the last dose), and two were due to unspecified causes (not progression or adverse event) (CS section 4.12.3.1).

In cohort 2, there were 226 deaths: 211 were due to progression, three due to grade 5 adverse events (CS section 4.12.3.1) and [redacted] (Supplemental Results Report IMVigor 210, pages 737-738).

Four of the participant deaths in cohort 1 and three in cohort 2 were due to Grade 5 adverse events, of which one (unspecified, in cohort 1) was treatment-related.

Summary of adverse events

Overall, atezolizumab appears to be reasonably well-tolerated given the advanced age of the population, and the adverse events data do not raise any safety concerns beyond those expected for an anti-cancer immunotherapy. The majority of deaths in the Imvigor 210 study were due to progressive disease, with only one death (in cohort 1) attributed as being treatment-related. Around one third of patients in each cohort experienced dose interruptions as a result of adverse events, whilst 7.6% of cohort 1 patients and 3.9% of cohort 2 patients had adverse events leading to withdrawal of atezolizumab.

3.4 Summary of the clinical effectiveness evidence

The published evidence base for effectiveness of first-line and second-line atezolizumab is based on a single phase II single-arm study, Imvigor 210. Limited additional supporting information is provided by the company from a phase I study which included patients receiving second-line atezolizumab. However, the patients received on average slightly less than the licensed dose. The primary outcome in Imvigor 210 was the objective response rate, whilst overall survival and progression-free survival were secondary outcomes. At the latest available data-cut, and based on independent review facility assessment using RECIST v1.1 criteria, first-line patients had a median overall survival of 15.9 months, median progression-free survival 2.7 months, an objective response rate of 22.7%, and the median duration of response had not yet

been achieved. Second-line patients had a median overall survival of 7.9 months, progression-free survival of 2.1 months, an objective response rate of 15.8%, and the median duration of response had not yet been achieved.

Overall, atezolizumab appears to be reasonably well-tolerated given the advanced age of the population, and the adverse events data do not raise any safety concerns beyond those expected for an anti-cancer immunotherapy.

Comparison of the clinical effectiveness of atezolizumab against comparator chemotherapy drugs was limited by a lack of evidence to allow the formation of a network, as the relevant comparators were either single-arm studies or single arms within controlled trials. To enable a network to be formed for meta-analysis, the company employed a simulated treatment comparison to 'predict' a matching atezolizumab arm for each comparator study. The resulting comparisons of atezolizumab against each comparator were then included in a network meta-analysis. The company determined that the proportional hazards assumption would be unlikely to hold for comparisons between atezolizumab and standard chemotherapy drugs. They selected a fractional polynomial model analysis approach for the network meta-analysis since higher-order fractional polynomial models are not dependent on the assumption of proportional hazards (but see below).

The company acknowledge that the results of the fractional polynomial network meta-analysis are unreliable and should be interpreted with caution.

The ERG has the following concerns regarding the simulated treatment comparison:

- A fundamental assumption of a simulated treatment comparison is that, ideally, all covariates (i.e. prognostic factors or effect modifiers for survival) have been included in the analysis. The company has included only three or four binary covariates (from age, sex, liver metastasis, performance status). This may limit how well-matched the simulated atezolizumab arms are to the comparator arms.
- Some aspects of the analysis are unclear, including the imputation approaches used to account for missing covariate values.
- The cumulative impact of small errors and inconsistencies in the data is unclear.

The ERG has the following concerns regarding the network meta-analysis:

- The company states that the reason for using fractional polynomial models was to allow analysis of comparisons which violate the proportional hazards assumption. However, after assessing model fit, the company selected the zero-order fractional polynomial model which assumes proportional hazards. The company does not discuss the plausibility of this model.
- Hazard ratios for overall survival were not used to inform clinical effectiveness of atezolizumab and were considered to be clinically implausible when applied in the economic analysis without adjustment.
- Hazard ratios for progression-free survival were considered to be clinically implausible and were not used to inform the clinical effectiveness or cost-effectiveness evaluation of atezolizumab.

4 COST EFFECTIVENESS

4.1 Overview of the company's economic evaluation

The company's submission to NICE includes:

- a review of published economic evaluations of chemotherapy treatment regimens for patients with advanced or metastatic urinary bladder cancer.
- a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of atezolizumab is compared with gemcitabine + carboplatin for patients with locally advanced or metastatic urothelial cancer for whom cisplatin-based chemotherapy is unsuitable and compared with docetaxel, paclitaxel and best supportive care for patients whose disease has progressed after prior chemotherapy.

4.2 Summary and critique of the company's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of chemotherapy treatment regimens for patients with advanced/metastatic urinary bladder cancer who have progressed after at least one prior chemotherapy (see section 3.1 of this report for our critique of the company's search strategy).

The inclusion and exclusion criteria for the systematic review are listed in CS Appendix 8.7. The inclusion criteria state that economic evaluations of chemotherapy treatment regimes in patients with advanced or metastatic urinary bladder cancer who have progressed after at least one prior chemotherapy regimen (or who are intolerant of cisplatin-based chemotherapy) would be included. No exclusion criteria are reported.

Forty-one studies were identified from screening 844 titles and abstracts, with a further three studies identified through hand-searching. Of these, 37 studies were excluded, mainly as the studies were reviews or editorials or were in the wrong patient population. Seven studies were included for full review (the CS does not report the references for these studies identified; they were provided by the company in clarification response B9). The company reported that none of these studies were relevant to the current submission and the CS does not provide any further details for these studies. The ERG is unclear why the company considered these studies not relevant to the current submission and we note that the company used two of these studies to inform their analyses of resource use[22] and HRQoL.[67]

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The ERG's critical appraisal of the submitted economic evaluation based on the NICE reference case requirements is summarised in Table 23.

Table 23 NICE reference case requirements

NICE reference case requirements	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Not completely	CS Table 2, CS section 1.1.1. The economic evaluation in the CS has combined two of the populations in the NICE scope to create one population whose disease has progressed (2L).
Comparator: As listed in the scope developed by NICE	Not completely	The CS does not include best supportive care for the 1L cohort and does not include retreatment with 1st line platinum-based chemotherapy for 2L treatment (CS Table 2, section 1.1.1).
Perspective on costs: NHS and PSS	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	CS section 4.1.
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	Time horizon of 20 years (CS Table 49).
Measuring and valuing health effects: Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	Health effects measured in QALYs. Utilities are mapped from EORTC QLQ C30 results to EQ-5D (CS section 5.4.6)
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% per annum for costs and health effects	Yes	CS Table 49.

1L: first-line; 2L: second-line

In general, the company's analysis conforms to NICE's reference case requirements, but the analysis differs from the NICE scope with regard to the populations and comparators.

4.3.2 Model Structure

The company constructed two cost-utility models for first-line and second-line treatment with atezolizumab. The model structure was identical for the two models. The models have a lifetime time horizon of 20 years, discounting of 3.5% per annum for costs and health benefits, a weekly cycle length and apply a half-cycle correction. The perspective of the analysis is the NHS and PSS. The CS states that the time horizon was sufficiently long to capture all meaningful differences between the treatments compared and that the perspective and discounting rate were as specified by the NICE reference case.[68] The ERG considers the perspective of the model and the choice of time horizon, cycle length and discounting rate are appropriate.

The models were constructed in Microsoft Excel and each consists of a partitioned survival model with three health states: 'progression-free survival', 'progressed disease and death. A schematic of the model (CS Figure 22) is shown in Figure 10 below. The CS states that this model was chosen as the structure and health states are in line with the clinical pathway and the model structure is consistent with the approaches used in earlier NICE appraisals for treatments with advanced or metastatic carcinoma, including the previous appraisal for urothelial cancer.[22]

The model uses parametric survival modelling to fit survival curves to the observed data for progression-free survival and overall survival (see more details in section 4.3.5). The model derives the proportion of patients in the progressed disease state as the difference between the progression-free survival and overall survival curves.

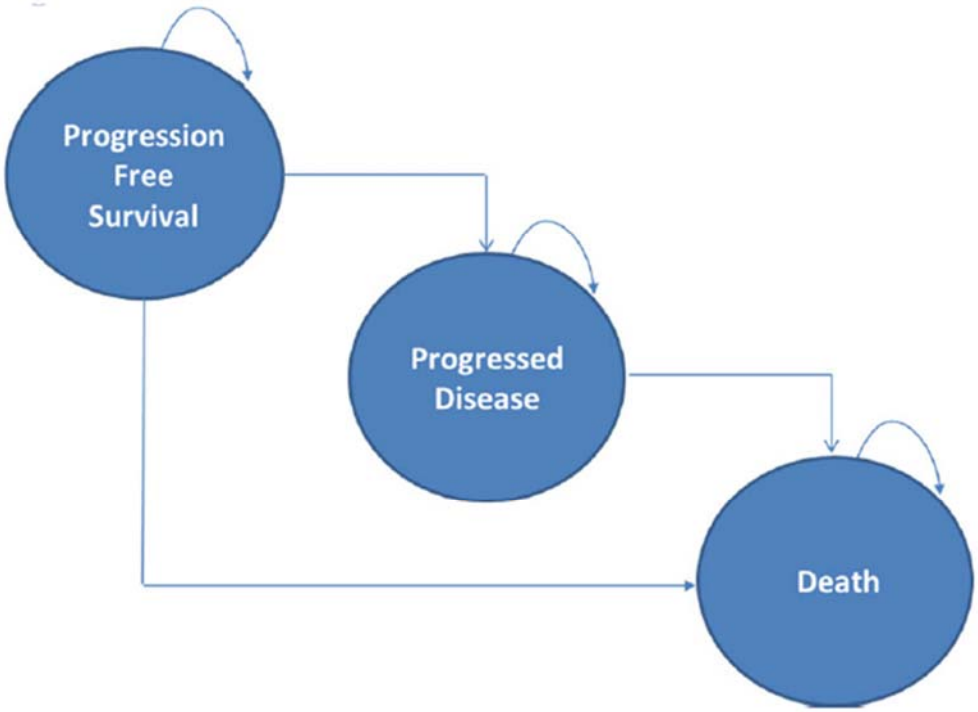

Figure 10 State model schematic (CS Figure 22)

Patients are treated with atezolizumab until disease progression unless they discontinue due to adverse events. Patients treated with the comparator treatment are treated for a specified number of treatment cycles, according to the marketing authorisation. On the basis of expert clinical advice, the company assumed that there are no subsequent lines of anti-cancer therapy for any treatment arm in either population following progression. The CS states that for second-line treatment this assumption was confirmed by the IMvigor 210 study where only 14.7% of patients receive subsequent treatment with gemcitabine with the majority only receiving palliative radiotherapy. For cisplatin-ineligible patients, the CS states that these might be expected to receive subsequent therapy, for example the NICE guidelines recommend either carboplatin + paclitaxel or gemcitabine + paclitaxel, but that incorporating these treatments is unlikely to have a significant effect on the incremental cost or effectiveness of second-line therapy. The ERG's clinical expert advisor agreed that it is reasonable to assume that most patients on second-line treatment would not receive subsequent anti-cancer therapy following disease progression.

The ERG considers the model structure to be an appropriate representation of the biological processes of advanced or metastatic urothelial cancer and appropriately represents the

treatment pathway. The CS presents the model structure with sufficient justification for the methodological and structural choices (CS Section 5.2). In general, the modelling approach appears appropriate.

4.3.3 Population

The company performed economic analyses for the treatment of two groups of adult patients with locally advanced or metastatic urothelial cancer: i) patients who are unsuitable for cisplatin-based chemotherapy; and ii) patients whose disease has progressed after prior chemotherapy. These patient groups are in accordance with the final scope issued by NICE. The company is anticipating marketing authorisation for these populations being granted [redacted].

The company primarily uses the open-label phase II study, IMvigor 210, as a source of clinical effectiveness parameters for atezolizumab in the economic model. As we describe in more detail above (section 3.1.3), this study includes two patient cohorts: i) cohort 1: patients who are cisplatin-ineligible and received atezolizumab as a first-line treatment option and ii) cohort 2: patients who received atezolizumab as second-line treatment, after progression on chemotherapy. The company aligned their modelled populations in the two cohorts with those in the Imvigor 210 study. The baseline characteristics of these two cohorts are presented in Table 9.

The mean ages of the first-line and second-line cohorts used in the economic models are 71.8 years and 65.6 years respectively, and are consistent with the baseline characteristics of the Imvigor 210 patients (Table 9).

Although Imvigor 210 is an international study (conducted in the USA, Canada, France, Germany, Italy, The Netherlands, Spain, and the UK), only 22 patients were from the UK (first-line: five out of 119; second-line: 17 out of 310). Following expert clinical advice, we do not have any concerns about the generalisability of patients in IMvigor10 to UK NHS patients.

The CS acknowledges that the use of data from the single-arm phase II study has limitations and states that these constraints will be overcome when ongoing phase III studies IMvigor130 (for cohort 1) and IMvigor211 (for cohort 2) are completed in 2020 and 2017 respectively.

For the economic analyses of second-line treatment, the company has merged cisplatin-ineligible and cisplatin-eligible patients into a single group who receive the same comparators i.e. docetaxel, paclitaxel and best supportive care. The CS states that the treatment patterns and response rates for patients in the second-line treatment cohort are unlikely to be different based on patients' eligibility for cisplatin, although no evidence is provided in support of this.

Sub group analysis

The scope does not specify any subgroups for the appraisal and the company has not conducted any subgroup analyses.

4.3.4 Interventions and comparators

The interventions and comparators used in the first-line and second-line patient cohorts within the economic models are summarised in Table 24.

Table 24 List of intervention and comparators used in the company's economic analyses

Patient cohort	Intervention	Comparators
First-line	Atezolizumab	Gemcitabine + carboplatin
Second-line	Atezolizumab	Docetaxel Paclitaxel Best supportive care

In summary, the comparators used in the economic models broadly align with the NICE scope for this appraisal, except for slight deviations, as discussed in section 2.3.

4.3.5 Treatment effectiveness and extrapolation

The clinical outcomes included in the CS model were progression-free survival, overall survival and time to treatment discontinuation (TTD). The company's approach for obtaining clinical effectiveness estimates for comparisons of atezolizumab against first-line and second-line chemotherapy treatments for use in the economic analysis is explained and critiqued in section 3.1 above. In summary, the company did not find any direct head-to-head comparisons of atezolizumab against chemotherapy and only single-arm studies of relevance were identified (as described above, section 3.1.3). To enable comparisons between atezolizumab and chemotherapy drugs the company conducted a simulated treatment comparison in which each individual comparator arm was compared against a 'predicted' atezolizumab arm. The predicted arm was based on a Cox regression prediction model informed by baseline covariates in the

comparator arm. These simulated atezolizumab-chemotherapy comparisons were then included by the company in network meta-analysis (using a fractional polynomial model) to produce survival hazard ratios for atezolizumab versus each comparator. We have summarised and critiqued the included comparator studies above in section 3.1.3 (their baseline characteristics are given in Table 10 and Table 11). We have also provided a summary and critique of the simulated treatment comparison and network meta-analysis methods in section 3.1.7; and the results of the meta-analysis in section 3.3.6.

For the economic analyses, Imvigor 210 was used as the primary data source for the atezolizumab arm in both the first-line and second-line patient cohorts. Estimates of the clinical effectiveness of atezolizumab versus first-line and second-line comparators were provided by hazard ratios from the company's network meta-analysis. The company used five methods to estimate treatment effects in their economic models (see Table 25):

i. Extrapolation from Imvigor 210
ii. Assumption based on the KEYNOTE-045 study: progression-free survival of gemcitabine + carboplatin, and that of docetaxel and paclitaxel are equal to progression-free survival of atezolizumab
iii. Mix cure rate model
iv. Proportional hazards model
v. Fractional polynomial with capped hazard ratio

These methods are described further in the following subsections.

Table 25 Methods to estimate treatment effects

Outcome	Intervention	Comparators		
First-line	**Atezolizumab**	**Gemcitabine + carboplatin**		
PFS	Extrapolation from IMvigor 210	Assumption: PFS of gemcitabine +carboplatin = PFS of atezolizumab		
OS	Mix cure rate model (uses data from IMvigor 210 and Life tables)	Results from fractional polynomial NMA with capped HR		
Second-line	**Atezolizumab**	**Best supportive care**	**Docetaxel**	**Paclitaxel**
PFS	Extrapolation from IMvigor 210	Use of proportional hazards model (by using the HR obtained from the fractional polynomial NMA)	Assumption: PFS of gemcitabine +carboplatin = PFS of atezolizumab	Assumption: PFS of gemcitabine +carboplatin = PFS of atezolizumab
OS	Mix cure rate model (uses data from IMvigor 210 and Life tables)	Results from fractional polynomial NMA with capped HR	Results from fractional polynomial NMA with capped HR	Results from fractional polynomial NMA with capped HR

HR: Hazard Ratio; NMA: network meta-analysis; PFS: progression-free survival

4.3.5.1 Progression-free survival

Atezolizumab (first-line and second-line)

In the company's base case, parametric distributions (exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz distributions) were fitted to the observed Kaplan-Meier data from the Imvigor 210 study to extrapolate progression-free survival curves for both first-line and second-line treatments. The company assessed the goodness of fit of these distributions by using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), visual inspection and clinical plausibility, following which the generalised gamma distribution was chosen for the base case in both the patient cohorts. The company also used the log-normal and log-logistic distributions in scenario analyses, but these did not have any significant impact on the base case ICERs (CS Table 93).

First-line comparator: gemcitabine + carboplatin

The CS states that the results of the fractional polynomial network meta-analysis (discussed earlier in section 3.3.6), when applied to the economic model, provided clinically implausible results. The company explored using the proportional hazards model and capping of hazard

ratios but argues that these approaches are not appropriate techniques to obtain progression-free survival for the comparator drugs. So, they applied an assumption that progression-free survival of gemcitabine + carboplatin is equivalent to that of atezolizumab. The CS does not justify this assumption but it mirrors an assumption that the company made for second-line comparisons (explained below) that progression-free survival curves for atezolizumab and the comparators are equivalent.

Second-line comparators: docetaxel, paclitaxel and best supportive care

For second-line comparisons, the progression-free survival of docetaxel and paclitaxel were assumed to be equivalent to that of atezolizumab. This assumption is based on an Australian phase III clinical study KEYNOTE-045[69] which included two patient cohorts: i) those who were treatment naive and ineligible for cisplatin-based chemotherapy; and ii) those who had previously received platinum-based chemotherapy. Although these patient populations align with those in this appraisal, KEYNOTE-045 compared pembrolizumab to investigator's choice of a 'blended comparison' of docetaxel, paclitaxel or vinflunine for which the data indicated a '*non-significant HR of 0.98 for PFS*' for pembrolizumab compared to the blended comparator (CS section 5.3.4). As the hazard ratio was not statistically significant and almost equivalent to 1.0, the company assumed that the progression-free survival curves for the comparators are equivalent to that of atezolizumab.

For best supportive care, the company assumed a proportional hazards model with a hazard ratio of 1.12 (CrI 0.91 to 1.37) based on the fixed-effect zero fractional polynomial model used in the economic analysis.

For validation, the company compared the progression-free survival model results against the observed clinical data from IMvigor 210 (CS Table 75). The CS states that the economic model overestimates median progression-free survival compared to the observed data.

ERG comments on the methods for modelling progression-free survival

The ERG views the standard method adopted to extrapolate progression-free survival data for both the first-line and second-line atezolizumab arms in the IMvigor 210 trial, by fitting parametric distributions, to be appropriate. In both patient cohorts, the gamma distribution is used for data extrapolation which appears to provide a good fit to the progression-free survival data, based upon AIC and BIC values and visual inspection of the survival curves.

The economic models provide an option which enabled the ERG to run the analyses not assuming that atezolizumab is equivalent to its comparators. For this scenario, in first-line treatment comparisons, the model uses parametric curves fitted to the gemcitabine + carboplatin progression-free survival data whereas for the second line treatment comparisons, the relative effects of the comparator arms i.e. docetaxel, paclitaxel and best supportive care are derived from the fractional polynomial models. In both the cases, the impacts on base case ICERs are minimal (see Table 26).

Table 26 Comparison of the CS base case results with the ERG's assumption on progression-free survival

Comparator	**ICER (£/QALY)**	
First-line	**CS Base case**	**ERG scenario: PFS of atezolizumab ≠ PFS of GEM + CAR**
Gemcitabine + carboplatin	£44,158	£43,841
Second-line	**CS Base case**	**ERG scenario: The relative effects of the comparators are obtained from FP models**
Docetaxel	£131,579	£132,250
Paclitaxel	£104,850	£99,996
Best supportive care	£98,208	£98,273

CAR: carboplatin; GEM: gemcitabine; FP: fractional polynomial; PFS: progression-free survival
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

The CS does not present any rationale for using the KEYNOTE-045 study to inform the progression-free survival parameter for the comparator arms. It is unclear if this study was identified from a systematic search. Further, IMvigor 210 and KEYNOTE-045 consist of different interventions i.e. atezolizumab and pembrolizumab, respectively. To assume that progression-free survival curves of the comparators in the current appraisal are similar to that of atezolizumab based on this Australian study implicitly indicates that progression-free survival of atezolizumab is similar to that of pembrolizumab. Whilst we acknowledge that atezolizumab and pembrolizumab belong to the same broad class of drugs, the CS does not provide any evidence that they will have similar effectiveness, and we note that they have different specific modes of action (atezolizumab is a PD-L1 inhibitor whilst pembrolizumab is a PD1 inhibitor). According to the ERG's clinical expert, there is insufficient information available on whether atezolizumab and pembrolizumab differ in effectiveness, but it would be reasonable to assume that they are similar.

4.3.5.2 Overall Survival

Atezolizumab (first-line and second-line)

The company uses a mix-cure rate model to extrapolate overall survival for the atezolizumab arms in both the patient cohorts. The mix -cure rate model estimates decline in mortality risk associated with cancer by accounting for cancer-related mortality risk and background mortality risk. Two populations - those with a low risk of cancer-related death and those with a high risk of cancer-related death are combined to produce an average survival curve for the whole population. The survival equations for these patient groups use 'cure fraction' as a factor determining trial population survival. The CS uses the dataset from the observed survival times in the IMvigor 210 study and background mortality risks from life tables. The CS assumes the cure fraction for atezolizumab is 0% in the base case (which implies 0% of patients will be at a lower risk of death due to the condition). Long-term survival data were extrapolated by fitting a generalised gamma distribution in the base case analyses. The company measured the goodness of fit using AIC and BIC statistics which justify the selection of this distribution (CS Table 53 and Table 54). Different 'cure fraction' rates ranging from 1% to 3% were assessed in scenario analyses. These alternative cure fraction rates do not have a significant impact on the base case ICERs.

First-line comparator: gemcitabine + carboplatin

To obtain overall survival curves for the comparator arm, the company uses the results from the fractional polynomial model (presented above in section 3.3.6). The CS states that using the data from the network meta-analysis results in the hazard ratio increasing linearly over time, which would inadvertently lead to clinically implausible results as the relative efficacy of atezolizumab continues to increase. As a result, the company capped the hazard ratio at the time point corresponding to the median follow-up duration of the study which, as reported by Bamias et al.[42] for the first-line cohort was at 8 months. Beyond this time point, the company assumed proportional hazards.

Second-line comparators: docetaxel, paclitaxel and best supportive care

The company used the same approach and assumption as for the first-line comparison to model overall survival for the second-line comparators. Hazard ratios were capped at the time points

corresponding to the median follow-up of the atezolizumab study which for the latest data-cut (see section 3.3) was at 21.16 months.

Table 27 and Table 28 show the parameter estimates, which the CS refers to as 'contrast estimates', from the fractional polynomial models used in the company's network meta-analysis, and the hazard ratios used in the company's economic analyses (for an overview of the fractional polynomial models see section 3.1.7 above). The derivation of hazard ratios from the contrast estimates is explained as follows:

$$\text{Log HR} = \text{Intercept} + (\text{slope}^* \text{ time points})$$

i.e., $$\text{HR} = e^{\text{Intercept} + (\text{slope}^* \text{ time points})}$$

where, time-points refer to time points in the Markov cycles.

Table 27 Contrast estimates from fractional polynomial models

Treatment	Intercept (median)	Intercept (lower bound)	Intercept (upper bound)	Slope (median)	Slope (lower bound)	Slope (upper bound)	Correlation between intercept and slope
First-line (from clarification response A33)							
Gemcitabine +carboplatin	0.21	-0.242	0.647	0.051	-0.009	0.112	-0.749
Second-line (from CS Table 24)							
BSC	0.547	0.238	0.848	-0.002	-0.038	0.034	-0.736
Paclitaxel	0.333	-0.280	0.901	0.003	-0.073	0.070	-0.738
Docetaxel	-0.168	-0.581	0.234	0.044	-0.008	0.092	-0.787

BSC: best supportive care

ERG comments on the methods for modelling overall survival

The company's approach to modelling survival in patients in the atezolizumab arm using a mix cure rate model appears to be reasonable. The ERG notes that the overall survival model results for atezolizumab compare well with the observed IMvigor 210 trial data (CS Table 76), based upon visual inspection.

Whilst the company has reported validation checks for the modelled overall survival results (by comparing the model results with results from clinical experts as shown in CS Table 77), the CS

does not report any sensitivity or scenario analyses with alternative parametric distributions. This is a major concern as the model results are very sensitive to the parametric distribution used for the intervention arm in both first-line and second-line comparisons. The CS also does not present any sensitivity analyses varying the treatment effect of atezolizumab compared to the comparator arms. Further, the CS does not report any sensitivity analyses varying the contrast estimates used within the fractional polynomial models. To address these issues, we conducted a range of sensitivity analyses, details of which are described below in section 4.4.

Table 28 Hazard ratios used in the company's economic analyses

First-line	**OS HR until 8 months**	**OS HR after 8 months**
Atezolizumab vs gemcitabine + carboplatin	0.62 (Crl: 0.47, 0.82) The value is obtained from the zero order FP model which is then used to estimate the HR at different time points until the follow up duration for the comparator study (i.e. at 8 months) at which point the HR is capped.	0.54 The economic model uses the value of 1.84 (i.e. HR of gemcitabine + carboplatin vs atezolizumab). This value is used based on the assumption of proportional hazards.
Second-line	**OS HR until 21.16 months**	**OS HR at and after 21.16 months**
Docetaxel vs atezolizumab	Results from the first-order FP model are used to estimate the HR until the time points correspond with the median follow up (i.e. at 21.16 months) at which point the HR is capped.	2.12 (this value is based on the assumption of proportional hazards)
Paclitaxel vs atezolizumab	Same as above	1.49 (this value is based on the assumption of proportional hazards)
BSC vs atezolizumab	Same as above	1.66 (this value is based on the assumption of proportional hazards)

HR: Hazard Ratio; FP: fractional polynomial; OS: overall survival

The company's choice of parametric curves for overall survival is based upon the fit with survival data for atezolizumab, assessed using AIC and BIC values and visual inspection of the parametric curves. The ERG notes that other parametric curves may also provide a good fit with the observed trial data and that the model also provides the option to use the Kaplan-Meier data with a parametric distribution for the tail of the curve. We also note that the AIC and BIC values only provide information on the fit to the observed data and do not inform the choice of the extrapolation beyond the trial, which should be based upon clinical plausibility.

The same parametric distribution is used for atezolizumab and its comparators but the company does not comment on how well the parametric distribution fits with the comparator trial data. The ERG compared the modelled overall survival results with the first-line survival results reported in the study by De Santis et al.[44] We extracted the Kaplan-Meier curve for gemcitabine + carboplatin from De Santis et al. (using Engauge digitiser). We then compared the curve with the modelled overall survival curves obtained using the company's base case results using the estimates from the fractional polynomial model and with the assumption of proportional hazards. As shown in Figure 11, the exponential distribution provides a better fit to the overall survival data in De Santis et al.[44] compared to the cure generalised gamma (i.e., the mix cure-rate model extrapolated using a generalised gamma distribution) used in the base case of the CS. As the follow-up duration for gemcitabine + carboplatin is significantly longer than for atezolizumab, it appears reasonable to base the parametric curve on the best fit for the gemcitabine + carboplatin arm, rather than the atezolizumab arm. Based on this observation, we consider that it would be appropriate to use the Kaplan-Meier data with an exponential tail to extrapolate first-line overall survival. This is explored in section 4.4 below.

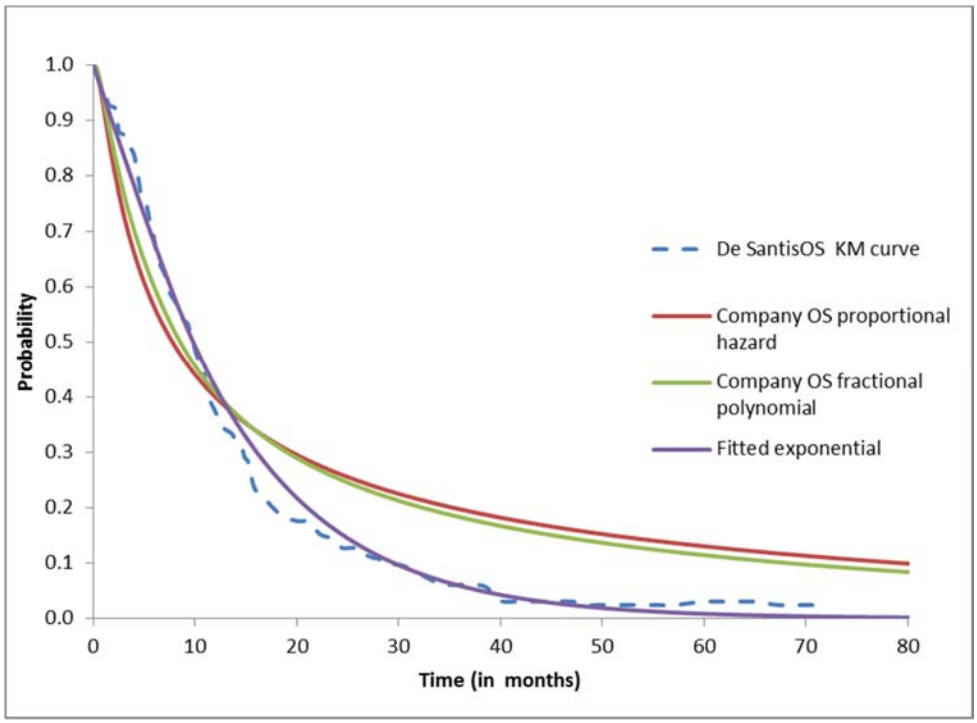

Figure 11 Comparison of the overall survival curves from De Santis et al. and the company's model

Similarly, for the second-line treatment comparisons, we compared the modelled overall survival for each of the comparator arms with the survival data presented by Bellmunt et al.[45] for best supportive care; Kim et al.[49] for docetaxel; and Lee et al[39] for paclitaxel. Of the five second-line comparator studies (i.e. those listed in Table 11), two reported survival data on best supportive care. We chose the study by Bellmunt et al.[45] to compare the modelled overall survival curve for best supportive care due to it having a larger sample size and longer follow up compared to the study by Noguchi et al.[46, 47] For docetaxel, the study by Kim et al.[49] was chosen over the study by Choueiri et al.[50] due to having a longer follow up duration. For paclitaxel, we used the only study that reported a survival curve for paclitaxel, by Lee et al.[39] A similar technique was used to extract Kaplan-Meier data for survival from these studies, as adopted for the first-line comparisons.

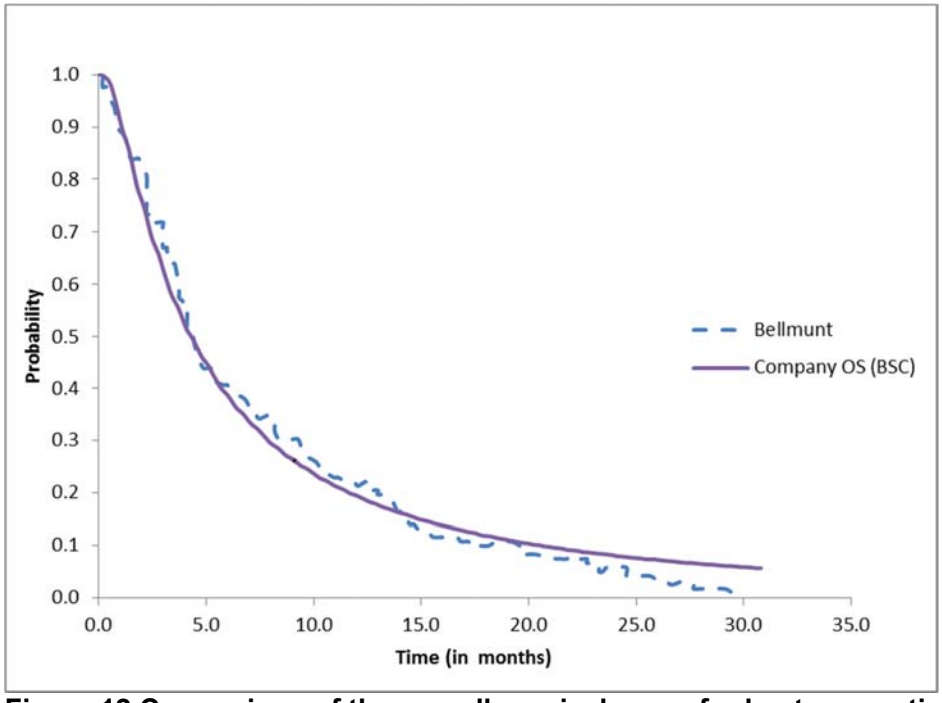

Figure 12 Comparison of the overall survival curve for best supportive care from Bellmunt et al. with the company's modelled curve

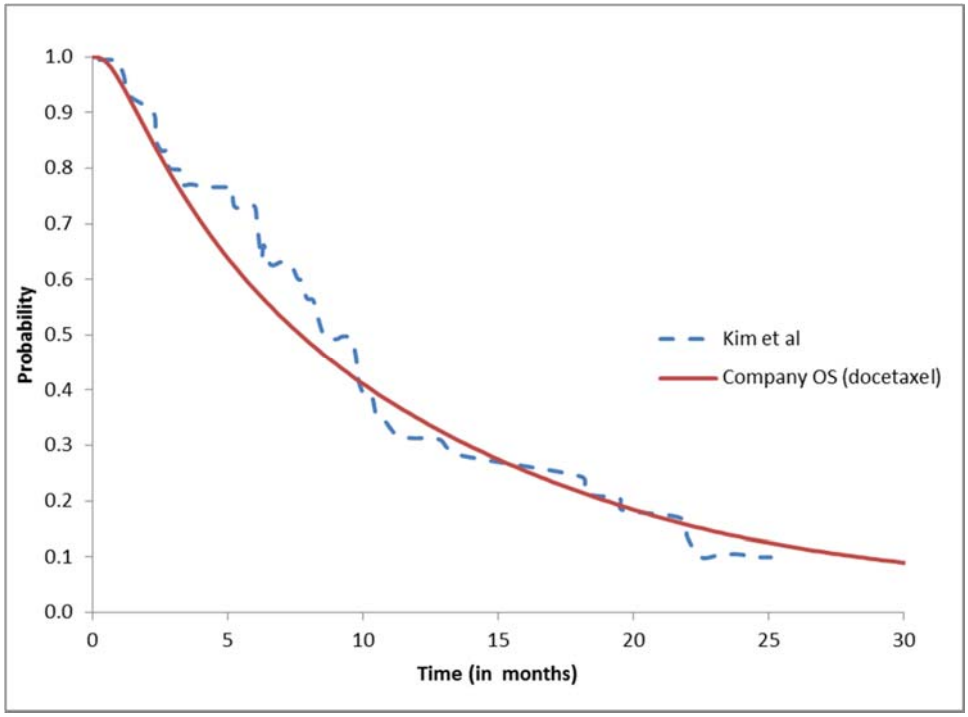

Figure 13 Comparison of the overall survival curve for docetaxel from Kim et al. with the company's modelled curve

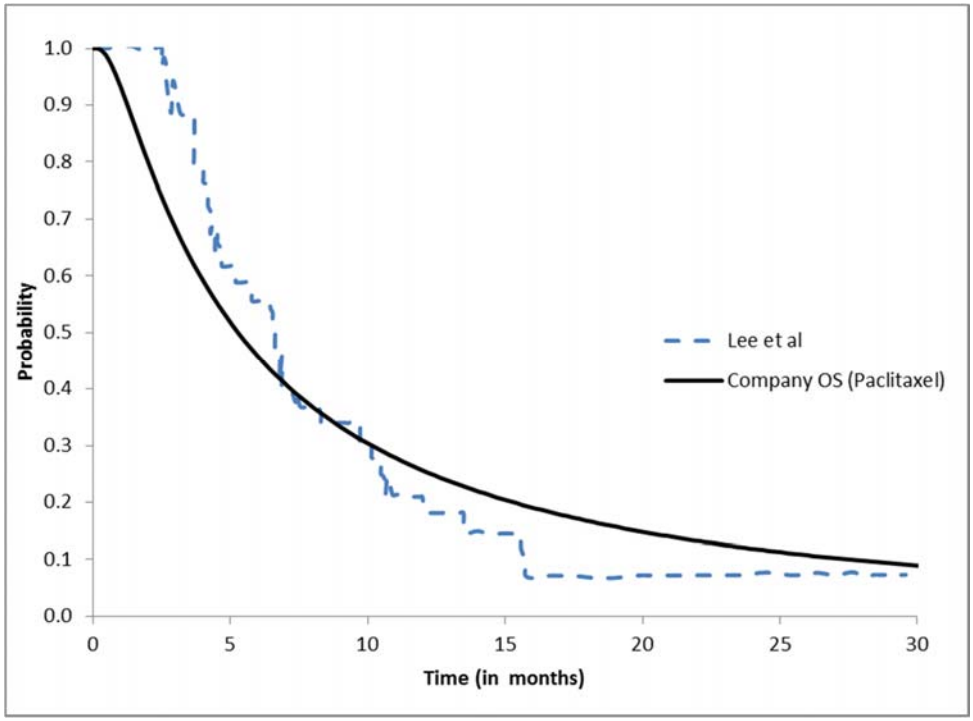

Figure 14 Comparison of the overall survival curve for paclitaxel from Lee et al. with the company's modelled curve

As shown in Figure 12, Figure 13, and Figure 14, the modelled overall survival curves for the second-line comparator arms are comparable with the survival curves reported by the studies of interest. To assess the most plausible distribution for extrapolating overall survival data, we compared different model fits for the atezolizumab arm and the best supportive care arm. The goodness of fit was measured primarily through visual inspection. We chose best supportive care for this comparison due to the available evidence being based on a larger sample size and a longer follow up period (see Table 11) for this comparator among the three comparator arms (docetaxel, paclitaxel and best supportive care) used in the economic analyses. Based on our observation, we view that Kaplan-Meier data and a Weibull curve would provide the most appropriate fit for extrapolating long term survival data. Further details of this analysis and alternative plausible survival distributions are presented in section 4.4.

The ERG notes that the company is inconsistent in the time points used to cap the hazard ratio across the two patient cohorts. As previously mentioned, the first-line hazard ratio is capped at 8 months whereas for the second-line comparisons, the cut-off is 21.16 months. For both first-line and second-line hazard ratios the assumption of proportional hazards is applied after the capping time point. The ERG conducted exploratory analyses for both first-line and second-line comparisons in which we varied the time points at which the assumption of proportional hazards starts (see section 4.4). Secondly, the ERG has concerns about the company's approach to cap the hazard ratio. The CS states this was done to arrive at clinically plausible results. However, this raises questions about whether the results from the fractional polynomial models used in the network meta-analysis are appropriate to inform the economic analyses if it is necessary to cap them in order to provide plausible results. We have performed exploratory analyses to see the effect on overall results of varying the slope of the contrast estimates. This was done to avoid needing to cap the hazard ratios. Further details of the analyses are presented in section 4.4 below.

4.3.5.3 Time to treatment discontinuation

In the CS, TTD for first- and second-line atezolizumab is captured in the model through patients transitioning in the model. Data for TTD for atezolizumab was taken directly from the IMvigor 210 study for the trial period. Beyond this time-frame, the company extrapolated discontinuation data by adopting the standard technique of fitting parametric distributions to the TTD Kaplan-Meier curves. Goodness of fit to the data was assessed using AIC and BIC and graphical

assessment. The CS states that for the first-line and second-line comparator arms, progression-free survival is used as a proxy for time on treatment. To assess uncertainty associated with TTD, the company has conducted scenario analyses in which progression-free survival is used as a proxy for time on treatment for the atezolizumab arm. The ICERs indicate that the results are sensitive to the way treatment duration is modelled. These are shown in detail in the ERG's additional analyses (section 4.4).

ERG comments on the methods for modelling time to discontinuation

On balance, for the base case, we agree with the company's approach to extrapolate TTD data for the first-line and second-line atezolizumab arms. However, they have used a generalised gamma distribution in both the patient cohorts, although the findings from the AIC and BIC statistics indicate that a Weibull function for first-line and a log-logistic function for second-line provide the best fit. Visual inspection of fitting different distributions shows that both Weibull and log-logistic for first-line treatment and other curves as stated in CS Table 67 for second-line treatment provide plausible fit to model TTD in the two patient cohorts. We ran the economic models with the alternative plausible distributions in both the patient cohorts, as discussed in the ERG's exploratory analyses in section 4.4.

In estimating TTD for the comparator arms in both the patient cohorts, the company contradicts their statement that '*PFS is not a good surrogate for treatment duration as it is likely to underestimate the true treatment duration expected in clinical practice, and as such, treatment cost*' (CS section 5.5.5, end of 1st paragraph within Atezolizumab section). The ERG notes that patients treated with first-line gemcitabine + carboplatin receive up to a maximum of six cycles of treatment and therefore TTD is not modelled according to progression-free survival. For second-line treatment, TTD associated with docetaxel and paclitaxel is modelled according to progression-free survival. However, as the costs associated with these drugs are minimal, the assumption (using progression-free survival as a proxy for TTD) does not have any significant impact on the overall model results. TTD does not apply to best supportive care as there is no associated treatment cost.

Whilst the company has conducted scenario analyses associated with the atezolizumab arm, no such analyses have been conducted for the comparator arms. This appears to be appropriate, based on the reasons outlined above. In summary, we view that the company's approach to modelling TTD within the current appraisal is reasonable.

4.3.5.4 Adverse events

The company does not model the impact of adverse events on HRQoL. The CS states that there are limited data on adverse events which is coupled with a lack of comparative data for HRQoL in metastatic urothelial carcinoma. These aspects make it challenging to incorporate the effects of adverse events on HRQoL in the economic analyses. The CS notes that EQ-5D which will be collected as part of an ongoing phase III trial (due to complete after the conclusion of the current technology appraisal) should provide more evidence on the impact of adverse events on HRQoL. However, costs associated with adverse events are incorporated in the economic models, details of which are explained below in section 4.3.7. The ERG supports these justifications with respect to adverse events.

4.3.6 HRQoL

The CS reports that HRQoL data specific to the decision problem will be available from ongoing phase III studies. Pending the completion of these studies, and for the purpose of this submission, the company conducted a systematic literature review to identify HRQoL studies for patients with advanced or metastatic urinary bladder cancer who have progressed after at least one prior chemotherapy regimen or who are intolerant of cisplatin-based chemotherapy. The electronic databases searched included Medline In-process, Embase and the Cochrane library and the search strategy (reported in CS Appendix 8.9) appears to have been appropriate according to our appraisal (section 3.1.1). The inclusion criteria specified utilities derived directly from trials, through generic preference-based instruments or through mapping studies. Studies that reported utilities in patients undergoing surgery or receiving chemotherapy were also included. After removing duplicates, the CS identified 127 references as being potentially relevant (CS Figure 30). However, after reviewing these references in detail, the company concluded that they were not relevant to the decision problem and excluded all of them. Following the exclusion of these studies, the company expanded their search criteria to include any publication reporting HRQoL data for patients diagnosed with urothelial/bladder cancer regardless of the line of treatment or the disease severity (CS Table 59). Once more, the CS reports that none of the studies identified were consistent with the reference case and therefore all the studies were excluded. The ERG agrees with the exclusions.

Having identified no relevant studies, the CS reports that relevant HTA submissions and cost-utility analyses identified during the company's review of economic evaluation publications were

re-visited (CS section 5.1; CS Table 60). Generally, the identified studies acknowledged a lack of appropriate utilities for the populations of interest and most of these studies employed mapping or preference-based elicitation from proxy populations.

Based on advice from the company's experts that utility values in the NICE guidance on vinflunine for treatment of transitional cell carcinoma of the urothelial tract[22] were too low, the company used utility values cited in the Australian Pharmaceutical benefits Advisory Committee (PBAC) cost-utility analysis for vinflunine[67] to carry out base-case cost-effectiveness analysis. The ERG's expert clinical advisor agreed that the vinflunine utility values from the NICE appraisal were too low.

The CS does not provide a complete list of the excluded 127 studies in the main text or the appendix. However, the ERG identified one additional study which included measures of HRQoL in patients with advanced urothelial carcinoma and which could potentially be used to estimate or inform utility scores: Soga et al. 2007.[70] The study by Soga et al. was is in a Japanese setting, where paclitaxel + carboplatin therapy was administered as second-line treatment to patients who had become resistant to platinum based chemotherapy. The study reports the EORTC QLQ-30 values at two time points – pre-treatment and post-treatment. We mapped these values to the EQ-5D and estimated single utility scores. The utility scores we estimated (0.707 and 0.673 for pre-treatment and post treatment respectively) indicate that patients have lower HRQoL on treatment than when not on treatment.

In the company submission, two health states account for changes in HRQoL in competing cohorts within the model. They are the 'on-treatment' or progression-free survival state and the 'off-treatment' or progressive state. The health state utility values used in the model are shown in Table 29 (CS Table 62). While utility scores are attached to these health states, the quality of life impact of adverse events is not accounted for in the model. Based on the opinion of the ERG's clinical advisor, the company's decision to ascribe a higher utility value to the 'on-treatment' state is counterintuitive, as patients are expected to have a lowered HRQoL during treatment due to the unpleasant effects of chemotherapy. The CS uses similar utility scores for both the intervention and the comparators. According to the ERG's clinical expert advisor, atezolizumab is likely to be more tolerable than the comparator chemotherapies due to its mechanism of action in the body. Therefore the assumption of similar utilities could possibly bias cost-effectiveness analysis in favour of the comparators.

Table 29 Summary of utility values for cost-effectiveness analysis (CS Table 62)

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
On-treatment	0.75 (0.150)	5.4.6	Derived from mUC patients in vinflunine Australian PBAC assesssment
Off-treatment	0.71 (0.142)	5.4.6	Derived from mUC patients in vinflunine Australian PBAC assesssment

mUC: metastatic urothelial carcinoma; PBAC: Pharmaceutical Benefits Advisory Committee

The PBAC cost-utility analysis for vinflunine[67] cited Rowen et al. 2011[71] as the source of the algorithms used in estimating utility values. Rowen et al. 2011 derived a preference based measure (EORTC-8D), which was applied to EORTC QLQ-C30 scores from a vinflunine trial to derive the utility scores for progression-free survival: vinflunine + best supportive care, 0.75; best supportive care, 0.78; and progressive disease, 0.71. The PBAC analysis also mentions a second paper by Mckenzie et al. 2009[72] which uses a mapping approach to derive preference-based utility scores from EORTC QLQ-C30. The values derived from Mckenzie et al. 2009 are lower and experts (as stated in the PBAC analysis) were said to be of the opinion that values derived from the Rowen et al. algorithm are likely to be more robust.

The CS reports sensitivity analyses that varied the utility scores. For both atezolizumab and the comparators, a lower value from the vinfluine NICE appraisal and an upper value of 1 were explored (CS Table 92). For the 'off-treatment' utility, the CS simply assumes a lower value of 0.5 and an upper value of 1. The CS sensitivity analyses (CS Figures 46 and 47, and CS Table 93) show that utility is one of the main drivers of cost-effectiveness. ERG analysis also confirms this. Therefore the ERG considers that, given the high uncertainty surrounding the base-case utility inputs in the CS model, HRQoL data derived directly from trials with atezolizumab and the comparators would lead to more robust conclusions.

The utility values used in the CS are not adjusted for age and disutilities arising from adverse events are not factored into the model. The CS states that, due to limited data, it was not feasible to model the effects of adverse reactions on HRQoL.

In the company's model, utilities are imputed in a way that is slightly inconsistent with the CS text: as stated in the CS, for atezolizumab, the 'on-treatment' utility in the model is 0.75 and the 'off-treatment' utility is 0.71; however, the base-case utilities for comparators are both set at 0.75. We carried out a scenario analysis where both utilities for atezolizumab are set at 0.75, in line with the assumption that atezolizumab is better tolerated than the comparators (see section 4.4 for details). In the same analysis we set the 'on-treatment' utility of atezolizumab to 0.71 and set the 'off-treatment' utility to 0.75 to reflect the disutilities commonly observed during treatment with chemotherapy.

4.3.7 Resource use and costs

The company conducted a systematic literature search for resource use among patients aged 18 years and above with advanced urothelial carcinoma, and their search strategy appears appropriate (section 3.1.1). The inclusion criteria specified that the outcomes of interest were direct costs, total cost, resource cost and cost drivers. The search was not restricted to studies conducted in the UK. The review identified 15 studies that met the broad search criteria of the CS. Twelve studies were further screened out and the rationale for their exclusion is stated in CS Appendix 8.11 (we note this is wrongly mentioned as Appendix 8.10 in the CS). The ERG agrees with company's rationale for excluding these studies. The three studies finally included were selected based on their relevance to the UK population. They are Seal et al. 2015[73]; Huillard et al. 2016[74]; and NICE 2013.[22]

Seal et al. 2015 estimated total all-cause costs attributable to medical services, inpatient visits and emergency department visits spanning a 6-month period pre- and post-metastatic cancer diagnosis. The setting of Seal et al. is in the US. Huillard et al. was a retrospective study that captured the proportion of patients admitted to an intensive care unit, and the utilisation of supportive care, among adults suffering from bladder cancer in their last month of life. The setting for Huillard et al. is France. The ERG notes that, although the CS states that these studies contain data of interest (See Table 64 of the CS and CS Section 5.5.1), they have not been incorporated into the model.

Resource use consists of the drug dose and its costs, administration costs per 21 day treatment cycle, adverse event management costs and weekly supportive care costs (health state costs). The CS makes the case that none of the studies identified in the company's search directly quantified costs and healthcare resource use for the population of interest from a UK NHS

perspective. The CS states that, following consultation with experts, the key sources for costs and resource inputs were a NICE appraisal on vinflunine[22] and NICE appraisals on non-small cell lung cancer.[75, 76]

While the CS model has a dose fixed at 1200mg on day one of each 21 day cycle for atezolizumab in line with ongoing IMVigor phase III trials, the dosing for comparators is in mg/m^2. The CS assumes that the average body surface area of patients in the IMvigor 210 study is representative of the model cohorts. The CS states that due to data constraints, dose modifications and treatment breaks are not assumed for atezolizumab or any of the comparators. As none of the comparators are licensed for use in metastatic urothelial carcinoma in the UK, the CS uses information from four sources. These sources are discussed in CS section 5.5.4 and listed in CS Table 65. This table is reproduced below in Table 30.

The cost of atezolizumab in the CS model is the proposed company cost stated in the CS. For the comparators (gemcitabine + carboplatin, docetaxel, and paclitaxel) the CS uses the costs stated in eMit (2015)[77] for the base-case analysis, and then estimates non-weighted averages from published list prices for scenario analysis. The ERG notes that while cost-effectiveness analysis results for the scenario analysis of the CS are given in CS Tables 93 and 94, and CS section 5.8.3, the sources of the above-mentioned non-weighted averages are not explicitly listed in the CS. Given the paucity of data, we believe the assumptions applied by company for estimating drug dose and cost to be reasonable.

Administration costs for all comparators are sourced from the National Schedule of Reference Costs - Year 2015-16 - NHS trusts and NHS foundation trusts. They are reported in Table 31 (CS Table 68). We note that an error has been made regarding the stated sources in the CS (2014-2015 instead of 2015-2016). The CS assumes the same administrative costs for atezolizumab as for docetaxel. No rationale is given for this assumption, but the ERG's clinical expert advisor suggested this is reasonable.

Table 30 Dose and drug costs for intervention and comparators (CS Table 65)

First-line	Dose	Source	List price	eMit price
Gemcitabine	1000mg/m^2 IV over 30 mins Day 1 and 8 of each 21 day cycle for maximum 6 cycles	SmPC, Guideline, phase III trial dose	200mg vial £31.60	200mg vial £3.99
Carboplatin	400mg /m^2 IV over 15 to 60 mins Day 1 of each 21 day cycle for maximum 6 cycles	SmPC,	50mg vial £21.74	50mg vial £3.57
Atezolizumab	1200mg IV over 60 mins for first infusion, thereafter 30 mins Day 1 of each 21 day cycle	Draft SmPC	1200mg vial £3807.69	n/a
Second-line	**Dose**	**Source**	**List price**	**eMit price**
Paclitaxel	80 mg/m^2 IV over 60 mins Weekly	Guideline, expert clinical advice	30mg vial £99.12 150mg vial £442.28	30mg vial £3.41 150mg vial £11.50
Docetaxel	75 mg/m^2 IV over 60 mins Day 1 of each 21-day cycle	SmPC, phase III trial	140mg vial £900.00	140mg vial £17.77
BSC	n/a	n/a	n/a	n/a
Atezolizumab	1200mg IV over 60 mins for first infusion, thereafter 30 mins Day 1 of each 21 day cycle	Draft SmPC	1200mg vial £3807.69	n/a

BSC: best supportive care; eMit: pharmaceutical electronic market information tool; IV: intravenous; SmPC: summary of product characteristics; n/a: not applicable

Table 31 Drug administration costs (CS Table 68)

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient Setting	SB12Z	£199	NHS reference costs 2015-16[78]
Docetaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB12Z	£199	NHS reference costs 2015-16[78]
Paclitaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB14Z	£304	NHS reference costs 2015-16[78]
Gemcitabine and carboplatin	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB13Z	£265	NHS reference costs 2015-16[78]

The company obtained the types and rates of adverse events for atezolizumab from IMvigor 210 (these are summarised above in section 3.3.7). Adverse event rates for the comparators were obtained from comparator studies that were included in the network meta-analysis of overall survival, but are not reported in the CS. The ERG noted some discrepancies in the adverse event data within the model (e.g. for second-line docetaxel, adverse events were taken from Chouieri et al.[50] only, not also from Kim et al.;[48, 49] and the adverse event rate for best supportive care was set to zero, although Bellmunt et al.[21, 45] reported a rate >0). The CS does not discuss these issues, although the ERG believes they are relatively unimportant compared to other sources of uncertainty in the company's analysis.

Details of adverse event costing are given in CS Table 70. Note that there are discrepancies between CS Table 70 and the company's model. For instance, while renal failure is listed in CS Table 70 as having a cost £310.00, it was omitted in the company's model. Leucopenia is said to cost £362.22 in CS Table 70 while in the model it is set at £362.66. The NICE appraisal[75]

referenced in the CS states a 2014 Department of Health cost of £354.72. The ERG notes that these errors have a negligible impact on the results of cost-effectiveness analysis. We also observed that references for certain adverse events (alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increase, diarrhoea, electrolyte abnormalities, hypophosphataemia and infection) are not included in the CS references. The ERG and NICE raised this issue with the company and the company provided the reference for these adverse events (clarification response B3).

The company's systematic review did not identify any relevant resource use data associated with health states in metastatic urothelial carcinoma. The CS states that resource use was elucidated through expert clinical advice, and deemed appropriate by the ERG and NICE appraisal committee on vinflunine. [22] The CS uses these same assumptions (summarised in Table B39 of the manufacturer submission for TA272, January 2013) in CS Table 69. We note that the health home visit cost is referenced as Curtis 2016 but that publication does not report this cost. The ERG and NICE queried this with the company and in response the company described the error as typographical (clarification response B1). The company stated that the correct reference for the health home visit cost is the manufacturer's submission for vinflunine. Health state costs are slightly higher in the CS and the company explained further in their clarification that they have been inflated to 2015/16 costs.

Resource utilisation for health states is estimated on a per cycle basis in the CS, calculated from separately stated unit costs and frequency of use per month. In the CS, the pre-progression state costs amounted to £111.85, while the post-progression costs amounted to £146.79. despite the paucity of data, the company's approach is consistent with the reference case. The CS reports one-way sensitivity analysis for monthly atezolizumab off-treatment supportive care costs, and comparator off-treatment supportive care costs, varying between a lower value of half the base case and an upper value increased by 50% of the base case value. The ERG notes that the values used in these sensitivity analyses are arbitrary but in the absence of relevant data they are reasonable to capture the high uncertainty surrounding the cost inputs.

4.3.8 Model validation

4.3.8.1 Internal consistency

The CS reports (CS section 5.10.1) that clinical experts were consulted to validate key aspects of the model including methodological and clinical assumptions. The assumptions included the model structure and health states, the prediction model, overall survival and progression-free survival extrapolation, utility values and resource use. The CS reports that internal quality control was completed for the two models by an external consultancy (ICON). The models were internally validated by checking formulas, cell references and model functionality. The models were 'pressure tested' by using extreme values and comparing these results with the expected outcomes.

The economic models are coded in Microsoft Excel and are fully executable and user-friendly. We have not undertaken a comprehensive check of all cells in the models; internal consistency checks have been performed and random checking of the models has been done for some of the key equations in the models. We have performed a detailed checking of all model inputs reported in the CS (white box testing); changing the parameter values produced intuitive results (black box testing) and from random checking the 'wiring' of the model appears to be accurate. Through our checking of the models, we have not identified any errors, except for some errors in the reporting of costs (as discussed in section 4.3.7).

4.3.8.2 External consistency

The CS has not compared the results from their modelling to other external models.

The ERG compared the costs and QALYs for best supportive care for the current submission to the previous submission for vinflunine. The results are shown in Table 32 below.

The costs for best supportive care in the previous vinflunine appraisal were almost double those for the current appraisal, largely as a result of differences in health state costs. The QALYs were less than half for best supportive care in the vinflunine appraisal compared to the current submission, due to the utility values for post-progression in the vinflunine submission being substantially lower than the current submission. The life years for best supportive care were lower for the vinflunine appraisal compared to the current submission, which may be due to a different distribution being chosen that had a shorter extrapolated 'tail'.

Table 32 Comparison of best supportive care results for the current submission and a previous submission on vinflunine

Comparator	Costs, £	Life years	QALYs
BSC (from vinflunine appraisal)	£8642	0.63	0.234
BSC (from atezolizumab appraisal)	£4836	0.75	0.55

BSC: best supportive care; QALY: quality-adjusted life year

4.3.9 Cost effectiveness Results

Results from the economic model (section 5.7 of the CS) are presented as the incremental cost per QALY gained for first-line atezolizumab compared with gemcitabine + carboplatin and for second-line comparisons with docetaxel, paclitaxel and best supportive care.

For the first-line base case an incremental cost per QALY gained of £44,158 per QALY is reported (see Table 33) for atezolizumab compared to gemcitabine + paclitaxel. For the second-line base case, the ICERs for atezolizumab compared to docetaxel, paclitaxel and best supportive care are £131,579, £104,850, £98,208 per QALY gained respectively.

Table 33 First-line base case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£77,211	3.74	2.69				
Gemcitabine + carboplatin	£18,106	1.84	1.35	£59,106	1.91	1.34	£44,158

ICER: incremental cost-effectiveness ratio; LYG: life years gained: QALYs: quality-adjusted life years

Table 34 Second-line base case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)[a]
Atezolizumab	£71,868	1.69	1.23				
Docetaxel	£9,439	1.04	0.76	£62,430	0.65	0.47	£131,579
Paclitaxel	£16,606	0.96	0.71	£55,262	0.73	0.53	£104,850
BSC	£4,836	0.75	0.55	£67,032	0.94	0.68	£98,208

ICER: incremental cost-effectiveness ratio; LYG: life years gained: QALYs: quality-adjusted life years

[a] Pairwise comparison with atezolizumab.

The CS summarises the results of the PSA by presenting these as ICERs in CS Tables 90 and 91. The ICER for first-line atezolizumab compared to gemcitabine + carboplatin is £47,593 per QALY gained and £129,333 per QALY for the second-line comparison to paclitaxel. The CS urges caution in the interpretation of the PSA results and states that they are unlikely to be reliable due to the high level of uncertainty in the fractional polynomial model.

The CS comments that the first-line base-case ICER is below the acceptable willingness to pay threshold for a treatment considered under the end-of-life criteria. The base case ICER based on the proposed list price of atezolizumab in second-line metastatic urothelial carcinoma treatment is above the acceptable threshold for all comparators.

4.3.10 Assessment of Uncertainty

One-way sensitivity analyses

The company varied the following parameters in deterministic sensitivity analyses: cost of atezolizumab, on-treatment utility (atezolizumab), on-treatment utility (comparator), off-treatment utility, off-treatment care costs (atezolizumab) and off-treatment care costs (comparator). The parameter values used in the analyses and rationale for their choice are shown in Table 35. Results of the analyses are displayed in Figure 15 to Figure 18.

Table 35 Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value	Rationale for value range
Monthly cost of atezolizumab	£5500	+ 50%	- 50%	
Atezolizumab on-treatment utility	0.750	0.653	1	Lower value: Prior NICE mUC appraisals Higher value: Maximum utility value
Comparator on- treatment utility	0.750	0.653	1	Lower value: Prior NICE mUC appraisals Higher value: Maximum utility value
Off-treatment utility	0.71	0.5	1	Lower value: 50% of possible utility value Higher value: 100% of possible utility value
Atezolizumab off-treatment supportive care costs	£146.79	+50%	-50%	
Comparator off- treatment supportive care costs	£146.79	+50%	-50%	

mUC metastatic urothelial carcinoma

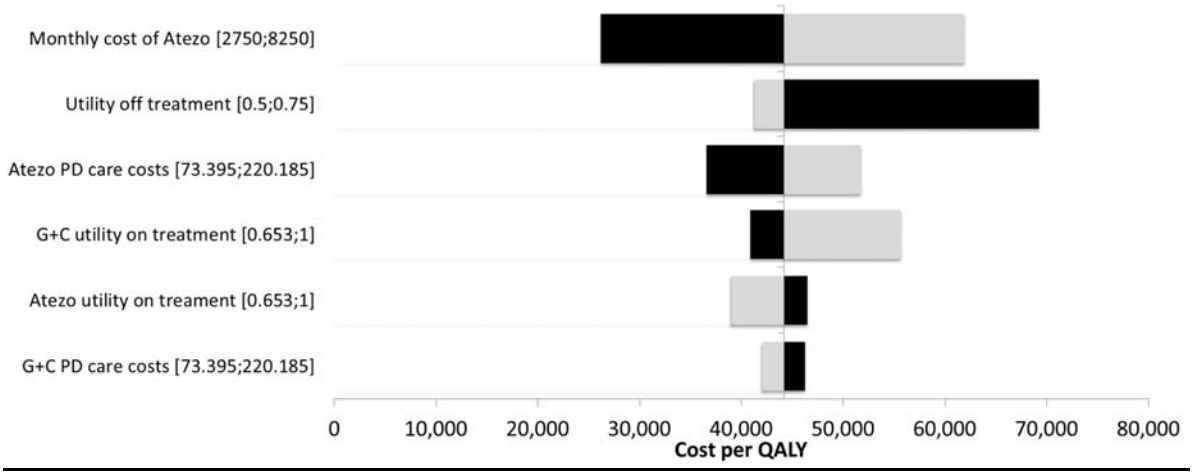

Figure 15 Univariate sensitivity analysis for comparison of first-line atezolizumab to gemcitabine + carboplatin (dark bar = lower value; light bar = higher value)

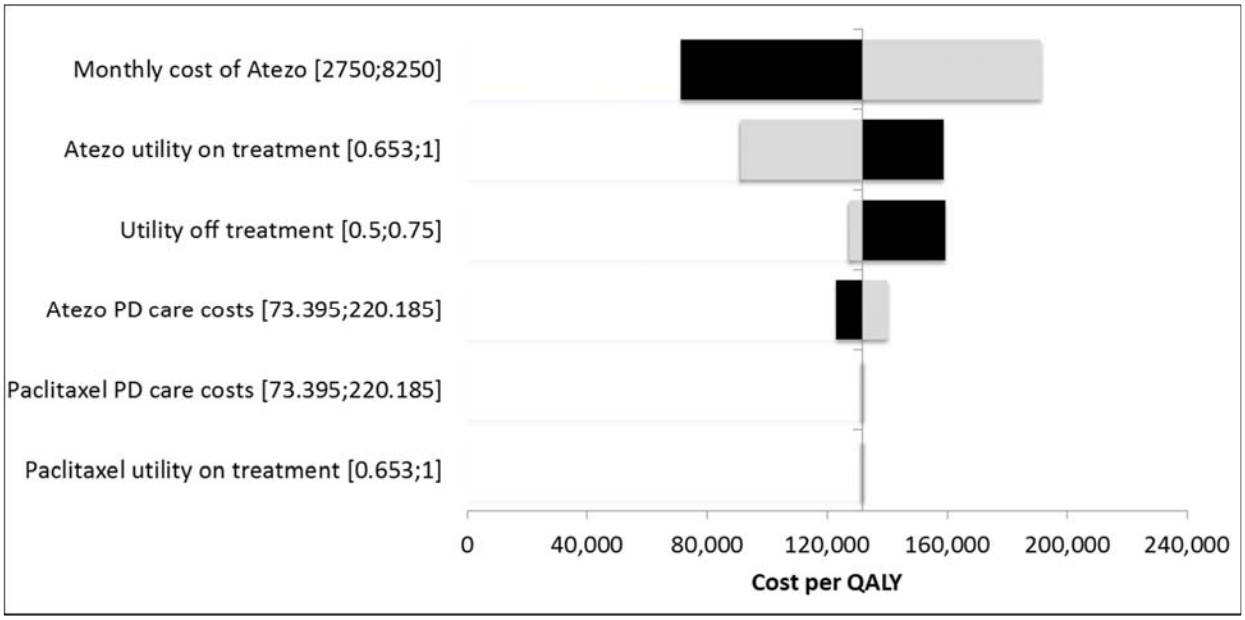

Figure 16 Univariate sensitivity analysis for comparison of second-line atezolizumab to docetaxel (dark bar = lower value; light bar = higher value)

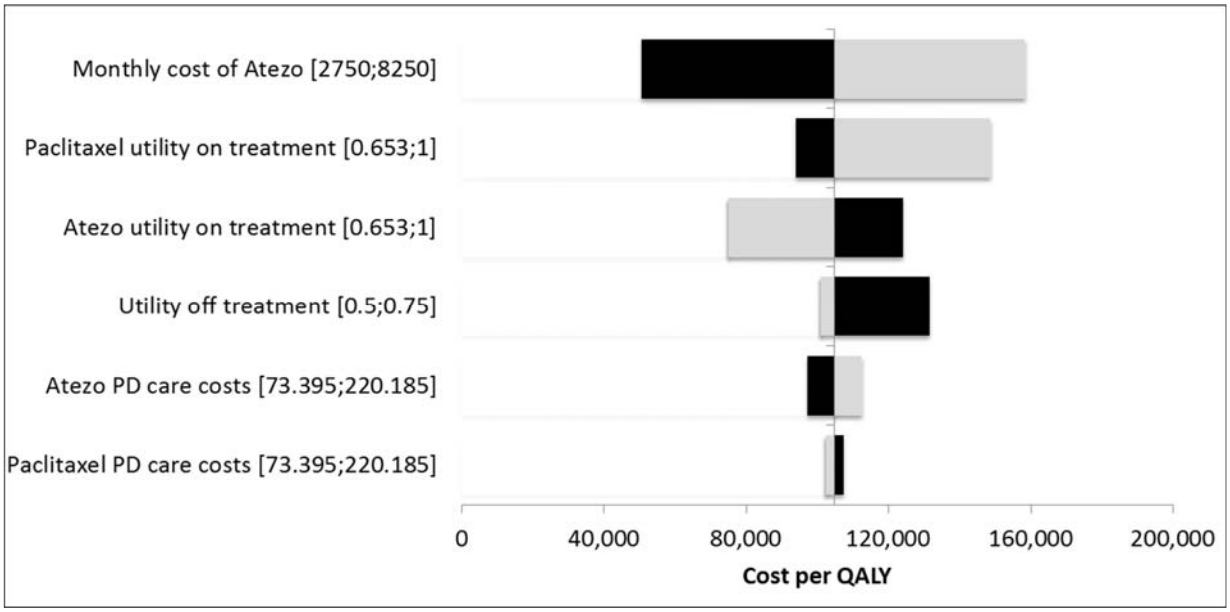

Figure 17 Univariate sensitivity analysis for comparison of second-line atezolizumab to paclitaxel (dark bar = lower value; light bar = higher value)

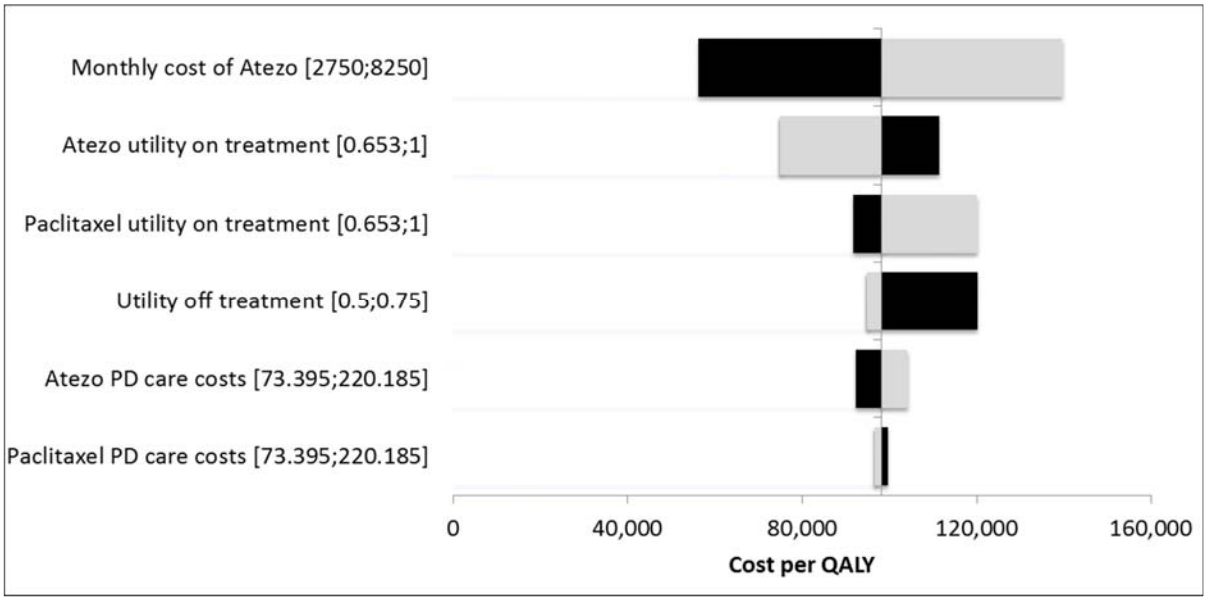

Figure 18 Univariate sensitivity analysis for comparison of second-line atezolizumab to best supportive care (dark bar = lower value; light bar = higher value)

The ERG notes that some of the input parameters have been varied in the sensitivity analyses and others have been varied in the scenario analyses. Some parameters have not been varied

in either analysis, such as alternative overall survival distributions. We note that the on-treatment utility and the treatment supportive costs for atezolizumab and its comparators have been varied independently. However, we consider that these parameters will be highly correlated between treatments.

The main drivers of the first-line economic analysis results are the price of atezolizumab and the utility of patients in the progressed disease state. The CS states that the ICER remains below the end-of-life willingness to pay threshold in the majority of scenarios explored. For the second-line results, the ICER is most sensitive to the price of atezolizumab. The ERG notes that the parametric survival functions for overall survival have not been varied in either the sensitivity analyses or the scenario analyses and these are also drivers of the first-line and second-line economic analysis results.

Scenario Analyses

The company conducted scenario analyses to assess uncertainty around structural assumptions and changes to input parameters for the model. The following scenarios were explored for parameter changes to: drug costs for comparators; alternative overall survival cure-rates; alternative progression-free survival parametric distributions; progression-free survival as a proxy for treatment duration for atezolizumab; on-treatment utilities; off-treatment utilities; time horizons of 10 years; and cost and effects discount rates.

Results are shown below in Table 36 and Table 37 for first-line comparisons (CS Table 93) and second-line comparisons (CS Table 94). The results are most sensitive to changes to assumptions around the treatment duration, the time horizon and off-treatment utility.

The ERG notes that there are no scenario analyses varying the distributions used for overall survival. The ERG investigated the effect of varying these parameters as reported in section 4.4 below.

Table 36 Scenario analysis results for first-line atezolizumab vs gemcitabine + carboplatin

Scenario	Parameter	Value	ICER vs gemcitabine + carboplatin
Base case	Comparator price	eMIT drug prices	£44,158
		List prices	£41,309
Base case	Cure rate	0%	
		1%	£44,026
		2%	£43,891
		3%	£43,754
Base case	Distribution PFS	Gamma	£44,158
		Log-normal	£44,075
		Log-logistic	£44,139
Base case	Comparator relative effect PFS	Equal to atezolizumab	
Base case	Treatment duration assumption	Actual treatment duration	£44,158
		Until progression	£64,365
Base case	Time horizon	20	£44,158
		10	£58,992
		15	£48,563
Base case	On-treatment utility (all products)	0.750	£44,158
	Atezolizumab on-treatment utility	0.800	£43,028
	GEM + CAR on-treatment utility	0.653	£40,884
Base case	Off-treatment utility	0.710	£44,158
		0.500	£69,252
		0.750	£41,307
Base case	Discount rate – effects and costs	3.5% for both	£44,158
	Discount rate - costs	1.5% (3.5% for effects)	£46,807
	Discount rate – effects	1.5% (3.5% for costs)	£37,859
	Discount rate – effects and costs	1.5% for both	£40,130

CAR: carboplatin; eMit: pharmaceutical electronic market information tool: GEM: gemcitabine; ICER: incremental cost-effectiveness ratio

Table 37 Scenario analysis results for second-line atezolizumab vs docetaxel, paclitaxel or best supportive care

Scenario	Parameter	Value	ICER vs docetaxel	ICER vs paclitaxel	ICER vs BSC
Base case	Comparator price	eMIT drug prices	£131,579	£104,850	£98,208
		List prices	£108,819	£72,477	£98,208
Base case	Cure rate	0%	£131,579	£104,850	£98,208
		1%	£126,277	£101,507	£95,403
		2%	£121,364	£98,369	£92,708
		3%	£116,805	£95,430	£90,115
Base case	Distribution PFS	Gamma	£131,579	£104,850	£98,208
		Log-normal	£131,509	£108,757	£97,819
		Log-logistic	£131,427	£109,624	£97,581
Base case	Comparator relative effect PFS	Equal to atezolizumab	£131,579	£104,850	£98,208
		FP	£132,250	£99,996	£98,273
Base case	Treatment duration assumption	Actual treatment duration	£131,579	£104,850	£98,208
		Until progression	£102,982	£78,727	£78,028
Base case	Time horizon	20	£131,579	£104,850	£98,208
		10	£158,410	£119,719	£109,318
		15	£139,012	£109,279	£101,541
Base case	On-treatment utility (all products)	0.750	£131,579	£104,850	£98,208
	Atezolizumab on-treatment utility	0.800	£120,864	£97,100	£92,507
	Comparator on-treatment utility	0.653	£117,567	£94,104	£91,738
Base case	Off-treatment utility	0.710	£131,579	£104,850	£98,208
		0.500	£159,492	£131,530	£120,299
		0.750	£127,334	£100,949	£94,889
Base case	Discount rate – effects and costs	3.5% for both	£131,579	£104,850	£98,208
	Discount rate - costs	1.5% (3.5% for effects)	£136,976	£108,999	£102,067
	Discount rate – effects	1.5% (3.5% for costs)	£116,599	£95,227	£89,962
	Discount rate – effects and costs	1.5% for both	£121,382	£98,995	£93,497

BSC: best supportive care; eMit: pharmaceutical electronic market information tool; ICER: incremental cost-effectiveness ratio; PFS: progression-free survival

Probabilistic Sensitivity Analyses

The company performed probabilistic sensitivity analyses using 1000 simulations. The simulation takes about 2 minutes to run. The distributions and sources to estimate parameters are reported in CS Table 71 (CS section 5.6). The analyses were based on the proposed list price of atezolizumab, and the eMIT drug prices for the comparators. Patient age, discount rate, time horizon and costs for the atezolizumab and the comparator treatments were not varied in the analyses. Utility values were varied using the beta distribution; the parametric survival curves were varied using the multivariate normal distribution; and costs were varied by the log-normal distribution. The ERG considers that the distributions used in the PSA were appropriate. We note that the on-treatment utilities for atezolizumab and the comparators have been varied independently and the treatment supportive costs for atezolizumab and its comparators have also been varied independently. However, we consider that the on-treatment utilities will be highly correlated between treatments and in the same way the supportive care costs will be highly correlated between treatments.

The results of the first-line and second-line PSA are presented in Table 38 and Table 39. The probability of first-line atezolizumab being cost-effective is 10.9% and 53.9% at willingness to pay thresholds of £30,000 and £50,000 per QALY respectively. The probability of second-line atezolizumab being cost-effective is 0% and 0% at willingness to pay thresholds of £30,000 and £50,000 per QALY respectively

The results for the PSA differ from those presented for the deterministic base case, with the PSA ICERs for atezolizumab about 10-20% higher than for the deterministic results. The first-line and second-line cost effectiveness acceptability curves are shown in Figure 19 and Figure 20. The probability of first-line atezolizumab being cost-effective is 10.9% and 53.9% at a willingness to pay thresholds of £30,000 and £50,000 per QALY respectively. The probability of second-line atezolizumab being cost-effective is 0% and 0% at willingness to pay thresholds of £30,000 and £50,000 per QALY respectively

Table 38 Probabilistic sensitivity analysis results for first-line treatment

	Costs	QALYs	ICER (£/QALY)
Atezolizumab	£82,893	2.775	
Gemcitabine + carboplatin	£20,605	1.467	£47,593

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

.

Table 39 Probabilistic sensitivity analysis results for second-line treatment

	Costs	QALYs	ICER (£/QALY)
Atezolizumab	£74,165	1.26	
Docetaxel	£10,621	0.82	£143,144
Paclitaxel	£18,075	0.83	£129,333
BSC	£5,637	0.58	£101,247

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

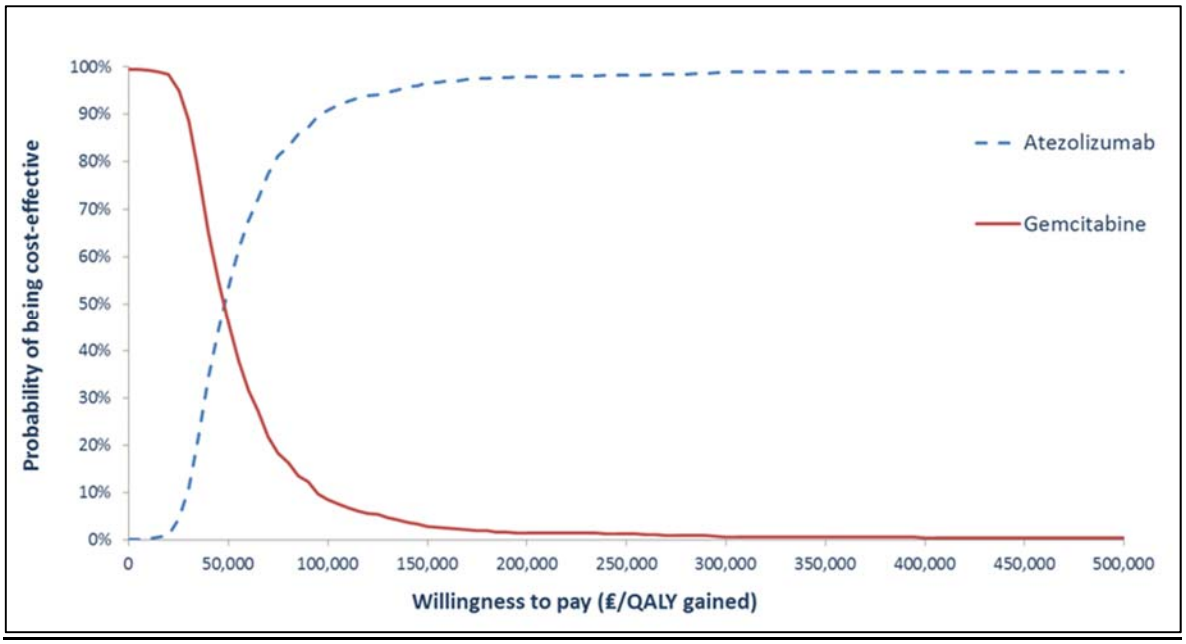

Figure 19 Cost-effectiveness acceptability curves for first-line treatment

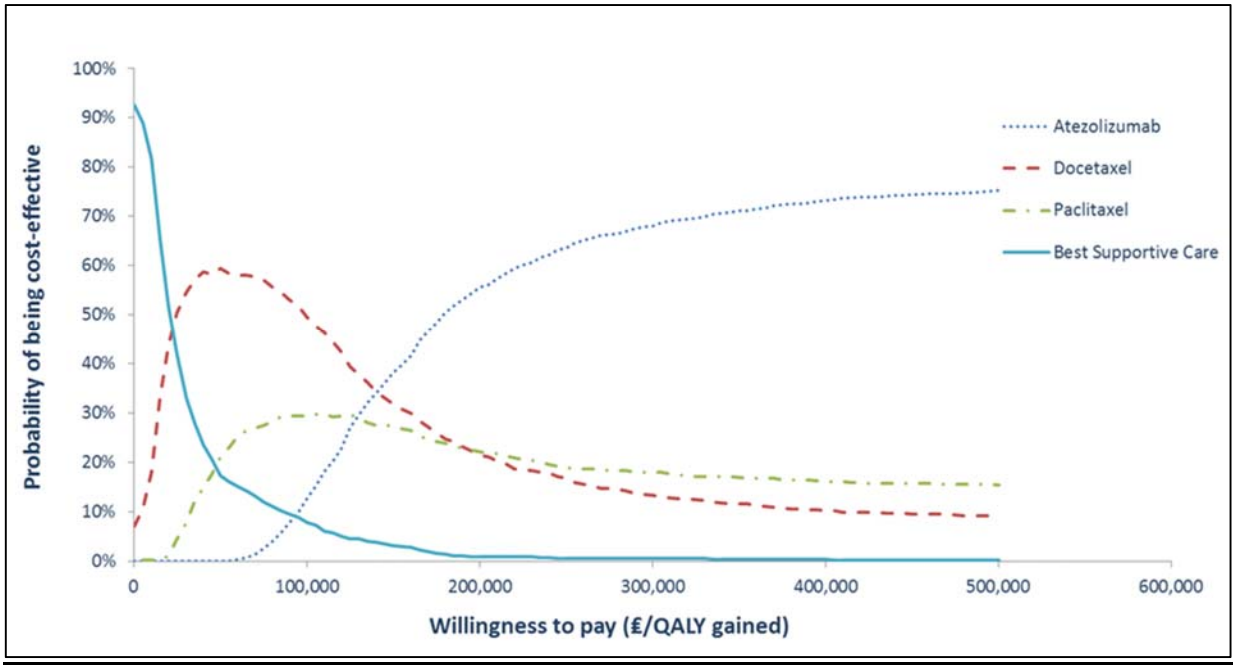

Figure 20 Cost-effectiveness acceptability curves for second-line treatment

The CS discusses the results of the PSA and states that they should be interpreted with caution, as they are unlikely to be reliable. The CS notes that there is a high level of uncertainty in the fractional polynomial model and the prediction model provides a skewed output for overall survival, which leads to an unrealistically large proportion of patients in the comparator arms surviving beyond 20 years for some of the probabilistic analyses.

4.4 Additional work undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost effectiveness analyses. This consists of five additional sensitivity analyses: i) for the parametric functions for extrapolating TTD and overall survival, ii) the treatment effect and iii) assumptions for the time point at which to cap hazard ratios; iv) varying contrast estimates and varying utility values.

i) Time to treatment discontinuation / overall survival extrapolation

The CS does not contain sensitivity analyses for different parametric distributions for TTD and overall survival. These were varied by the ERG for alternative plausible parametric distributions for first-line and second-line treatment comparisons in Table 40 and Table 41. The model allows

the use of the Kaplan-Meier data for the first part of the survival curve, followed by a parametric function for the extrapolation of the tail of the curve. Changing the parametric distributions for TTD and overall survival has a significant effect on the model results. Changing both parametric functions for TTD and overall survival shows there is considerable uncertainty in the model results. For example, with the log-logistic function for TTD and the Weibull function for overall survival, the ICER increases from the base case of £44,158 to £124,485 per QALY for first-line atezolizumab compared to gemcitabine + carboplatin. For second-line comparisons, with the log-logistic function for TTD and lognormal function for overall survival, the ICER increases from the base case of £104,850 to £165,527 per QALY for atezolizumab compared to paclitaxel. As shown in Table 40, other choices of parametric distribution produce even higher ICERs.

Table 40 ERG sensitivity analyses selecting different parametric functions for extrapolating TTD and overall survival for first-line treatment

First-line		
Parameter	**Value**	**ICER (£/QALY) vs gemcitabine + carboplatin**
TTD	Base case (gamma)	£44,158
	Weibull	£42,683
	Log-logistic	£66,750
OS	Base case (cure generalised gamma)	£44,158
	Log-logistic	£51,387
	K-M + Weibull tail	£79,592
	K-M + Gompertz tail	£101,711
TTD / OS	Base case	£44,158
	TTD: log-logistic; OS: K-M + Weibull	£124,485
	TTD: log-logistic; OS: K-M + Gompertz	£159,590

ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; TTD: time to treatment discontinuation

Table 41 ERG sensitivity analyses selecting different parametric functions for extrapolating TTD and overall survival for second-line treatment

Second-line				
Parameter	**Value**	**ICER (£/QALY) vs docetaxel**	**ICER (£/QALY) vs paxlitaxel**	**ICER (£/QALY) vs BSC**
TTD	Base case (gamma)	£131,579	£104,850	£98,208
	Weibull	£119,025	£93,370	£89,322
	Log-logistic	£180,213	£149,491	£133,035
OS	Base case (cure generalised gamma)	£131,579	£104,850	£98,208
	Lognormal	£172,146	£131,214	£120,612
	Log-logistic	£149,321	£117,785	£110,144
	K-M + Weibull tail	£287,175	£176,090	£153,806
	K-M + Gompertz tail	£310,246	£182,347	£158,396
TTD / OS	Base case	£131,579	£104,850	£98,208
	TTD log-logistic; OS lognormal	£211,180	£165,527	£147,261
	TTD log-logistic; OS K-M + Weibull tail	£302,826	£187,599	£162,359
	TTD log-logistic; OS K-M + Gompertz tail	£324,116	£192,246	£165,707

ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; TTD: time to treatment discontinuation

ii) Treatment effect

The CS does not contain sensitivity analyses varying the treatment effect of atezolizumab. The ERG varied the treatment effect according to the lower and upper bounds of the contrast estimates for overall survival. The contrast estimates consist of two parameters: intercept and slope from the fractional polynomial model and bounds have been provided for both these parameters. It is unclear which values should be used when varying the contrast estimates, so the intercept parameter values have been varied only and the slope parameter kept constant. The effect of varying these parameters is shown in Table 42. The sensitivity analyses show that the ICER varies substantially at the lower and upper bounds. For the first-line comparison, the ICER varies between £33.432 and £191,793 per QALY gained for atezolizumab compared to gemcitabine + carboplatin. For second-line comparisons, atezolizumab is dominated by its comparator using the intercept lower bound (i.e. atezolizumab is more expensive and less

effective than its comparators). Using the intercept upper bound, the ICER for atezolizumab is £87,990 versus docetaxel, £68,427 versus paclitaxel and £79,017 versus best supportive care. For comparison, we have also included a sensitivity analysis for first-line treatment using the upper and lower confidence interval for the hazard ratio assuming proportional hazards. Using these values, there is a much smaller variation in ICER than for the analysis with the fractional polynomial contrast estimates.

Table 42 ERG sensitivity analyses comparing atezolizumab vs comparators for treatment effect

Parameter	First-line	ICER (£/QALY)		
		vs gemcitabine + carboplatin		
Treatment effect, OS	Fractional polynomial	£44,158		
	Fractional polynomial (Intercept lower bound)	£191,793		
	Fractional polynomial (Intercept higher bound)	£33,432		
	Proportional hazard, HR = 0.62	£46,562		
	HR = 0.47	£36,488		
	HR = 0.82	£87,898		
	Second-line	**vs docetaxel**	**vs paxlitaxel**	**vs BSC**
	Base case	£131,579	£104,850	£98,208
	Fractional polynomial (Intercept lower bound)	Dominated [a]	Dominated [a]	Dominated [a]
	Fractional polynomial (Intercept higher bound)	£87,990	£68,427	£79,017

BSC: best supportive care; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year
[a] Atezolizumab is more expensive and less effective than its comparators

iii) Capping of hazard ratios

As discussed in section 4.3.5, the ERG has some concerns around the parameter estimates derived from the network meta-analysis using the fractional polynomial model approach. The company caps the hazard ratio at different time points for first-line and second-line comparisons. The ERG investigated changing the time point at which the hazard ratios are capped and reducing the contrast estimate slope parameter so that it is no longer necessary to cap the hazard ratios.

The effects of changing the time point at which the hazard ratios are capped are shown in Table 43. The time points were varied so that they are the same for first-line and second-line comparisons. The results show that for the second-line comparison of atezolizumab versus docetaxel there is a large impact on the ICER, which increases to £310,395 per QALY.

Table 43 ERG sensitivity analyses varying the time until hazard ratios are capped

Parameter	First-line	ICER (£/QALY)		
		vs gemcitabine + carboplatin		
Time to cap hazard ratios	8 months (base case)	£44,158		
	21.16 months	£35,764		
	Second-line	**vs docetaxel**	**vs paxlitaxel**	**vs BSC**
	21.16 months (base case)	£131,579	£104,850	£98,208
	8 months	£310,395	£107,514	£97,397

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

iv) Reducing the slope parameter for the contrast estimates

The effect of reducing the slope contrast estimate so that capping the hazard ratios is no longer needed is shown in Table 44. The time to cap the hazard ratio was increased to 20 years (i.e. at the end of the model duration). As for the preceding analysis, the largest effect of varying the slope parameter is for the second-line comparison between atezolizumab and docetaxel, with the ICER increasing to £193,686 per QALY.

Table 44 ERG sensitivity analyses varying the slope parameter

Parameter	First-line	ICER (£/QALY)		
		vs gemcitabine + carboplatin		
Slope parameter estimate	0.051 (base case)	£44,158		
	0.01	£47,505		
	Second-line	**vs docetaxel**	**vs paxlitaxel**	**vs BSC**
	0.044 (base case)	£131,579	£104,850	£98,208
	0.02	£193,686	£101,835	£99,417

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

v) Utility values

The assumptions used by the company for health state utility values differed from the advice received by the ERG from their clinical expert. We considered that patients on-treatment with

atezolizumab would have a higher HRQoL than those on gemcitabine + carboplatin, docetaxel or paclitaxel. The CS and the ERG's assumption for the utility values for the on-treatment and off-treatment utility values for the pre-progression health state are shown in Table 45. The results of the sensitivity analyses using the ERG's assumption for the utility values are shown in Table 46. The ICER decreases slightly for the analyses for atezolizumab compared to gemcitabine + carboplatin (first-line), docetaxel and paxlitaxel (second-line) and increases slightly for atezolizumab compared to best supportive care (second-line).

Table 45 Pre-progression utility values used in the CS and the ERG analysis

	CS Pre-progression utility		**ERG pre-progression utility values**	
	Atezolizumab	Comparators	Atezolizumab	Comparators
On-treatment	0.75	0.75	0.75	0.71
Off-treatment	0.71	0.75	0.75	0.75

Table 46 ERG sensitivity analyses with changes to the assumptions for pre-progression health state utility values

Parameter	**First-line**	**ICER (£/QALY)**		
		vs gemcitabine + carboplatin		
Utility values	Base case	£44,158		
	ERG assumption	£43,317		
	Second-line	**vs docetaxel**	**vs paxlitaxel**	**vs BSC**
	Base case	£131,579	£104,850	£98,208
	ERG assumption	£127,528	£101,654	£99,409

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

ERG base case analysis

Table 47 lists the assumptions used for the ERG base case, along with their justifications. The first-line treatment results for the ERG base case are shown in Table 48 and the second-line treatment results in Table 49. The ERG considers this presents the most representative analysis of the available evidence for atezolizumab for first- and second-line treatment compared to its comparators.

Table 47 Assumptions for the ERG base case analysis

Treatment line	Parameter	Value	Justification
First- and second-line	Utility	As shown in Table 45	Clinical expert advice to ERG
First-line	OS	K-M + exponential tail	Best fit for atezolizumab and gemcitabine + carboplatin
	TTD	Weibull	Best fit according to AIC and/ BIC
Second-line	OS	KM + Weibull tail	Best fit for atezolizumab and BSC
	TTD	Log-logistic	Best fit according to AIC and BIC

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; K-M: Kaplan-Meier; OS: overall survival; QALY: quality-adjusted life year; TTD: time to treatment discontinuation; AIC Akaike Information Criteria; BIC Bayesian Information Criteria

Table 48 ERG first-line base case analysis results

	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
Atezolizumab	£60,650		1.32		
Gemcitabine + carboplatin	£12,469	£48,181	0.81	0.51	£93,948

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

The ERG base case ICER for first-line atezolizunab compared to gemcitabine + carboplatin is £93,948 per QALY gained. The overall survival curves for first-line treatment for the observed trial data compared with the company's fitted curves and the ERG's base case are shown in Figure 21.

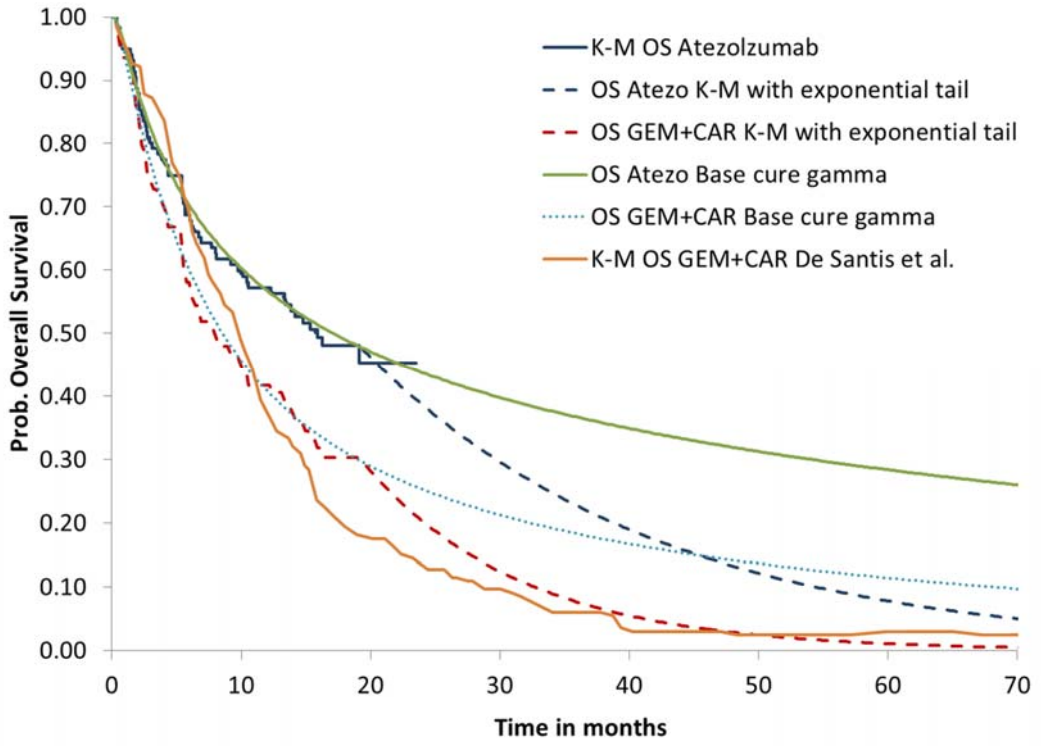

Figure 21 Overall survival curves for first-line treatment for observed trial data compared with company's fitted curves and ERG's base case

Table 49 ERG second-line base case analysis results

	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
Atezolizumab	£66,254		0.84		
Docetaxel	£8,196	£58,059	0.64	0.20	£288,247
Paclitaxel	£13,615	£52,640	0.55	0.29	£180,901
BSC	£4,090	£62,164	0.47	0.37	£166,805

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

The ERG base case ICER for second-line atezolizumab compared to docetaxel, paclitaxel and best supportive care is £288,247, £180,901 and £166,805 per QALY gained respectively. The overall survival curves for second-line treatment for atezolizumab compared to best supportive care for the observed trial data compared with the company's fitted curves and the ERG's base case are shown in Figure 22.

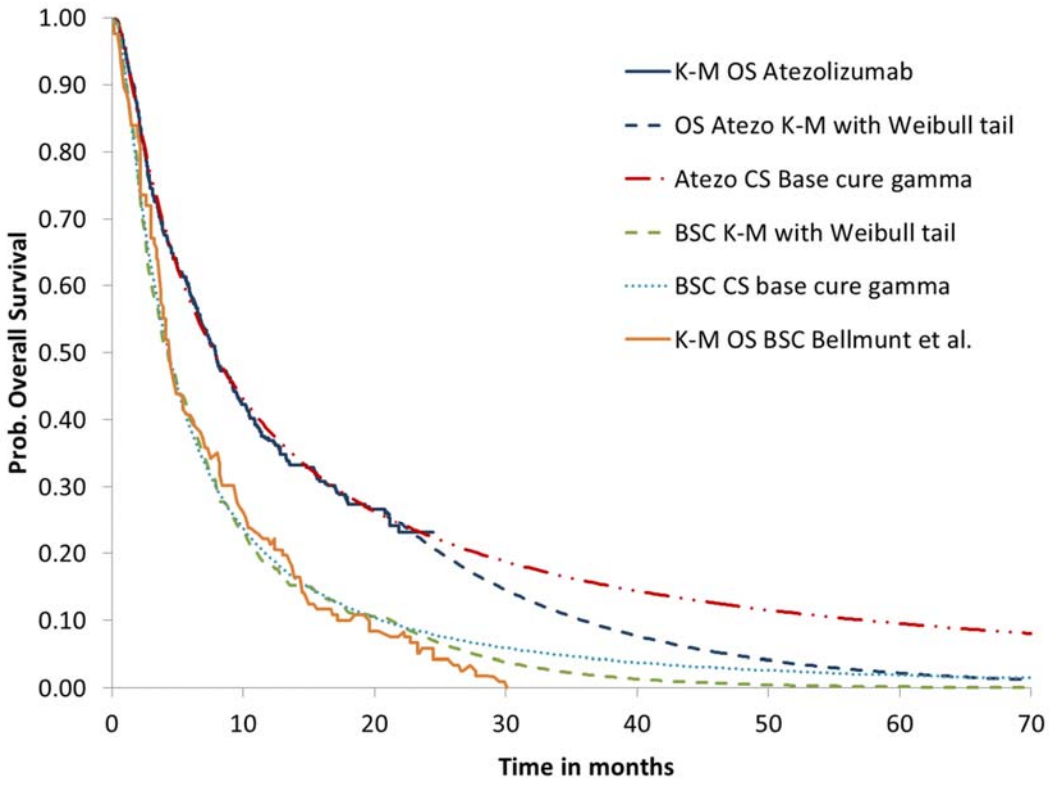

Figure 22 Overall survival curves for second-line treatment for observed trial data for atezolizumab and best supportive care compared with company's fitted curves and ERG's base case

4.5 Conclusions on cost effectiveness

The company used a model structure commonly used for economic models of cancer treatment with health states for progression-free survival, progression and death. The ERG considers the model structure to be appropriate for the decision problem.

The company used methods that are consistent with NICE methodological guidelines. The population differs from that specified from the NICE scope as the second-line treatment combines two populations: people whose disease has progressed after platinum-based chemotherapy and people for whom cisplatin-based chemotherapy is unsuitable; and those whose disease has progressed after platinum-based therapy. The comparators differ from those specified in the NICE scope as the CS does not include retreatment with first-line platinum-based chemotherapy for patients who have progressed.

The core clinical evidence for atezolizumab was from single-arm studies and there are no direct head-to-head studies between atezolizumab and its comparators. There is a weak evidence base for the comparator treatment with most studies including small number of patients. The clinical data for atezolizumab is from the phase II single-arm iMvigor 210 study.

The company comparison between atezolizumab and its comparator uses contrast estimates from the company's network meta-analysis that used a fractional polynomial model approach. The ERG has identified a number of methodological issues with the company's network meta-analysis that cast doubt on the validity of the results of the analyses. However, we note that, in general, the key driver of the model is the choice of parametric function used to extrapolate overall survival and TTD. We also note that the company has not fully explored the uncertainty around overall survival and TTD through the use of sensitivity analyses. Further, the company has chosen parametric functions for overall survival and TTD that are most favourable to atezolizumab. The ERG considers that other parametric functions are also plausible and these result in atezolizumab being much less cost-effectiveness than reported in the CS base case.

5 END OF LIFE

According to the NICE criteria for End of life, the following criteria should be satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company has considered the criteria for end of life. The CS states that median survival with or without treatment with systemic therapy is between 8-15 months.

The company considers that the mean overall survival results better reflect the outcomes of patients and the mean results are more than 3 months for atezolizumab, when taking results from the economic analysis, as shown in Table 50.

Table 50 Mean and median survival for atezolizumab compared to comparators (CS section 4.13.3)

		Mean	Median
First-line	Atezolizumab	55.3 months	17.1 months
	Gemcitabine + carboplatin	25.1 months	8.5 months
Second-line	Atezolizumab	22.7 months	7.9 months
	Docetaxel	12.9 months	7.6 months
	Paclitaxel	12.2 months	5.3 months
	BSC	9.4 months	4.4 months

The ERG notes that if the median overall survival results are used for both end-of-life criteria, atezolizumab in second-line would not meet the criteria for extension of life as it does not extend overall survival by more than 3 months. If the mean overall survival results are used for both end-of-life criteria, atezolizumab does not meet the criteria for a short life expectancy as the mean overall survival survival for gemcitabine + carboplatin is greater than 2 years. Therefore we consider it is uncertain whether both first-line and second-line atezolizumab has met the end-of-life criteria.

6 INNOVATION

The company makes the case for innovation in CS section 2.5. They state that as the first immunotherapy for locally advanced or metastatic urothelial carcinoma, atezolizumab represents a 'new paradigm' in treatment and is a clinically significant innovative therapeutic option. The ERG notes that a NICE appraisal is currently in development for another immunotherapy for urothelial cancer, pembrolizumab (ID1019). The CS summarises recent advances in conventional chemotherapy that have resulted in gains in progression-free survival but not overall survival, or improvements in tolerability only. It asserts that in contrast, atezolizumab exploits evolutionary mechanisms that can maintain responses in some patients.

Atezolizumab has been granted 'breakthrough therapy designation' by the US FDA in 2014 (granted to potential new drugs where early clinical evidence suggests substantial improvement compared with existing therapies) and 'Promising Innovative Medicine' by the Medicines and Healthcare Products Regulatory Authority in 2016. It was considered under the early access to medicines scheme (EAMS), which aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when

there is a clear unmet medical need. A positive EAMS scientific opinion was issued by the MHRA in January 2017:

'*Atezolizumab has been shown to slow the progression of cancer and increase patient survival in a condition where other treatments currently have poor results (about 20% of patients alive after 12 months). With regard to the medicine's side effects, the most frequent were mild to moderate in severity and less frequent than with chemotherapy. Advanced cancer of the bladder and urinary system is a fatal condition and currently few therapies are available with low efficacy'*

The MHRA also noted that the effects of atezolizumab have not been compared to those of current treatments in the same study, and that the company has committed to provide further data when they become available.[66]

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

Strengths

The company has conducted thorough searches and, despite some inconsistencies in application and reporting of the eligibility screening process appears to have identified all of the key studies on atezolizumab and the scoped comparators.

Limitations

There are methodological weaknesses in the company's network meta-analysis and in the simulated treatment comparison which supports it, as discussed in detail in section 3.1.7. The company acknowledges that the results of the analysis are limited by lack of studies. Hazard ratios for overall survival gave implausible results when included in the economic model without adjustment, whilst hazard ratios for progression-free survival also gave implausible results and were not used in the economic analysis. Results of the meta-analysis are not discussed by the company as evidence for the clinical effectiveness of atezolizumab.

Uncertainties

The company has not provided any 'reality checks' to gauge whether their analysis results might be reasonable or subject to bias. Uncertainties arising at different steps of the analysis are not discussed or propagated through to the final results so the cumulative impact of small errors and inconsistencies identified by the ERG is unclear.

The CS acknowledges the complexity of the fractional polynomial model approach (section 4.10.10) and the very limited evidence base to which it could be applied (CS section 4.10.11.1) which suggests that the fractional polynomial method may not have been the most appropriate approach to use. Other possible approaches for analysing the data (e.g. using an accelerated failure time model) were not considered.

Given that fractional polynomial network meta-analysis is a relatively complex method that involves numerous computational steps, it is important that the analysis approach is reported clearly and as fully as possible. The company's description of the methods is rather limited and it is possible that some methodological issues might have gone undiscovered by the ERG (several aspects of the methodology were only revealed indirectly in clarification responses).

7.2 Summary of cost effectiveness issues

The CS includes evidence on the cost effectiveness of atezolizumab for patients with advanced or metastatic urothelial carcinoma. Treatment with atezolizumab is compared to gemcitabine + carboplatin for 1st line treatment and compared to docetaxel, paclitaxel, and best supportive care for 2nd line treatment. The model structure adopted is generally appropriate and consistent with the clinical disease pathway. The model contains health states of progression-free, progressed disease and death and uses survival curves for progression-free survival and overall survival, based upon clinical evidence. The clinical evidence comprises of single-arm studies which leads to considerable uncertainty. The CS acknowledges the uncertainty around the model results and the weak evidence base for the comparator trials and states that much of this uncertainty will be resolved through on-going phase III trials. On this basis, the company proposes that atezolizumab be made available for patients via the Cancer Drugs fund.
The CS base case for first-line atezolizumab compared to gemcitabine + carboplatin is £44,158 per QALY gained. The ICERs for second-line atezolizumab are £131,579 versus docetaxel, £104,850 versus paclitaxel and £98,208 versus best supportive care. The CS included

deterministic sensitivity analyses for selected input parameters and scenario analyses. However, the CS does not include sensitivity analyses varying the parametric survival curves chosen for overall survival and TTD and these are shown to have a large impact on model results. The company's probabilistic sensitivity analyses showed that the probability of first-line atezolizumab being cost-effective is 10.9% and 53.9% at willingness to pay thresholds of £30,000 and £50,000 per QALY respectively. The probability of second-line atezolizumab being cost-effective is 0% and 0% at willingness to pay thresholds of £30,000 and £50,000 per QALY respectively.

The ERG conducted sensitivity analyses evaluating alternative parametric survival functions for overall survival and TTD, different assumptions for utility estimates and varying the treatment effect of atezolizumab. The ERG's alternative base case analysis for first-line atezolizumab compared to gemcitabine + carboplatin is £93,948 per QALY and for second-line atezolizumab compared to docetaxel, paclitaxel and best supportive care is £288,247, £180,901 and £166,805 per QALY respectively. However, the ERG considers there is considerable uncertainty in the model results.

8 REFERENCES

1. CRUK (Cancer Research UK). Types of bladder cancer: CRUK; 2017 [Available from: http://about-cancer.cancerresearchuk.org/about-cancer/bladder-cancer/types-stages-grades/types].
2. Rouprêt M, Babjuk M, Böhle A, Burger M, Compérat E, Cowan N, et al. Guidelines on urothelial carcinomas of the upper urinary tract. European Association of Urology, 2015.
3. Macmillan Cancer Support. Staging and grading for early bladder cancer 2017 [Available from: http://www.macmillan.org.uk/cancerinformation/cancertypes/bladder/symptomsdiagnosis/gradingstaging/earlygradingstaging.aspx].
4. Macmillan Cancer Support. Grading and staging for invasive and advanced bladder cancer 2017 [Available from: http://www.macmillan.org.uk/cancerinformation/cancertypes/bladder/symptomsdiagnosis/gradingstaging/invasivegradingstaging.aspx].

5. Witjes J, Compérat E, Cowan N, De Santis M, Gakis G, James N, et al. Guidelnes on muscle-invasive and metastatic bladder cancer. EAU (European Association of Urology); 2015. p. 1-60.
6. CRUK (Cancer Research UK). Locally advanced bladder cancer: CRUK; 2017 [Available from: http://www.cancerresearchuk.org/about-cancer/bladder-cancer/treatment/locally-advanced].
7. CRUK (Cancer Research UK). Bladder cancer risks and causes: CRUK; 2017 [Available from: http://about-cancer.cancerresearchuk.org/about-cancer/bladder-cancer/risks-causes].
8. CRUK (Cancer Research UK). Bladder cancer statistics: CRUK; 2017 [Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer].
9. Witjes J, Lebret T, Compérat E, Cowan N, De Santis M, Bruins H, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol. 2017;71(3):462-75.
10. CRUK (Cancer Research UK). Bladder cancer incidence statistics: CRUK; 2017 [Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence#heading-Zero].
11. Kaufman A, Shipley W, Feldman A. Bladder cancer. Lancet. 2009;374:239-49.
12. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER cancer statistics review, bladder section, 1975-2008 2011 [Available from: http://seer.cancer.gov/csr/1975_2008].
13. CRUK (Cancer Research UK). Bladder cancer mortality statistics: CRUK; 2017 [Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/mortality].
14. CRUK (Cancer Research UK). Bladder cancer survival statistics: CRUK; 2017 [Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/survival].
15. NICE (National Institute for Health and Care Excellence). Bladder cancer: diagnosis and management. NICE guideline ng2: NICE; 2015 [1-56]. Available from: http://www.nice.org.uk/guidance/ng2].
16. Sharma S, Ksheersagar P, Sharma P. Diagnosis and treatment of bladder cancer. Am Fam Physician. 2009;80(7):717-23.

17. de Vos F, de Wit R. Choosing chemotherapy in patients with advanced urothelial cell cancer who are unfit to receive cisplatin-based chemotherapy. Ther Adv Med Oncol. 2010;2(6):381-8.
18. American Cancer Society. Bladder cancer 2015 [Available from: http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics].
19. De Santis M, Bellmunt J, Mead G, Kerst J, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. J Clin Oncol. 2009;27(33):5634-9.
20. Bellmunt J, Orsola A, Leow J, Wiegel T, De Santis M, Horwich A. Bladder cancer: EMSO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25:iii40-iii8.
21. Bellmunt J, Fougeray R, Rosenberg J, von der Maase H, Schultz F, Salhi Y, et al. Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. Ann Oncol. 2013;24:1466-72.
22. NICE (National Institute for Health and Care Excellence). Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract: NICE; 2013 [Available from: https://www.nice.org.uk/guidance/ta272].
23. Lamb B, Vasdev N, Jalil R, Mcmenemin R, Hughes S, Payne H, et al. Second-line chemotherapy for advanced bladder cancer: A survey of current UK practice. Urol Oncol. 2014;32:52e.11-52.e17.
24. Food and Drug Administration. Atezolizumab for urothelial carcinoma 2016 [Available from: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm501878.htm].
25. Chou R, Selph SS, Buckley DI, Gustafson KS, Griffin JC, Grusing SE, et al. Treatment of muscle-invasive bladder cancer: A systematic review. Cancer. 2016;122(6):842-51.
26. Giannatempo P, Pond GR, Sonpavde G, Raggi D, Naik G, Galsky MD, et al. The impact of adding taxanes to gemcitabine and platinum chemotherapy for the first-line therapy of advanced or metastatic urothelial cancer: A systematic review and meta-analysis. Eur Urol. 2016;69(4):624-33.
27. Necchi A, Pond GR, Raggi D, Giannatempo P, Vogelzang NJ, Grivas P, et al. Efficacy and safety of gemcitabine plus either taxane or carboplatin in the first-line setting of metastatic urothelial carcinoma: A systematic review and meta-analysis. Clin Genitourin Cancer. 2017;15(1):23-30.e2.

28. Raggi D, Miceli R, Sonpavde G, Giannatempo P, Mariani L, Galsky MD, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: A systematic review and meta-analysis. Ann Oncol. 2016;27(1):49-61.
29. Sonpavde G, Pond GR, Choueiri TK, Mullane S, Niegisch G, Albers P, et al. Single-agent taxane versus taxane-containing combination chemotherapy as salvage therapy for advanced urothelial carcinoma. Eur Urol. 2016;69(4):634-41.
30. Wu X-J, Zhi Y, He P, Zhou X-Z, Zheng J, Chen Z-W, et al. Comparison of single agent versus combined chemotherapy in previously treated patients with advanced urothelial carcinoma: a meta-analysis. Onco Targets Ther. 2016;15(9):1535-43.
31. NCCC (National Collaborating Centre for Cancer). Bladder cancer: diagnosis and management. NICE Guideline 2 Evidence Review: NCCC; 2015 [Available from: https://www.nice.org.uk/guidance/ng2/evidence/evidence-review-487511101].
32. Bellmunt J. Treatment of metastatic urothelial cancer of the bladder and urinary tract: Wolters Kluwer UpToDate®; 2017 [Available from: http://www.uptodate.com/contents/treatment-of-metastatic-urothelial-cancer-of-the-bladder-and-urinary-tract].
33. Yafi F, North S, Kassouf W. First- and second-line therapy for metastatic urothelial carcinoma of the bladder. Curr Oncol. 2011;18(1):e25-e34.
34. Meluch A, Greco F, Burris H, O'Rourke T, Ortega G, Steis R, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol. 2001;19(12):3018-24.
35. Ko Y, Canil C, Mukherjee S, Winquist E, Elser C, Eisen A, et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single-group, multicentre, phase 2 study. Lancet Oncol. 2013;14:769-76.
36. Vaishampayan U, Faulkner J, Small E, Redman B, Keiser W, Petrylak D, et al. Phase II trial of carboplatin and paclitaxel in cisplatin-pretreated advanced transitional cell carcinoma: a Southwest Oncology Group study. Cancer. 2005;104:1627-32.
37. Vaughn D, Srinivas S, Stadler W, Pili R, Petrylak DP, Sternberg C, et al. Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase 2 study. Cancer. 2009;115:4110-7.
38. Lee J, Park H, Lim J, Kwon G, Kim C, Song J, et al. Phase II study of a polyethoxylated castor oil-free, polymeric micelle formulation of paclitaxel for patients with advanced

urothelial cancer previously treated with gemcitabine and platinum. J Clin Oncol. 2011;29 suppl 7: abstr 272.

39. Lee J-L, Ahn J-H, Park S, LIm H, Kwon J, Ahn S, et al. Phase II study of a cremophor-free, polymeric micelle formulation of paclitaxel for patients with advanced urothelial cancer previously treated with gemcitabine and platinum. Invest New Drugs. 2012;30:1984-90.
40. Balar A, Galsky M, Rosenberg J, Powles T, Petrylak D, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: single-arm, multicentre, phase 2 trial. Lancet. 2017;389:67-76.
41. Rosenberg J, Hoffman-Censits J, Powles T, van der Heijden M, Balar A, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387:1909.
42. Bamias A, Lainakis G, Kastritis E, Antoniou N, Alivizatos G, Koureas A, et al. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. Oncology. 2007;73:290-7.
43. De Santis M, Bellmunt J, Mead G, Kerst J, Leahy M, Daugaard G, et al. Randomized phase II/III trial comparing gemcitabine/carboplatin (GC) and methotrexate/ carboplatin/vinblastine (MCAVI) in patients (pts) with advanced urothelial cancer (UC) unfit for cisplatin based chemotherapy (CHT): Phase III results of EORTC study 30986. J Clin Oncol. 2010;28: 18s suppl: abstr LBA4519.
44. De Santis M, Bellmunt J, Mead G, Kerst J, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30(2):191-9.
45. Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, et al. Phase III trial of influnine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009;27(27):4454-61.
46. Noguchi M, Matsumoto K, Uemura H, Arai G, Eto M, Naito S, et al. Randomized phase II study of personalized peptide vaccination in patients with advanced bladder cancer progressing after chemotherapy. J Clin Oncol. 2014;32: 5 suppl; abstr 3092.

47. Noguchi M, Matsumoto K, Uemura H, Arai G, Eto M, Naito S, et al. An open-label, randomized phase II trial of personalized peptide vaccination in patients with bladder cancer that progressed after platinum-based chemotherapy. Clin Cancer Res. 2016;22(1):54-60.
48. Kim Y, Choi M, Hong J, Maeng C, Lee S, Hwang I, et al. A phase II trial of weekly docetaxel for second line treatment of urothelial carcinoma. J Clin Oncol. 2013;31 suppl: abstr e15613.
49. Kim Y, Lee S, Park S, Park S, Hwang I, Lee S, et al. A phase II study of weekly docetaxel as second-line chemotherapy in patients with metastatic urothelial carcinoma. Clin Genitourin Cancer. 2016;14(1):76-81.
50. Choueiri T, Ross R, Jacobus S, Vaishampayan U, Yu E, Quinn D, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol. 2012;30(5):507-12.
51. Albers P, Siener R, Hartlein M, Fallahi M, Haeutle D, Perabo F, et al. Gemcitabine monotherapy as second-line treatment in cisplatin-refactory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. Onkologie. 2002;25:47-52.
52. Kouno T, Ando M, Yonemori K, Matsumoto K, Shimizu C, Katsumata N, et al. Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. Eur Urol. 2007;52:1115-22.
53. NIH (National Institutes of Health). Quality assessment tool for case series studies: NIH; 2014 [Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series].
54. NIH (National Institutes of Health). Quality assessment tool for before-after (pre-post) studies with no control group: NIH; 2014 [Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after].
55. Therasse P, Arbuck S, Eisenhauer E, Wanders J, Kaplan R, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205-16.
56. Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60.

57. Llovet J, Di Bisceglie A, Bruix J, Kramer B, Lencioni R, Zhu A, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698-711.
58. EMEA (European Agency for the Evaluation of Medicinal Products). Points to consider on multiplicity issues in clinical trials: EMEA; 2002 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003640.pdf].
59. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017;18(3):312-22.
60. Phillippo D, Ades A, Dias S, Palmer S, Abrams K, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submisions to NICE. Sheffield: Decision Support Unit, ScHARR, University of Sheffield, 2016.
61. ESMO (European Society for Medical Oncology). Performance scales: Karnofsky & ECOG scores: ESMO; 2017 [Available from: http://oncologypro.esmo.org/Guidelines-Practice/Practice-Tools/Performance-Scales].
62. Sterne J, White I, Carlin J, Spratt M, Royston P, Kenward M, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393:1-5.
63. Jansen J. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61:1-14.
64. Turner R, Jackson D, Wei Y, Thompson S, Higgins J. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med. 2015;34:984-98.
65. Jansen J, Trikalinos T, Cappelleri J, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: An ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17:157-73.
66. MHRA (Medicines and Healthcare products Regulatory Agency). Early access to medicines scheme (EAMS) scientific opinion: Atezolizumab for locally advanced or metastatic urothelial carcinoma: MHRA; 2017 [Available from: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-atezolizumab-for-locally-advanced-or-metastatic-urothelial-carcinoma].

67. PBAC (Pharmaceutical benefits advisory committee). Vinflunine public summary document: PBAC; 2015 [Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-11/files/vinflunine-psd-november-2015.pdf].
68. NICE (National Institute for Health and Care Excellence). Guide to the methods of technology appraisal 2013: NICE; 2013 [Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781].
69. Bellmunt J, de Wit R, Vaughn D, et al. KEYNOTE-045: open-label, phase III study of pembrolizumab versus investigator'schoice of paclitaxel, docetaxel, or vinflunine for previously treated advanced urothelial cancer. Society for Immunotherapy of Cancer Annual Meeting; November 9-13; National Harbor, MD2016.
70. Soga N, Onishi T, Arima K, Sugimura Y. Paclitaxel carboplatin chemotherapy as a second-line chemotherapy for advanced platinum resistant urothelial cancer in Japanese cases. Int J Urol. 2007;14(9):828-32.
71. Rowen D, Brazier J, Young T, Gaugris S, Craig BM, King MT, et al. Deriving a preference-based measure for cancer using the EORTC QLQ-C30. Value Health. 2011;14(5):721-31.
72. McKenzie L, Van Der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. Value Health. 2009;12(1):167-71.
73. Seal B, Shermock K, Asche C, Chang J, Kreilick C, Yao J, et al. Evaluating the cost of treating bladder cancer with and without metastases. Value Health. 2015;18(3):A201.
74. Huillard O, Goldwasser F, Morin L. Aggressiveness of care at the end of life in patients with localized and advanced bladder cancer. J Clin Oncol 2016.
75. NICE (National Institute for Health and Care Excellence). Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900]: NICE; 2017 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag524].
76. NICE (National Institute for Health and Care Excellence). Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy: NICE; 2017 [Available from: https://www.nice.org.uk/guidance/ta428].
77. Department of Health. Drugs and pharmaceutical electronic market information (eMit): Department of Health, England, UK; 2015 [Available from:

https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit].

78. Department of Health. NHS reference costs 2015-2016: Department of Health, England, UK; 2015 [Available from: https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016].
79. Akaza H, Naito S, Usami M, Miki T, Miyanaga N, Taniai H. Efficacy and safety of gemcitabine monotherapy in patients with transitional cell carcinoma after cisplatin-containing therapy: a Japanese experience. Jpn J Clin Oncol. 2007;37:201-6.
80. Albers P, Park S, Niegish G, Fechner G, Steiner U, Lehmann J, et al. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. Ann Oncol. 2011;22:288-94.
81. Han K, Joung J, Kim T, Jeong I, Seo H, Chung J, et al. Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy. Br J Cancer. 2008;98:86-90.
82. Ikeda M, Matsumoto K, Tabata K, Minamida S, Fujita T, Satoh T, et al. Combination of gemcitabine and paclitaxel is a favourable option for patients with advanced or metastatic urothelial carcinoma previously treated with cisplatin-based chemotherapy. Jpn J Clin Oncol. 2011;41:1214-20.
83. Matsumoto K, Irie A, Satoh T, Okazaki M, Iwamura M, Baba S. Gemcitabine and paclitaxel chemotherapy as a second-line treatment for advanced or metastatic urothelial carcinoma. Int J Urol. 2007;14:1000-4.
84. Srinivas S, Guardino A. A nonplatinum combination in metastatic transitional cell carcinoma. Am J Clin Oncol. 2005;28:114-8.
85. Suyama T, Ueda T, Fukasawa S, Imamura Y, Nakamura K, Miyasaka K, et al. Combination of gemcitabine and paclitaxel as second-line therapy for advanced urothelial carcinoma. Jpn J Clin Oncol. 2009;39:244-50.
86. Vaughn D, Manola J, Dreicer R, See W, Levitt R, Wilding G. Phase II study of paclitaxel plus carboplatin in patients with advanced carcinoma of the urothelium and renal dysfunction (E2896): a trial of the Eastern Cooperative Oncology Group. Cancer. 2002;95:1022-7.

9 APPENDICES

Appendix 1 ERG summary of studies which reported Kaplan-Meier curves but were excluded by the company

Study	Comparator	K-M curves reported	Required prognostic factors			
			Age >65	Sex	Liver met	ECOG PS ≥1
Akaza 2007 [79]	GEM n=44	OS	Reported	Reported	Reported	Reported
Albers 2002 [51]	GEM n=28	OS, TTP [a]	NR	NR	reported	NR
AUO trial [80]	GEM + PTX n=96	OS	NR [b]	NR	NR	NR
Han 2008 [81]	MVAC n=30	OS	NR [b]	Reported	Reported	Reported
Ikeda 2011 [82]	GEM + PTX n=24	OS	NR [b]	Reported	Reported	Reported
Ko 2013 [35]	Nab-PTX n=47	OS, PFS	NR [b]	Reported	Reported	Reported
Kouno 2007 [52]	CAR + PTX n=31	OS, PFS	NR [b]	Reported	Reported	PS >1
Matsumoto 2007 [83]	GEM + PTX n=10	OS	NR [b]	Reported	NR	Reported
Srinivas 2005 [84]	GEM + PTX n=18	OS	NR [b]	Reported	Reported	NR
Suyama 2009 [85]	GEM + PTX n=30	OS	NR [b]	Reported	Reported	NR
Vaishampayan 2005 [36]	CAR + PTX n=44	OS, PFS	NR [b]	Reported	NR	PS >1
Vaughn 2002 [86]	CAR + PTX n=37	OS [a]	NR [b]	Reported	Reported	Reported
Vaughn 2009 [37]	VFL n=151	OS, PFS	Reported	Reported	Reported	Reported [c]

CAR: carboplatin; GEM: gemcitabine; ECOG: Eastern Collaborative Oncology Group; K-M: Kaplan-Meier; met: metastases; MVAC; methotrexate, vinblastine, doxorubicin and cisplatin; Nab: nanoparticle albumin bound; NR: not reported; OS; overall survival; PFS: progression-free survival; PS: performance status; PTX: paclitaxel; TTP: time to progression; VFL: vinflunine

[a] Reported for subgroup(s) only

[b] median and range reported, not the specified cut-off proportion (the company employed a calculation to estimate the proportion aged >65 years from the median age – see section 3.1.7

[c] reported Karnofsky score, which maps directly to ECOG score[61]

Appendix 2 Summary of study PCD4989g

The CS provides supporting results from the phase I study PCD4989g (CS Section 4.11.11.3) and therefore we have summarised the characteristics of the study here (although, as noted above, this study did not meet the company's eligibility criteria). PCD4989g was a single-arm study that aimed to assess the safety and tolerability of atezolizumab, to determine the maximum tolerated dose, to evaluate the dose-limiting toxicity, and to identify a recommended phase II dose (CS section 4.11.11). According to the study protocol (provided by the company in response to clarification questions A40 and A42), PCD4989g had a broad disease scope and included patients with locally advanced or metastatic solid tumours or haematologic malignancies. A cohort of participants with locally advanced or metastatic urothelial carcinoma within the study (n=95) is relevant to the current appraisal. In clarification response A41 the company stated that 86 of these patients initially received 15 mg/kg atezolizumab intravenously every three weeks and nine received 1200 mg intravenously every three weeks but that the protocol was amended such that all 95 patients subsequently received the fixed dose of 1200 mg. The company also stated that average weight of patients was 80kg. In these patients 15 mg/kg would give on average a total dose of 1200 mg. However, the company also stated in clarification response A41 that patients received relatively less exposure at the anticipated licensed dose of 1200 mg, without stating the magnitude of the difference.

Study characteristics

At the clinical data cut-off in March 2016 the study included 95 patients with locally advanced or metastatic urothelial carcinoma, 72 of whom (75.6%) were male and 74 (77.8%) had white ethnicity. The majority of patients were ≥65 years old, with a median age of 66.0 years (range 36-89 years). Baseline characteristics of the participants are given in CS Table 40 and we have reproduced these here in Table 51.

Table 51 Baseline characteristics of participants in study PCD4989g

Baseline characteristic	Total (n=95)	
Age	Median	66.0
	Range	36–89
Gender	Male	72 (75.8%)
Baseline ECOG PS	0	37 (38.9%)

	1	58 (61.1%)
Visceral Metastases at study entry	Yes	74 (77.9%)
Liver metastases at study entry	Yes	35 (36.8%)
Haemoglobin level <10g/dL	Yes	18 (18.9%)
Prior Therapy (Adjuvant, Neoadjuvant)	0	1 (1.1%)
	1	0 (0%)
	2	17 (17.9%)
	3	15 (15.8%)
	4	14 (14.7%)
	5	17 (17.9%)
	≥6	31 (32.6%)
Prior Therapy with Platinum Based Regimen	Cisplatin-based	73 (76.8%)
	Carboplatin-based	37 (38.9%)
Time from prior chemotherapy (≤3 months)	Yes	39 (41.9%)

Results

In the bladder cancer subgroup of the PCD4989g study the median survival was 10.1 (95% CI 7.29, 16.99) months and progression free survival was 1.8 (95% CI 1.4, 3.3) months (Table 52). The corresponding results for cohort 2 of IMvigor201 are included in Table 52 for comparison.

Table 52 Survival outcomes for bladder cancer patients in study PCD4989g

Outcome (95% CI) **(RECIST v1.1; IRF assessed)**	**Imvigor 210 cohort 2** **All patients, N = 310**	**PCD4989g** **N=94 [a]**
Overall survival, median, months	7.9 (6.7–9.3)	10.1 (7.29, 16.99)
12 months survival, %	36.9% (31.4–42.3)	NR
Progression-free survival, median, months	2.1 (2.1–2.1) [b]	1.8 (1.4, 3.3)

CI: confidence interval; IRF: independent review facility; NE: not estimable
[a]as confirmed in clarification A41, not all participants received the licensed dose, results are supportive data only.
[b] ERG unclear why confidence interval as reported in the CS has zero range

In the bladder cancer subgroup of PCD4989g, 25.5% of participants achieved an objective response (Table 53) and 9.6% achieved a complete response (investigator assessment). The duration of response was 22.1 months (investigator assessment; median duration of response was not reached for independent review facility assessment). The corresponding results for cohort 2 of IMvigor201 are included in Table 53 for comparison.

Table 53 Response outcomes for bladder cancer patients in study PCD4989g

Outcome (95% CI) (RECIST v1.1; IRF assessed unless stated)	**Imvigor 210 cohort 2 All patients, N = 310**	**PCD4989g n=94[a]**
ORR, %	15.8 (11.9–20.4) [a]	25.5 (17.09, 35.57) [c]
Complete response, %	6.1% (3.7–9.4)	9.6 (4.47, 17.40) [d]
Duration of response, % with event	34.7 [b]	Not reported
Duration of response, median months	22.6	22.1 (12.12, NE) [c,d]

CI: confidence interval; IRF: independent review facility; NE: not evaluable; ORR, objective response rate
[a]ORR per immune-modified RECIST was 19.7% (95% CI 15.4–24.6).
[b]32 participants (65.3%) were ongoing at the time of the analysis.
[c]as confirmed in clarification A41, not all participants received the licensed dose; results are supportive data only.
[d]by investigator assessment, using RECIST v1.1

Appendix 3 ERG's critical appraisal of the included studies (Table 54 to Table 56)

Table 54 CS and ERG quality assessments of atezolizumab studies

		Imvigor 210	PCD4989g
Study question or objective stated?	**CS :**	Yes	Not assessed
	ERG :	Yes	Yes
Population clearly described, including case definition?	**CS:**	Balar 2017: No; Rosenberg 2016 & CSR: Yes	Not assessed
	ERG:	Yes	Yes
Were all eligible participants that met the prespecified entry criteria enrolled? (ERG additional question)	**CS:**	Not assessed	Not assessed
	ERG:	Could not determine	Could not determine
Comment: For Imvigor 210, insufficient detail provided in the publications and CSR to determine			
Were subjects comparable? [a]	**CS:**	Balar 2017: could not determine Rosenberg 2016 & CSR: No	Not assessed
	ERG:	Yes	Yes
Was the intervention clearly described?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes
Were outcome measures clearly defined, valid, reliable and implemented consistently?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes
Were outcome assessors blinded? (ERG additional question)	**CS:**	Not assessed	Not assessed
	ERG:	Not reported [b]	No
Was the sample size sufficiently large to provide confidence in the findings? (ERG additional question)	**CS:**	Not assessed	Not assessed
	ERG:	Yes	Yes
Was the length of follow-up adequate?	**CS:**	Yes	Not assessed
	ERG:	Yes (ongoing)	Yes
Were the statistical methods well described?	**CS:**	Balar 2017: No; Rosenberg 2016 & CSR: Yes	Not assessed
	ERG:	Yes	No
Were the results well described?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes

[a] ERG assessed whether the participants were comparable to the NICE scope, unclear what was assessed by the company.
[b] independent review of the responses of all patients included a blinded review of computed tomography and/or magnetic resonance imaging scans.

Table 55 CS and ERG quality assessments of first-line comparator studies

		Bamias 2007	De Santis 2012
Study question or objective stated?	**CS :**	Yes	Not assessed
	ERG :	Yes	Yes
Population clearly described, including case definition?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes
Were all eligible participants that met the prespecified entry criteria enrolled? (ERG additional question)	**CS:**	Not assessed	Not assessed
	ERG:	Could not determine	Yes
Comment: For Bamias, insufficient detail provided in the publication to determine if all participants who were potentially eligible were enrolled.			
Were subjects comparable? [a]	**CS:**	No	Not assessed
	ERG:	Could not determine	Yes
Comment: For Bamias, CS states no previous chemotherapy allowed, but also states previous neoadjuvant or adjuvant treatment was permitted provided that there was at least a 12-month treatment-free interval; no details of prior treatment given in the baseline characteristics table.			
Was the intervention clearly described?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes
Were outcome measures clearly defined, valid, reliable and implemented consistently?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes
Were outcome assessors blinded? (ERG additional question)	**CS:**	Could not determine [b]	No [b]
	ERG:	Not reported	NR
Was the sample size sufficiently large to provide confidence in the findings? (ERG additional question)	**CS:**	Not assessed	Not assessed
	ERG:	Could not determine	Yes
Comment: For Bamias, n=34, sample size determined on response rate, not survival outcomes			
Was the length of follow-up adequate?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes
Were the statistical methods well described?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes
Were the results well described?	**CS:**	Yes	Not assessed
	ERG:	Yes	Yes

[a]ERG assessed whether the participants were comparable to the NICE scope, unclear what was assessed by the company
[b]CS appendix 8.3 p. 41 Table 2, Cochrane risk of bias for RCTs.

Table 56 CS and ERG quality assessments of second-line comparator studies

		Bellmunt 2009	Choueiri 2012	Kim 2013, 2016	Lee 2011, 2012	Noguchi 2014, 2016
Study question or objective stated?	**CS :**	Not assessed	Not assessed	Yes	Yes	Not assessed
	ERG :	Yes	Yes	Yes	Yes	Yes
Population clearly described, including case definition?	**CS:**	Not assessed	Not assessed	Yes	Yes	Not assessed
	ERG:	Yes	Yes	Yes	Yes	Yes
Were all eligible participants that met the prespecified entry criteria enrolled? (ERG additional question)	**CS:**	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
	ERG:	CD	Yes	CD	CD	Yes
Comment: For Bellmunt, Kim and Lee, insufficient detail was provided in the publications to determine if all participants who were potentially eligible were enrolled.						
Were subjects comparable? [a]	**CS:**	Not assessed	Not assessed	No	No	Not assessed
	ERG:	Yes	Yes?	Yes?	Yes	Yes
Comment: Kim 2016: includes progression after ≤ 1 platinum-based regimens (includes 3rd line)?. Choueiri 2012 includes progression after platinum-cased regimen, 3 systemic therapies and prior paclitaxel allowed?						
Was the intervention clearly described?	**CS:**	Not assessed	Not assessed	Yes	Yes	Not assessed
	ERG:	Yes	Yes	Yes	Yes	No
Comment: Noguchi 2016 gives limited details of best supportive care						
Were outcome measures clearly defined, valid, reliable and implemented consistently?	**CS:**	Not assessed	Not assessed	Yes	Yes	Not assessed
	ERG:	Yes	Yes	Yes	Yes	Yes
Were outcome assessors blinded? (ERG additional question)	**CS:**	No[b]	Unclear [b]	No [b]	No [b]	No [b]
	ERG:	Not reported	Not reported	Not reported	Not reported	Not reported
Comment: Choueiri 2012 described as double-blind, but details not reported.						
Was the sample size sufficiently large to provide confidence in the findings? (ERG additional question)	**CS:**	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
	ERG:	Yes	Yes	CD	CD	No
Comment: Kim 2016 n=31, sample size determined on ORR not survival outcomes. Lee 2012 n=37, sample sized determined on ORR. Noguchi 2016 authors note small sample size as limitation.						
Was the length of follow-up adequate?	**CS:**	Not assessed	Not assessed	Yes	Yes	Not assessed
	ERG:	Yes	Yes	Yes	Yes	Yes
Were the statistical methods well described?	**CS:**	Not assessed	Not assessed	Yes	Yes	Not assessed
	ERG:	Yes	Yes	Yes	Yes	Yes
Were the results well described?	**CS:**	Not assessed	Not assessed	Yes	Yes	Not assessed
	ERG:	Yes	Yes	Yes	Yes	Yes

CD: could not determine

[a] ERG assessed whether the participants were comparable to the NICE scope, unclear what was assessed by the company

[b] CS appendix 8.3 p. 42 Table 3, Cochrane risk of bias for RCTs.

Appendix 4 ERG's critical appraisal of the simulated treatment comparison

Recommendation (from DSU guidance[60])	ERG appraisal
Submissions using population-adjusted analyses in an unconnected network need to provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison. (Guidance,[60] section 4.2.4)	The CS does not discuss whether the extent of systematic error due to imbalance in unaccounted for covariates is acceptable and no estimates are presented for the degree of likely bias. The CS does, however, note caveats around the estimates and that the outcomes of the network meta-analysis are uncertain, producing clinically implausible results.
For an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables. (Guidance,[60] section 4.2.5)	It is unlikely that all effect modifiers and prognostic variables have been identified. The Cox regression models contained a maximum of four identified prognostic factors (two of which did not appear to affect model fit and some of which were estimated by imputation).
Indirect comparisons should be carried out on the linear predictor scale, with the same link functions that are usually employed for those outcomes. (Guidance,[60] section 4.2.6)	The comparisons appropriately use a transformed scale; log-hazard for time to event outcomes and a log odds scale for binary outcomes.
The target population for any treatment comparison must be explicitly stated, and population-adjusted estimates of the relative treatment effects must be generated for this target population. (Guidance,[60] section 4.2.7)	The target population is explicitly stated for the two populations in the decision problem. However, the CS does not explain whether the population adjustment would deliver treatment effect estimates for that target population (e.g. the shared effect modifier assumption is not considered).
Reporting requirements (Guidance,[60] section 4.2.8): 1. The variables available in each study should be listed, along with their distributions. 2. Evidence for effect modifier status should be given, along with the proposed size of the interaction effect and the imbalance between study populations. The resulting potential bias reduction compared with a standard indirect comparison should be considered. 3. Measures of uncertainty (e.g. confidence intervals) should be presented alongside any estimates. 4. Estimates of systematic error before and after population adjustment should be presented. 5. Estimates should be presented for the appropriate target population. 6. In order to convey some clarity about the impact of any population adjustment, a crude unadjusted difference should be presented alongside the simulated treatment comparison estimate.	1. The variables available in each study along with their distributions are not presented. 2. Evidence for effect modifier status, and the proposed size of the interaction effect, are not reported. The imbalance between study populations is noted (CS section 4.10.6). The resulting potential bias reduction compared with a standard indirect comparison is not reported. 3. Measures of uncertainty: 95% credible intervals are reported, bootstrapping and Bayesian methods were used. Uncertainty around reconstructed digitised survival curves is not reported. 4. Estimates of systematic error before and after population adjustment are not presented 5. The CS does not comment on the representativeness of the aggregate population to the true target population. 6. The CS does not provide a crude unadjusted difference alongside the STC estimate for comparison (not provided in response to clarification request A15).

Appendix 5 ERG's critical appraisal of the network meta-analysis

Criterion	ERG assessment
NMA purpose	
1. Are the NMA results used to support the evidence for the clinical effectiveness of the intervention?	**No.** The Executive summary states the results are subject to uncertainty; CS section 4.13 (Interpretation of clinical evidence) does not mention the NMA.
2. Are the NMA results used to support the evidence for the cost-effectiveness of the intervention?	**Partly.** Results were used for OS but the values were capped. The results for PFS were not used.
Evidence selection	
3. Are inclusion/exclusion criteria adequately reported?	**Partly.** Criteria are specified in several different places in the CS and not applied consistently (see section 3.1.2).
4. Is quality of the included studies assessed?	**Yes**, although there are limitations with the approach taken (see section 3.1.4), and it includes studies that are not relevant to the NMA.
Methods – statistical model	
5. Is the statistical model described?	**Yes**, but only briefly
6. Has the choice of outcome measure used in the analysis been justified?	**Not explicitly**, but the most appropriate outcome for this cancer assessment, OS, was analysed and reported. Other relevant outcomes analysed were PFS, 12-month survival and ORR but of these only PFS results are reported. These outcomes could have been used to support the clinical effectiveness conclusions but were not.
7. Has a structure of the network been provided?	**No.**
8. Is homogeneity considered?	**Yes**, but only qualitatively.
9. Are the studies homogenous in terms of patient characteristics and study design?	**No.** Below CS Table 17 the CS states that "there are a number of differences between included trials that require some caution when interpreting the results, such as: differences in patient populations including baseline risk, treatment history, differences in trial designs, particularly in regard to primary efficacy outcome(s) measurements". In response to clarification question A24 the company stated that "it was necessary to include studies of heterogeneous populations due to the lack of alternative data" but the company did not refer to any specific variables. In the summary of study heterogeneity, CS Figure 4 shows "moderate" heterogeneity for 1L. In 2L, there was "low-moderate heterogeneity" for both the BSC and docetaxel comparisons, and "moderate" heterogeneity for the paclitaxel comparison, but these categories were not explained in the CS or in the company's response to clarification question A26. The CS does not provide baseline characteristics for comparators so the ERG tabulated these (Table 10 & Table 11). There are some differences between the comparator studies (e.g. patients' age; proportions with comorbidities; performance status), and also differences when

	comparing the atezolizumab cohorts against the comparator studies (e.g. proportion with visceral metastases; performance status) (section 3.1.7).
10. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	**No.** The CS states that sensitivity analyses were undertaken with different priors for between-study heterogeneity, but results of these are not presented. They were provided by the company in response to clarification question A30 for 2L treatment comparisons but not for 1L comparisons.
11. Is the assumption of similarity stated?	**No.** An implicit assumption is that the studies are similar since the prediction model should have matched them on key effect modifiers and prognostic variables. However, due to uncertainties around the covariates for effect modifiers and prognostic variables (section 3.1.7) it is unclear whether the similarity assumption is likely to hold.
12. Is any of the programming code used in the statistical programme provided (for potential verification)?	**Yes,** in CS appendix 8.6
Sensitivity analysis	
13. Does the study report sensitivity analyses?	**No.** The CS states that sensitivity analyses were performed with different priors and a random effects model but does not report results. The results were provided in response to clarification question A30 for 2L treatment comparisons but not for 1L comparisons.
Results	
14. Are the results of the NMA presented?	**Partly.** Results for OS are presented (CS 4.10.11.1 and 4.10.11.2) but are not discussed. PFS results are stated to be clinically implausible and are presented separately in CS Appendix 8.5 (not discussed). 12-month OS and ORR are not presented (CS states available on request).
15. Does the study describe an assessment of the model fit?	**Yes,** model fit was compared using DIC and unspecified “additional criteria” due to the complexity of the fractional polynomial models (CS p. 85. 88, 93, appendix 8.5)
16. Has there been any discussion around the model uncertainty?	**Partly.** Uncertainty is briefly mentioned in CS section 4.10.13 but the CS does not discuss all possible sources of uncertainty or consider which would have the most impact on the results.
17. Are the point estimates of the relative treatment effects accompanied by some measure of variance such as confidence intervals?	**Partly.** Unlabelled uncertainty ranges are displayed for the predicted atezolizumab OS curves (CS Figures 8-14) and log hazard function curves (CS Figures 15-17) but not explained or discussed. Upper and lower bounds of the log-hazard function (contrast estimate slope and intercept) are provided for 2L only (CS Table 24 and clarification response A30).
Discussion - overall results	
18. Does the study discuss both conceptual and statistical heterogeneity?	Partly. The CS does not explicitly discuss the types of heterogeneity present. However, the CS states that priors were used to represent between-study heterogeneity, and in clarification response A28 the company stated that random-effects models were included to allow for between-study heterogeneity. As noted above (items 8 and 9) the CS reports some aspects of conceptual heterogeneity qualitatively.
Discussion - validity	

19. Are the results from the indirect/NMA compared, where possible, to those just using direct evidence?	**Partly.** Visual naive comparisons between survival curves can be made by inspecting CS Figures 8-14. These are not discussed in detail in the CS. However, the CS does state that for 1L the predicted atezolizumab OS K-M curves were almost identical to the original OS K-M curve from cohort 1 of Imvigor 210 (CS Figures 8 and 9). In contrast, for 2L there were differences between the predicted and observed atezolizumab OS K-M curves, which the CS points out, e.g. for CS Figure 10. The company explained in clarification response A15 that the network meta-analysis consisted only of direct comparisons. They provided results for the pairwise direct comparisons analysed separately and these concur with the network meta-analysis results. This is to be expected as the same underlying fractional polynomial model was used for both analyses.

1L: first-line; 2L: second-line; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival

Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 03 April** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Assumption regarding progression-free-survival extrapolation of comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, paragraph 2 Relating to the following statement: '*The company assumes that progression-free survival for atezolizumab is equivalent to its comparators'* This approach was not taken for the second-line comparison to best-supportive-care, in which results of the network meta-analysis (NMA) are utilised for progression-free-survival (PFS). Additionally, the statement is currently misleading as it suggests this approach was the preferred choice for extrapolating PFS. As stated on page 153 of the CS, when applied in the economic model extrapolated results of the NMA were clinically implausible, with PFS and overall survival (OS) curves crossing. Alternative options were explored, and as discussed on page 156 of the CS, assumption of equivalent PFS between atezolizumab and comparators was the conservative approach taken until comparative phase III data are available.	Proposed amendment to: *'Until controlled phase III data are available, the company takes a conservative approach by assuming that progression-free survival for atezolizumab is equivalent to the first-line comparators, and the second-line comparators docetaxel and paclitaxel. Proportional hazard was assumed for second-line best supportive care '.*	The statement is incorrect for implementation of 2L best-supportive care PFS results in the model. The statement is misleading for other comparisons as it suggests this approach was the preferred choice for extrapolation of comparator PFS within the economic model, rather than a pragmatic and conservative solution.	We agree that the distinction between first-line and second-line assumptions is not clear on page 14. The sentence in paragraph 2 has been amended as suggested to: '*The company assumes that progression-free survival for atezolizumab is equivalent to that of the first-line comparators, and to the second-line comparators docetaxel and paclitaxel. Proportional hazards were assumed for comparisons against second-line best supportive care*.'

Issue 2 Incorrectly stated comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, paragraph 4 The first-line comparator is reported as *gemcitabine + paclitaxel*. Comparator should be '*gemcitabine + carboplatin*' as is stated in table 1	Suggest amendment to: *For the base case the incremental cost per QALY gained is £44,158 for first-line atezolizumab compared to gemcitabine + carboplatin (Table 1)*	Correction of stated comparator	We agree, typographic error. This has been amended to 'gemcitabine + *carboplatin*'.

Issue 3 Utilisation of hazard ratio to inform atezolizumab clinical efficacy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16, fifth bullet on page, page 64 last bullet. Relating to the following statement: *'Hazard ratios for overall survival were not used to inform clinical effectiveness of atezolizumab and were considered to be clinically implausible when applied in the economic analysis without adjustment'* Hazard ratios (HRs) are not available for atezolizumab, as comparative data are not currently available. HRs for comparator OS were taken from the NMA, and	Suggest removal of following bullet: *'Hazard ratios for overall survival were not used to inform clinical effectiveness of atezolizumab and were considered to be clinically implausible when applied in the economic analysis without adjustment'*	The sentence is currently misleading as it suggests hazard ratios are available for atezolizumab, and were not used in the CS.	Not a factual inaccuracy. The 5th bullet point on page 16 is referring to hazard ratios from the network meta-analysis. The last bullet on page 64 correctly states that the meta-analysis is not used to provide any evidence for the clinical effectiveness of atezolizumab.

applied to the atezolizumab clinical effectiveness data, taken directly from the IMvigor 210 study.			

Issue 4 Areas of uncertainty of network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17, paragraph 1 Relating to the following statement: *'Uncertainties arising at different steps of the simulated treatment comparison and meta-analysis are not discussed or propagated through to the final results so the cumulative impact of small errors and inconsistencies identified by the ERG is unclear.'* Page 94 and 95, section 4.10.13 of the CS provides an appraisal of the indirect treatment comparison methodology. Furthermore, page 28 of section 1.3 of the CS recognise the uncertainty of the ITC and limitations of the data feeding into the NMA.	Suggest removal of bullet.	It is misleading to state that uncertainty of the simulated treatment comparison and meta-analysis has not been discussed in the CS. The limitations of the STC and NMA are discussed in the CS. Despite this uncertainty, no other approach is proposed in the ERG report.	Not a factual inaccuracy. The ERG statement correctly reflects ERG concerns that there are uncertainties at the simulated treatment comparison and network meta-analysis steps and the uncertainty arising at these steps is not discussed in the CS. There are uncertainties associated with the STC covariates, with the handling of missing data, and with the choice of models in the NMA but it is not clear in the CS how important these are or what their cumulative implications are.

Issue 5 Reporting of network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 paragraph 2 and page 136 paragraph 3 The ERG report states the description of the NMA methodology is limited and several aspects of the methodology were only revealed indirectly in clarification responses. All clarification questions were responded to fully and very few related to the methodology of the NMA.	We propose the statement is amended to reflect that minimal requests for methodology explanation were included in clarification questions, and all requested detail was provided.	This statement within the ERG report is misleading, as it suggests requested explanations during clarification questions were not provided. No additional requests for explanation or methodology were included in clarification questions.	Not a factual inaccuracy. The ERG has an obligation to state any limitations to reporting of the methods since this affects our ability to appraise the CS. NICE DSU and ISPOR (among others) provide guidance on analysis methods that should be reported for simulated treatment comparisons and network meta-analyses, and the CS description of methods is limited in comparison. The statements referred to on page 17 do not criticise the company's clarification responses.

Issue 6 Reporting of QoL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, paragraph 1 Relating to the statement: '*However, the CS does not actually report health-related quality of life; therefore, the company's decision problem is*	Suggest removal of this sentence	The sentence suggests health-related quality of life data are not discussed within the CS.	Not strictly a factual inaccuracy but we agree that our statement may seem harsh given that the CS does report a systematic review and extensive effort to locate HRQoL data. The sentence on page 27 has been changed to:

misleading.' Health-related quality-of-life are discussed in section 5.4.3 of the CS, which states these data are not available from the currently available trial evidence for atezolizumab.			'*However, the CS systematic review of health-related quality of life did not identify any relevant data for this outcome*.'

Issue 7 Systematic literature review screening process

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31 paragraph 3, titled: Summary of the screening process. Relating to the following statement: *'In CS Figure 3 the numbers of excluded publications is incomplete (373 of 631 recorded only).'* This statement suggests excluded publications were not accounted for within the PRISMA flow chart. This is misleading as the number of excluded studies is accounted for. However the reason for exclusion was provided during response to clarification questions.	We propose the following amendment: *'In CS Figure 3 the reason for exclusion of publications is incomplete (373 of 631 recorded only). The company clarified that the remaining 258 records were excluded because no outcomes of interest were reported (clarification response A7)'.*	Figure 3 of the CS includes all 631 excluded studies. The current wording suggests excluded studies were not accounted for.	Not strictly a factual error but we agree that the meaning could be ambiguous. We have replaced '*numbers of excluded publications*' with '*reason for exclusion of publications*' as suggested.

Issue 8 Included studies within network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 paragraph 2, page 62 paragraph 2, and page 63 table 12 The report states inconsistency between the breadth of the PFS and OS networks, which is incorrect. Studies were identified for the comparators described as 'priority 1' on page 57 of the CS. As described on this page, this list is wider than that of the NICE scope. As described on pages 63 and 64 of the CS, studies were then assessed for NMA feasibility, for which the availability of the outcomes of interest were required. The resulting studies are listed in tables 13 and 14 of the CS. As described on page 69 of the CS, the final step was assessment for feasibility for inclusion within the time-to-event analyses of PFS and/or OS, for which KM data were required. As stated on page 69 of the CS, only the studies for comparators of	We propose the statements are amended to reflect that the approach to the NMA was consistent between PFS and OS.	These statements suggest an inconsistent approach was taken to the NMA for PFS and OS, and that this approach may bias the results of the NMA.	Not factual inaccuracies. The company's query here does not identify any specific errors in the ERG report; it merely restates the screening process described in the CS.

interest to the decision problem were described in further detail – as listed in table 15 and 16 of the CS. The overall network includes all studies with available PFS and OS KM data, but these are not further described in the main CS as they are not of interest to the decision problem. They appear within the CS appendices. Furthermore, inclusion or not of these studies does not impact the NMA results			

Issue 9 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51, line 2 IMvigor 201 should read IMvigor 210	IMvigor 201 amended to IMvigor 210	Typographical error	We agree, typographic error. This has been corrected as suggested.

Issue 10 Response evaluable patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 paragraph 3 (section 3.1.6). Relating to the following statement: *'The ERG notes that the CS does*	Suggest removal of the following sentence: *'The ERG notes that the CS does not present the numbers for the response-evaluable population in cohorts 1 and 2'*	This sentence incorrectly states the numbers for the response evaluable population are not reported in the CS.	We agree. Text on page 52 has been amended to '*According to footnotes for CS Tables 31 and 34, the response evaluable population was 99/119 patients in cohort 1 and all patients in*

not present the numbers for the response-evaluable population in cohorts 1 and 2' Footnotes below Tables 31 and 34 in the CS report the evaluable populations of Cohort 1 and 2 respectively.			*cohort 2*.'

Issue 11 Rationale of prognostic factors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55 paragraph 3: *'No justification is given in the CS for any of these covariates being prognostic factors'* and page 58 bullet 2: *'The selection of the covariates in the prediction model is not well justified and is subject to a number of uncertainties.'* Section 4.10.4 of the CS provides the logic and rationale regarding the choice of prognostic factors within the STC.	We propose amendment of the sentences to: *'Given the limitations of research in mUC it is difficult to perform a robust analysis to identify all prognostic factors'*, And *'The selection of the covariates in the prediction model is justified but is subject to uncertainty.'*	It is acknowledge the limitations of clinical research in mUC make identification of prognostic factors challenging, however the CS does provide rationale for choice of factors, and no additional factors are proposed in the ERG report.	Page 55: We agree that the ERG wording may be too strong and we have reworded the text to replace "*No justification*" with "*Limited justification*" and deleted '*any of*'. The CS does not justify the specific cut-off used for age or performance status; and no explanation is given why visceral metastasis (which is a prognostic factor and was more frequently reported than liver metastasis in primary studies) was not considered. Low haemoglobin concentration is stated as being a prognostic factor but was not included even though most second-line studies reported this. Page 58: Not a factual inaccuracy. As noted above,

			the specific cut-offs are not explained and not all possible prognostic factors or effect modifiers were explored in analyses.

Issue 12 Imputation of missing covariates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55 paragraph 4, and page 58 bullet 3. The report states that a single data calculation method was used to impute missing data within the simulated treatment comparison. As described in response to clarification question A31, missing covariate values were imputed by generating - at every bootstrap iteration - a different value. This is a form of multiple imputation. Sampling a different value at every bootstrap iteration ensures the uncertainty in the predicted missing prognostic factors is captured (in contrast, for example, to single imputation methods).	We propose the statement is amended to reflect that multiple imputation was used to impute missing data in the simulated treatment comparison.	Inaccurate description of the method for imputing missing values.	We agree that the approach used could be described as a form of multiple imputation and that the ERG text does not mention the repeated sampling element. However, the random samples used for imputation were constrained to fall within a range of values reported by the small number of primary studies that did not have missing data. Therefore the imputation may not have captured the full range of clinically plausible values (the company does not discuss the distribution of values for each covariate that resulted from the imputation). We have amended the text on page 55 for clarification.

Issue 13 Identification of prognostic factors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58, relating to bullet: *'Relatively few covariates were used in the prediction model'* This statement suggests important, alternative covariates were excluded.	We propose the statement is amended to: *'Relatively few covariates were used in the prediction model, however no additional covariates were identified by the ERG'*	It is acknowledge the limitations of clinical research in mUC make identification of prognostic factors challenging, however the CS does provide rationale for choice of factors, and no additional factors are proposed in the ERG report..	Not a factual inaccuracy. A fundamental assumption of simulated treatment comparison is that all effect modifiers and prognostic variables have been included. To say that relatively few covariates were used in the prediction model is reasonable given that only 3-4 covariates were included.

Issue 14 Incorrect reporting of common AEs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79, last paragraph. Relating to the following statement: *'The most frequent side effects, affecting at least 20% of the patients, were fatigue (tiredness), decreased appetite, nausea (feeling sick), and dyspnoea (shortness of breath)* These side effects are incorrectly listed as occurring in at least 20% of patients.	Suggest amendment to: *'The most frequent side effects affecting at least 10% of the patients in cohort 1 were fatigue, diarrhoea and pruritus; and in cohort 2 fatigue, pruritus, decreased appetite, chills, nausea, pyrexia, rash, vomiting, and arthralgia.'*	The report incorrectly reports the frequency of side effects.	Not strictly a factual inaccuracy, as we have clearly cited the EAMS Public Assessment Report (PAR) for atezolizumab (ERG Reference 66) which states these were the frequencies of adverse events. However, the EAMS PAR does not appear to concur with the CS or clinical study report on the frequencies of adverse events. We have therefore changed the text on page 79 to

Table 43 and 46 of CS includes treatment-related side effects of cohort 1 and 2 respectively.			refer instead to treatment-related adverse events as per CS Tables 43 and 46.

Issue 15 Atezolizumab treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 91: Relating to the following statement: *'Patients are treated with atezolizumab until disease progression unless they discontinue due to adverse events.'* Treatment with atezolizumab in the IMvigor 210 study was continued until loss of clinical benefit, or unmanageable toxicity; as described in section 5.5.5, page 190 of the CS. This statement on page 91 of the ERG report does not accurately describe the treatment duration with atezolizumab. Treatment duration is modelled using time-to-treatment discontinuation results from the IMvigor210 study.	Suggest amendment to: '*Patients are treated with atezolizumab until loss of clinical benefit or unmanageable toxicity*.'	Incorrect reporting of treatment discontinuation from the IMvigor 210 study, and anticipated licence.	We agree. The sentence on page 91 has been amended as suggested to: '*Patients are treated with atezolizumab until loss of clinical benefit or unmanageable toxicity*.'

Issue 16 Study location for KEYNOTE-045

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 and 97 refer to the KEYNOTE-045 study as an 'Australian phase III clinical study'. This study is an international study.	Removal of the word 'Australian' on pages 96 and 97	By referring to this study as Australian, it infers all patients were recruited from Australia. The study is international.	We agree. The word '*Australian*' has been removed on both pages.

Issue 17 Assumption regarding progression-free-survival extrapolation of comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97, paragraph 2. Relating to the following statement: *'The CS does not present any rationale for using the KEYNOTE-045 study to inform the progression-free survival parameter for the comparator arms'*. Pages 155 and 156 of the CS discuss the rationale for use of the KEYNOTE-045 PFS hazard ratio, until comparative data are available for atezolizumab.	Removal of the sentence: *'The CS does not present any rationale for using the KEYNOTE-045 study to inform the progression-free survival parameter for the comparator arms'*. Amendment to: *'The CS expert clinical advisors proposed the KEYNOTE-045 data may be a useful surrogate for atezolizumab, until controlled phase III data are available'.*	This statement is misleading as it suggests no rationale are provided for use of these data. Rationale is provided within the CS on pages 155 and 156	We agree. The sentence has been reworded as "*The CS justifies the use of the KEYNOTE-045 study to inform the progression-free survival parameter for the comparator arms, based on expert clinical advice*".

Issue 18 Method for assessing goodness of OS extrapolation fit

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 104 Relating to the following statement: '*The goodness of fit was measured primarily through visual inspection*.' With the available information within the ERG report, no criteria other than visual fit were used to assess alternative OS extrapolations.	Suggest amendment of the sentence to: '*The goodness of fit was measured only through visual inspection*.'	Accurate description of criteria used for alternative OS extrapolation, as per the available information within the report.	We agree. The sentence is reworded as *"The goodness of fit was measured through visual inspection"*.

Issue 19 Reported utilities scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG analysis
Page 109, paragraph 1 last sentence Relating to the following statement: *'In the same analysis we set the 'on-treatment' utility of atezolizumab to 0.71 and set the 'off-treatment' utility to 0.75 to reflect the disutilities commonly observed during treatment with*	Suggest amendment of the sentence to: *'In the same analysis we set the 'on-treatment' utility of comparators to 0.71 and set the 'off-treatment' utility to 0.75 to reflect the disutilities commonly observed during treatment with chemotherapy'*	Typographical error	We agree. The sentence has been changed to: *'In the same analysis we set the 'on-treatment' utility of comparators to 0.71 and set the 'off-treatment' utility to 0.75 to reflect the disutilities commonly observed during treatment with chemotherapy'*

chemotherapy' We believe this analysis is varying the comparator utility rather than the atezolizumab utility.			

Issue 20 Correction of clarification questions number

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 113, last sentence paragraph 1 The sentence refers to the response to clarification response 'B3'. We believe this should read clarification response 'B4'.	Suggest amendment of the sentence to: *'The ERG and NICE raised this issue with the company and the company provided the reference for these adverse events (clarification response B4)'*	Typographical error	We agree. The reference has been amended to clarification response B4.

Issue 21 Commercial in confidence data not highlighted

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115, table 32. The total costs for BSC in the atezolizumab appraisal should be highlighted as commercial in confidence.	Marking of BSC total costs (from atezolizumab appraisal) as commercial in confidence.	Commercial in confidence information.	We agree. This value has been marked as commercial in confidence.

ERG changes made in response to company erratum (received by ERG 19 April 2017)

Issue 22. First-line network-meta-analysis model selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 16, 61, 87, and 100 relating to statements on selection of the zero-order model for the first-line network meta-analysis. Due to a typographical error within the CS, it was incorrectly stated the zero-order model was selected. Within a provided erratum the typographical error has been corrected to state the first-order gompertz model was selected. As such, statements within the ERG report relating to the zero-order model now also require adjustment.	Removal of the following text Page 16 *The company suggests that the proportional hazards assumption is unlikely to hold for comparisons of atezolizumab against standard chemotherapy drugs; however, they based their network meta-analysis for first-line comparisons on a zero-order version of the fractional polynomial model which assumes proportional hazards. The company does not discuss the plausibility of this model.* Page 87 *The company states that the reason for using fractional polynomial models was to allow analysis of comparisons which violate the proportional hazards assumption. However, after assessing model fit, the company selected the zero-order fractional polynomial model which assumes proportional hazards. The company does not discuss the plausibility of this model.*	A typographical error within the CS resulted in incorrect statements regarding model selection for the first-line network meta-analysis.	Not an ERG factual inaccuracy. The ERG has made amendments to correct the company's typographic error. Page 16: We have removed the text as suggested (i.e. the first bullet point on page 16 has been removed) Page 61: We have amended the first sentence in the second paragraph on page 16, as suggested. This now reads: *For first-line treatment comparisons of overall survival the company selected the first-order Gompertz fractional polynomial model.* Page 87: We have removed the text as suggested (i.e. the first bullet point on page 87 has been removed)

	Suggested amendment of text Page 61 *For first-line treatment comparisons of overall survival the company selected the first-order gompertz fractional polynomial model. The CS states that second-order fractional polynomial models were not considered due to the limited evidence base. Given the fit of the zero-order model it might be assumed that hazards were proportional in the comparison of atezolizumab to gemcitabine + carboplatin, although this is not stated in the CS. Visual inspection of overall survival curves (CS Figures 8 and 9) suggests that hazards may not have been proportional (in one study the curves cross) but the CS does not comment on this. The network meta-analysis section of the CS does not provide any information about time-dependency of the hazard ratio. However, in reporting the economic analysis (CS section 5.3.6) the CS states that the hazard ratio increased linearly over time and required capping to avoid clinically implausible values (see section 4.3.5).* Suggested amendment of text Table 28, page 100 From:		Page 100: We have amended the text within Table 28 as suggested.

	0.62 (Crl: 0.47, 0.82) *The value is obtained from the zero order FP model which is then used to estimate the HR at different time points until the follow up duration for the comparator study (i.e. at 8 months) at which point the HR is capped.* To: *Results from the first-order FP model are used to estimate the HR until the time points correspond with the median follow up (i.e. at 8 months) at which point the HR is capped*		

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma

ERRATUM to the Evidence Review Group Final Report

This document contains an erratum to the Evidence Review Group (ERG) report following the factual accuracy check by Roche

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Date completed 12th April 2017 (updated with company erratum 19th April 2017)

Changes made to the ERG report are indicated in *blue italicised text* for the following pages: 14, 16*, 27, 31, 51, 52, 55, 61*, 79, 87*, 91, 96, 97, 100*, 104, 109, 113, 115 (* indicates changes in response to a company erratum)

The company constructed two partitioned survival models in Microsoft Excel with identical model structure. The models compared first-line atezolizumab with gemcitabine + carboplatin; and second-line atezolizumab with docetaxel, paclitaxel and best supportive care. The models have a lifetime time horizon of 20 years, with discounting of 3.5% per annum for costs and health benefits, a weekly cycle length and a half-cycle correction. The perspective of the analysis is for the NHS and Personal Social Services. The models have three health states: 'progression-free survival', 'progressed disease' and 'death'.

The models use clinical trial data for atezolizumab from IMvigor 210, a single-arm phase II study. Clinical trial data for the comparators are derived from studies found through a systematic search of the clinical literature. The model uses parametric survival modelling to fit survival curves to the observed data for progression-free survival and overall survival for atezolizumab. *The company assumes that progression-free survival for atezolizumab is equivalent to that of the first-line comparators, and to the second-line comparators docetaxel and paclitaxel. Proportional hazards were assumed for comparisons against second-line best supportive care.* For the comparators' overall survival, the overall survival curves for atezolizumab are adjusted using the results of the company's fractional polynomial model. The model derives the proportion of patients in the progressed disease state as the difference between the progression-free survival and overall survival curves. The generalised gamma distribution was used for progression-free survival and overall survival for first-line and second-line comparisons.

Utility estimates were taken from the Australian Pharmaceutical Benefits Advisory Committee (PBAC) cost-utility analysis for vinflunine, in which quality of life values from the EORTC QLQ Q30 questionnaire for patients with advanced urothelial carcinoma who had received vinflunine were mapped to EQ-5D values. Atezolizumab is administered intravenously every three weeks and the recommended dose is 1200mg at a proposed list price of £3807.69 per dose. The cost of comparator treatments are taken from the pharmaceutical electronic market information tool (eMit) and their doses are as recommended by their Summaries of Product Characteristics. Health state costs are based on those used in the NICE technology appraisal for vinflunine (TA272).

The results of the economic model are presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per quality-adjusted life-year (QALY). For the base case the incremental cost per QALY gained is £44,158 for first-line atezolizumab compared to gemcitabine + *carboplatin* (Table 1). The ICERs for second-line atezolizumab compared to

Commentary on the robustness of submitted evidence

Strengths

The company has conducted thorough searches and, despite some inconsistencies in application and reporting of the eligibility screening process appears to have identified all of the key studies on atezolizumab and the scoped comparators.

The model structure is representative of the clinical pathway for patients with advanced or metastatic urothelial carcinoma. The company conducted a systematic review to identify cost-effectiveness, HRQoL and cost studies and values from this review were utilised in the model. The models are intuitive and user-friendly.

Weaknesses and areas of uncertainty

Weaknesses

The ERG has the following concerns regarding the simulated treatment comparison:

- It is based on a very small set of covariates.
- Some aspects of the analysis are unclear, including how the company accounted for missing covariate values.
- The cumulative impact of small errors and inconsistencies in the data is unclear.

The ERG has the following concerns regarding the network meta-analysis:

- Hazard ratios for overall survival were not used to inform clinical effectiveness of atezolizumab and were considered to be clinically implausible when applied in the economic analysis without adjustment.
- Hazard ratios for progression-free survival were considered to be clinically implausible and were not used to inform the clinical effectiveness or cost-effectiveness evaluation of atezolizumab.

and health-related quality of life. *However, the CS systematic review of health-related quality of life did not identify any relevant data for this outcome.* The outcomes are appropriate and clinically meaningful to patients, and the ERG considers that all important outcomes, other than quality of life, have been included in the decision problem.

Economic analysis

The economic analysis described in the decision problem conforms with the NICE reference case and is appropriate for the NHS. The company conducted a cost-utility analysis with a 20-year time horizon, which is considered sufficiently long to reflect any differences in costs or outcomes. Costs are considered from the NHS and Personal Social Services perspective

Other relevant factors

The NICE scope does not specify any subgroups that should be considered, and in line with this none are considered in the company's cost-effectiveness analysis, although clinical effectiveness evidence is presented according to PD-L1 expression subgroups.

No issues related to equity or equality have been identified by the NICE scope, the company decision problem, or the ERG.

- to the “priority” comparators specified in CS section 4.1.4, and no reasons are given in CS Figure 3 as to why studies were excluded at these screening steps.

Eligible outcomes

The CS lists 12 eligible outcomes (CS Table 10), and these are reflective of the NICE scope and the company’s decision problem. However, the CS states that only four of these outcomes were considered for the network meta-analysis: overall survival, 12-month survival, progression-free survival and objective response rate (CS section 4.10.5). No reason is given in the CS for focusing on these outcomes, although the ERG agrees that overall survival and progression-free survival are important outcomes for the evaluation of urothelial cancer treatments.

Eligible study designs

Randomised controlled trials (RCTs), non-randomised trials, and single-arm studies were eligible, and this seems appropriate. Phase I studies were excluded.

Summary of the screening process

CS section 4.1.3.2 (Review strategy) briefly describes the eligibility screening process, and provides a PRISMA flow chart (CS Figure 3). In CS Figure 3 the *reason for exclusion of* publications is incomplete (373 of 631 recorded only). The company clarified that the remaining 258 records were excluded because no outcomes of interest were reported (clarification response A7).

The CS does not state how many reviewers conducted the eligibility screening process but the company confirmed (clarification question A6) that titles/abstracts and full texts were assessed by two reviewers. The CS does not report whether any types of bias may have arisen during the eligibility screening.

According to the CS, the literature was initially screened on titles and abstracts using the eligibility criteria listed in CS Table 10. The remaining publications and internet search results were then assessed based on the full-text versions, yielding a data set of n=233 publications for inclusion in a ‘qualitative synthesis’ to ascertain feasibility of a network meta-analysis.

3.1.5 Description and critique of the company's outcome selection

The NICE scoped outcomes of overall survival, progression-free survival, response rates and adverse effects of treatment were measured in IMvigor*210* and PCD4989g. The NICE scoped outcome of HRQoL was not reported in any of the primary studies making up the evidence base, although this is not made clear in the company's decision problem.

Efficacy results are presented in the CS for various data-cuts (which we have summarised in section 3.3). In the Imvigor 210 study, objective response rate was the primary outcome. This was assessed by an independent review facility (IRF) using the RECIST (Response Evaluation Criteria In Solid Tumours) v1.1 criteria which is a standard approach for determining tumour size.[55] In cohort 2 investigator-assessed modified RECIST immune response criteria were also used which quantify only the viable portions of the tumour (references are provided[56, 57]). The CS states that the modified criteria are not yet used in standard practice (CS section 4.13.2). In clarification response A35 the company stated that the rationale for using the modified RECIST criteria was to account for the possibility of 'pseudoprogression' (i.e. where tumour size reflects immune cell infiltration rather than active cancer), and the potential for delayed anti-tumour activity.

The ERG has focused on reporting outcomes for the most recent data-cut and, where reported, we present results obtained using both RECIST methods. We have focused on the assessments by the independent review facility because these should be at lower risk of bias than investigator assessments. However, the CS does not report whether the independent review facility was blinded to any aspects of the Imvigor 210 study design, and does not explain whether the independent review facility was related to an independent data monitoring committee which is described in CS section 4.11.6. The CS states that there was a high concordance rate between independent review facility and investigator assessments (94%; CS section 4.11.10.3), but does not report results from both assessment approaches for the latest data-cut (20-month follow-up).

Secondary outcomes were the duration of response and progression-free survival assessed using RECIST v1.1 criteria by the independent review facility and investigator; overall survival; and 1-year survival; and these are appropriate endpoints.

Safety outcomes reported in the CS include treatment-emergent adverse events (no definition is provided in the CS or the clinical study report), serious adverse events, and adverse events of special interest. Those of special interest were immune-mediated adverse events and renal function events which are anticipated effects of using a monoclonal antibody therapy. Another possible adverse event of special interest could be infusion related reactions. Rates of these are presented for both cohorts of the Imvigor 210 study, although the CS does not list them as specific events of special interest. Overall, the safety outcomes reported are those that the ERG would expect to be provided for a monoclonal antibody anticancer therapy.

In summary, the ERG considers that the selected outcomes are appropriate to the NICE scope, with the exception that no data on HRQoL were available.

3.1.6 Description and critique of the company's approach to trial statistics

The CS states that effectiveness analyses in IMVigor 210 were performed on the intention-to-treat (ITT) population. This is not defined in the CS but the company explained (clarification response A37) that it refers to enrolled patients who received any amount of study drug. The company also stated in the clarification response that an exception to this involves objective response rate analyses, which were performed on the objective response-evaluable population, defined as ITT patients who have measureable disease per RECIST v1.1 criteria at baseline. *According to footnotes for CS Tables 31 and 34, the response evaluable population was 99/119 patients in cohort 1 and all patients in cohort 2.*

The CS reports using a hierarchical fixed-sequence testing procedure to compare the primary endpoint, objective response rate, between atezolizumab and a historical response rate of 10%. Hypothesis testing was carried out on three pre-defined populations (based on decreasing proportion of PD-L1 expression) sequentially on the basis of independent review-assessed objective response rate according to RECIST v1.1 followed by investigator assessed objective response rate according to modified RECIST criteria. If no statistical significance was detected at a particular level in the hierarchy, no further hypothesis testing was done. The ERG agrees that this is an appropriate statistical approach and is consistent with statistical recommendations of the EMEA.[58]

the resulting 'predicted controlled trials' can then be incorporated into a network meta-analysis, with atezolizumab as the common link.

The company's approach to the STC prediction model is described briefly in CS section 4.10.8. The first step in the STC analysis approach is to identify the covariates (i.e. the prognostic factors and effect modifiers for survival) that will be used in the prediction model. We note that the assumption of an unanchored STC is that all effect modifiers and prognostic factors are accounted for, which is considered 'largely impossible' to meet, leading to an unknown amount of bias in the unanchored estimate.[60] It is important therefore that as many of the key covariates as possible can be identified and included in the analysis to reduce the bias.

STC prediction covariates

The CS specifies four covariates which they used in their prediction model: the proportions of patients who: were aged > 65 years; were male; had liver metastases; and had ECOG performance status ≥1 (equivalent to Karnofsky performance status ≤90%[61]) (CS Table 17). *Limited justification is given in the CS for these covariates being prognostic factors* or effect modifiers. The CS states that due to the limited amount of data available in metastatic urothelial cancer, studies were included when ≥1 out of the four predictors were reported, although included studies for comparators of interest all reported a minimum of three of the four factors (CS section 4.10.4).

The CS states (section 4.10.13) that where trials did not report baseline values for the covariates of interest, the missing values were imputed by generating*, at every bootstrap iteration,* random values from a uniform distribution, with boundaries defined by the range of reported values across the studies included in the analysis. As the company acknowledges in the CS (and also in clarification response A31) this approach has limitations. The ERG believes that this approach *may not have captured the full range of clinically plausible values and* a *more extensive* multiple imputation approach would have been more appropriate. Multiple imputation aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them.[62] *The company does not report or discuss the distributions of the imputed covariates.*

In response to a clarification request from the ERG and NICE, the company explained that the age cut-off of ≥65 years was selected as this was considered a clinically important age cut-off, but they did not give any empirical evidence for this (clarification response A17). The company also provided a description of a targeted literature search, not reported in the CS, which they

explored in sensitivity analysis (CS section 4.10.11.12); however, no sensitivity analysis is reported (this, together with sensitivity analysis of the heterogeneity priors was subsequently provided by the company in clarification response A30).

Model selection for first-line comparisons

For first-line treatment comparisons of overall survival the company selected the *first-order Gompertz fractional polynomial model.* The CS states that second-order fractional polynomial models were not considered due to the limited evidence base. Given the fit of the zero-order model it might be assumed that hazards were proportional in the comparison of atezolizumab to gemcitabine + carboplatin, although this is not stated in the CS. Visual inspection of overall survival curves (CS Figures 8 and 9) suggests that hazards may not have been proportional (in one study the curves cross) but the CS does not comment on this. The network meta-analysis section of the CS does not provide any information about time-dependency of the hazard ratio. However, in reporting the economic analysis (CS section 5.3.6) the CS states that the hazard ratio increased linearly over time and required capping to avoid clinically implausible values (see section 4.3.5).

Model selection for second-line comparisons

For second-line treatment comparisons of overall survival the company selected the Gompertz (i.e. first-order) fractional polynomial model, as this had the lowest DIC among three fixed-effects models that were compared (CS Table 23). Second-order models were considered, and had lower DIC values indicating better fit, but the CS states these exhibited large posterior correlations (>0.9) indicative of over-fitting and so were not used. Posterior correlations were also relatively large (>0.8) for the selected Gompertz model but the CS does not discuss this. Hazard ratio time curves are presented for comparisons of atezoluzumab against best supportive care, paclitaxel and docetaxel (CS Figures 15-17) with the corresponding parameter estimates (CS Table 24), and these indicate that the hazard ratio for the atezolizumab-docetaxel comparison decreased with time. In reporting the economic analysis (CS section 5.3.6) the CS states that the hazard ratios for second-line comparisons increased linearly over time and required capping to avoid clinically implausible values (see section 4.3.5).

Overall survival on second-line paclitaxel, compared with second-line atezolizumab (one study), is shown in Figure 9.

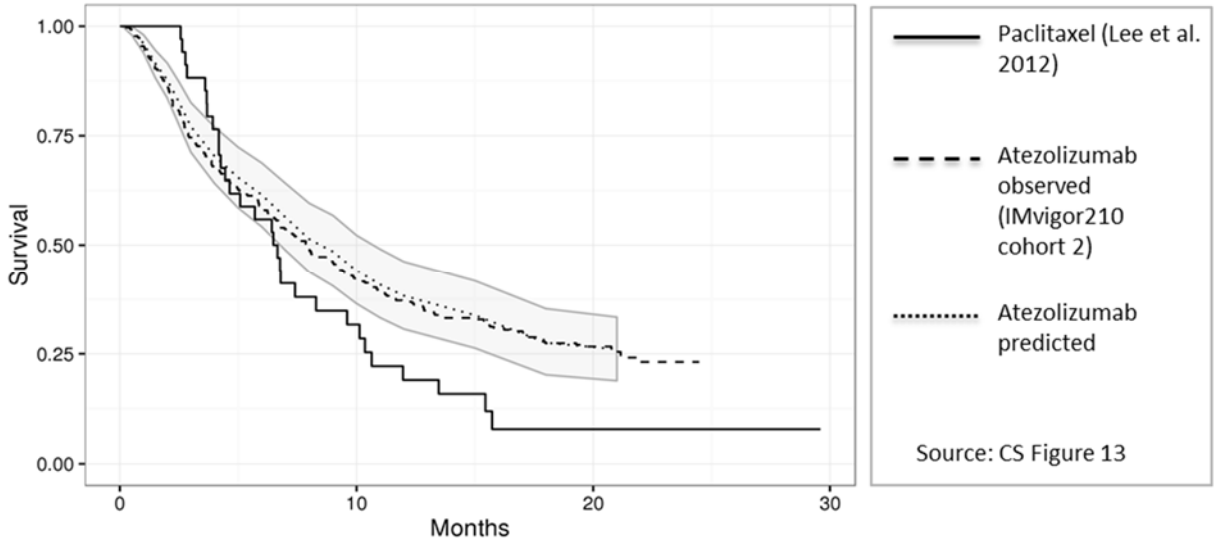

Figure 9 Overall survival curves for second-line paclitaxel (Lee et al. 2012) and atezolizumab

3.3.7 Adverse events

The CS presents safety endpoints from the two cohorts of the Imvigor 210 study and the PCD4989g study (minimal data) in CS section 4.12.3. We have summarised adverse event information from the PCD4989g study here, although the company stated that patients in PCD4989g received less than the licensed atezolizumab dose (see Appendix 2). No pooled adverse event data from the three sources of evidence are presented in the CS.

The rate of any adverse event was around 96-98% in the Imvigor 210 study (Table 20). Rates were generally similar across the two cohorts, where reported. *The most frequent treatment-related adverse events (affecting >10% of patients) were: Cohort 1: fatigue (30%), diarrhoea (12%) and pruritis (11%) (CS Table 43); Cohort 2: fatigue (30.6%), nausea (26.5%), pyrexia (22.3%), vomiting (19.4%), arthralgia (17.7%), pruritis (11.9%), rash (11.6%), decreased appetite (11.3%) and chills (10.6%) (CS Table 46)* Serious adverse events were experienced in 38% of patients in cohort 1 and 47% in cohort 2. The most commonly reported serious adverse events, reported in at least 2.5% of participants, were acute kidney injury, small intestinal obstruction, renal failure, sepsis and diarrhoea in cohort 1 (proportions are not reported in the CS). In cohort 2 the most commonly reported serious adverse events, reported in at least 3 participants, [redacted] (data from

The ERG has the following concerns regarding the network meta-analysis:

- Hazard ratios for overall survival were not used to inform clinical effectiveness of atezolizumab and were considered to be clinically implausible when applied in the economic analysis without adjustment.
- Hazard ratios for progression-free survival were considered to be clinically implausible and were not used to inform the clinical effectiveness or cost-effectiveness evaluation of atezolizumab.

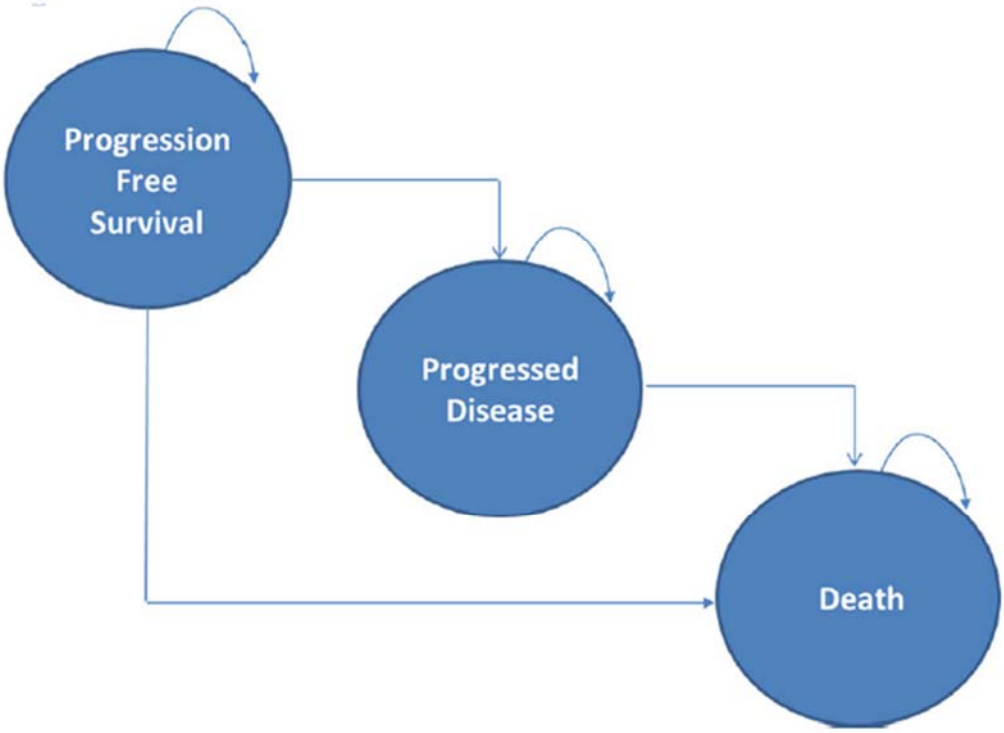

Figure 10 State model schematic (CS Figure 22)

Patients are treated with atezolizumab until *loss of clinical benefit or unmanageable toxicity*. Patients treated with the comparator treatment are treated for a specified number of treatment cycles, according to the marketing authorisation. On the basis of expert clinical advice, the company assumed that there are no subsequent lines of anti-cancer therapy for any treatment arm in either population following progression. The CS states that for second-line treatment this assumption was confirmed by the IMvigor 210 study where only 14.7% of patients receive subsequent treatment with gemcitabine with the majority only receiving palliative radiotherapy. For cisplatin-ineligible patients, the CS states that these might be expected to receive subsequent therapy, for example the NICE guidelines recommend either carboplatin + paclitaxel or gemcitabine + paclitaxel, but that incorporating these treatments is unlikely to have a significant effect on the incremental cost or effectiveness of second-line therapy. The ERG's clinical expert advisor agreed that it is reasonable to assume that most patients on second-line treatment would not receive subsequent anti-cancer therapy following disease progression.

The ERG considers the model structure to be an appropriate representation of the biological processes of advanced or metastatic urothelial cancer and appropriately represents the

ratios but argues that these approaches are not appropriate techniques to obtain progression-free survival for the comparator drugs. So, they applied an assumption that progression-free survival of gemcitabine + carboplatin is equivalent to that of atezolizumab. The CS does not justify this assumption but it mirrors an assumption that the company made for second-line comparisons (explained below) that progression-free survival curves for atezolizumab and the comparators are equivalent.

Second-line comparators: docetaxel, paclitaxel and best supportive care

For second-line comparisons, the progression-free survival of docetaxel and paclitaxel were assumed to be equivalent to that of atezolizumab. This assumption is based on *a phase III* clinical study KEYNOTE-045[69] which included two patient cohorts: i) those who were treatment naive and ineligible for cisplatin-based chemotherapy; and ii) those who had previously received platinum-based chemotherapy. Although these patient populations align with those in this appraisal, KEYNOTE-045 compared pembrolizumab to investigator's choice of a 'blended comparison' of docetaxel, paclitaxel or vinflunine for which the data indicated a '*non-significant HR of 0.98 for PFS*' for pembrolizumab compared to the blended comparator (CS section 5.3.4). As the hazard ratio was not statistically significant and almost equivalent to 1.0, the company assumed that the progression-free survival curves for the comparators are equivalent to that of atezolizumab.

For best supportive care, the company assumed a proportional hazards model with a hazard ratio of 1.12 (Crl 0.91 to 1.37) based on the fixed-effect zero fractional polynomial model used in the economic analysis.

For validation, the company compared the progression-free survival model results against the observed clinical data from IMvigor 210 (CS Table 75). The CS states that the economic model overestimates median progression-free survival compared to the observed data.

ERG comments on the methods for modelling progression-free survival

The ERG views the standard method adopted to extrapolate progression-free survival data for both the first-line and second-line atezolizumab arms in the IMvigor 210 trial, by fitting parametric distributions, to be appropriate. In both patient cohorts, the gamma distribution is used for data extrapolation which appears to provide a good fit to the progression-free survival data, based upon AIC and BIC values and visual inspection of the survival curves.

The economic models provide an option which enabled the ERG to run the analyses not assuming that atezolizumab is equivalent to its comparators. For this scenario, in first-line treatment comparisons, the model uses parametric curves fitted to the gemcitabine + carboplatin progression-free survival data whereas for the second line treatment comparisons, the relative effects of the comparator arms i.e. docetaxel, paclitaxel and best supportive care are derived from the fractional polynomial models. In both the cases, the impacts on base case ICERs are minimal (see Table 26).

Table 26 Comparison of the CS base case results with the ERG's assumption on progression-free survival

Comparator	**ICER (£/QALY)**	
First-line	**CS Base case**	**ERG scenario: PFS of atezolizumab ≠ PFS of GEM + CAR**
Gemcitabine + carboplatin	£44,158	£43,841
Second-line	**CS Base case**	**ERG scenario: The relative effects of the comparators are obtained from FP models**
Docetaxel	£131,579	£132,250
Paclitaxel	£104,850	£99,996
Best supportive care	£98,208	£98,273

CAR: carboplatin; GEM: gemcitabine; FP: fractional polynomial; PFS: progression-free survival
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

The CS *justifies the use of the KEYNOTE-045 study to inform the progression-free survival parameter for the comparator arms, based on expert clinical advice.* It is unclear if this study was identified from a systematic search. Further, IMvigor 210 and KEYNOTE-045 consist of different interventions i.e. atezolizumab and pembrolizumab, respectively. To assume that progression-free survival curves of the comparators in the current appraisal are similar to that of atezolizumab based on *this study* implicitly indicates that progression-free survival of atezolizumab is similar to that of pembrolizumab. Whilst we acknowledge that atezolizumab and pembrolizumab belong to the same broad class of drugs, the CS does not provide any evidence that they will have similar effectiveness, and we note that they have different specific modes of action (atezolizumab is a PD-L1 inhibitor whilst pembrolizumab is a PD1 inhibitor). According to the ERG's clinical expert, there is insufficient information available on whether atezolizumab and pembrolizumab differ in effectiveness, but it would be reasonable to assume that they are similar.

used for the intervention arm in both first-line and second-line comparisons. The CS also does not present any sensitivity analyses varying the treatment effect of atezolizumab compared to the comparator arms. Further, the CS does not report any sensitivity analyses varying the contrast estimates used within the fractional polynomial models. To address these issues, we conducted a range of sensitivity analyses, details of which are described below in section 4.4.

Table 28 Hazard ratios used in the company's economic analyses

First-line	OS HR until 8 months	OS HR after 8 months
Atezolizumab vs gemcitabine + carboplatin	0.62 (Crl: 0.47, 0.82) *Results from the first-order FP model are used to estimate the HR at different time points until the time points correspond with the median follow up* (i.e. at 8 months) at which point the HR is capped.	0.54 The economic model uses the value of 1.84 (i.e. HR of gemcitabine + carboplatin vs atezolizumab). This value is used based on the assumption of proportional hazards.
Second-line	**OS HR until 21.16 months**	**OS HR at and after 21.16 months**
Docetaxel vs atezolizumab	Results from the first-order FP model are used to estimate the HR until the time points correspond with the median follow up (i.e. at 21.16 months) at which point the HR is capped.	2.12 (this value is based on the assumption of proportional hazards)
Paclitaxel vs atezolizumab	Same as above	1.49 (this value is based on the assumption of proportional hazards)
BSC vs atezolizumab	Same as above	1.66 (this value is based on the assumption of proportional hazards)

HR: Hazard Ratio; FP: fractional polynomial; OS: overall survival

The company's choice of parametric curves for overall survival is based upon the fit with survival data for atezolizumab, assessed using AIC and BIC values and visual inspection of the parametric curves. The ERG notes that other parametric curves may also provide a good fit with the observed trial data and that the model also provides the option to use the Kaplan-Meier data with a parametric distribution for the tail of the curve. We also note that the AIC and BIC values only provide information on the fit to the observed data and do not inform the choice of the extrapolation beyond the trial, which should be based upon clinical plausibility.

As shown in Figure 12, Figure 13, and Figure 14, the modelled overall survival curves for the second-line comparator arms are comparable with the survival curves reported by the studies of interest. To assess the most plausible distribution for extrapolating overall survival data, we compared different model fits for the atezolizumab arm and the best supportive care arm. The goodness of fit was measured through visual inspection. We chose best supportive care for this comparison due to the available evidence being based on a larger sample size and a longer follow up period (see Table 11) for this comparator among the three comparator arms (docetaxel, paclitaxel and best supportive care) used in the economic analyses. Based on our observation, we view that Kaplan-Meier data and a Weibull curve would provide the most appropriate fit for extrapolating long term survival data. Further details of this analysis and alternative plausible survival distributions are presented in section 4.4.

The ERG notes that the company is inconsistent in the time points used to cap the hazard ratio across the two patient cohorts. As previously mentioned, the first-line hazard ratio is capped at 8 months whereas for the second-line comparisons, the cut-off is 21.16 months. For both first-line and second-line hazard ratios the assumption of proportional hazards is applied after the capping time point. The ERG conducted exploratory analyses for both first-line and second-line comparisons in which we varied the time points at which the assumption of proportional hazards starts (see section 4.4). Secondly, the ERG has concerns about the company's approach to cap the hazard ratio. The CS states this was done to arrive at clinically plausible results. However, this raises questions about whether the results from the fractional polynomial models used in the network meta-analysis are appropriate to inform the economic analyses if it is necessary to cap them in order to provide plausible results. We have performed exploratory analyses to see the effect on overall results of varying the slope of the contrast estimates. This was done to avoid needing to cap the hazard ratios. Further details of the analyses are presented in section 4.4 below.

4.3.5.3 Time to treatment discontinuation

In the CS, TTD for first- and second-line atezolizumab is captured in the model through patients transitioning in the model. Data for TTD for atezolizumab was taken directly from the IMvigor 210 study for the trial period. Beyond this time-frame, the company extrapolated discontinuation data by adopting the standard technique of fitting parametric distributions to the TTD Kaplan-Meier curves. Goodness of fit to the data was assessed using AIC and BIC and graphical

In the company's model, utilities are imputed in a way that is slightly inconsistent with the CS text: as stated in the CS, for atezolizumab, the 'on-treatment' utility in the model is 0.75 and the 'off-treatment' utility is 0.71; however, the base-case utilities for comparators are both set at 0.75. We carried out a scenario analysis where both utilities for atezolizumab are set at 0.75, in line with the assumption that atezolizumab is better tolerated than the comparators (see section 4.4 for details). In the same analysis we set the 'on-treatment' utility of *comparators* to 0.71 and set the 'off-treatment' utility to 0.75 to reflect the disutilities commonly observed during treatment with chemotherapy.

4.3.7 Resource use and costs

The company conducted a systematic literature search for resource use among patients aged 18 years and above with advanced urothelial carcinoma, and their search strategy appears appropriate (section 3.1.1). The inclusion criteria specified that the outcomes of interest were direct costs, total cost, resource cost and cost drivers. The search was not restricted to studies conducted in the UK. The review identified 15 studies that met the broad search criteria of the CS. Twelve studies were further screened out and the rationale for their exclusion is stated in CS Appendix 8.11 (we note this is wrongly mentioned as Appendix 8.10 in the CS). The ERG agrees with company's rationale for excluding these studies. The three studies finally included were selected based on their relevance to the UK population. They are Seal et al. 2015;[73] Huillard et al. 2016;[74] and NICE 2013.[22]

Seal et al. 2015 estimated total all-cause costs attributable to medical services, inpatient visits and emergency department visits spanning a 6-month period pre- and post-metastatic cancer diagnosis. The setting of Seal et al. is in the US. Huillard et al. was a retrospective study that captured the proportion of patients admitted to an intensive care unit, and the utilisation of supportive care, among adults suffering from bladder cancer in their last month of life. The setting for Huillard et al. is France. The ERG notes that, although the CS states that these studies contain data of interest (See Table 64 of the CS and CS Section 5.5.1), they have not been incorporated into the model.

Resource use consists of the drug dose and its costs, administration costs per 21 day treatment cycle, adverse event management costs and weekly supportive care costs (health state costs). The CS makes the case that none of the studies identified in the company's search directly quantified costs and healthcare resource use for the population of interest from a UK NHS

referenced in the CS states a 2014 Department of Health cost of £354.72. The ERG notes that these errors have a negligible impact on the results of cost-effectiveness analysis. We also observed that references for certain adverse events (alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increase, diarrhoea, electrolyte abnormalities, hypophosphataemia and infection) are not included in the CS references. The ERG and NICE raised this issue with the company and the company provided the reference for these adverse events (clarification response *B4*).

The company's systematic review did not identify any relevant resource use data associated with health states in metastatic urothelial carcinoma. The CS states that resource use was elucidated through expert clinical advice, and deemed appropriate by the ERG and NICE appraisal committee on vinflunine.[22] The CS uses these same assumptions (summarised in Table B39 of the manufacturer submission for TA272, January 2013) in CS Table 69. We note that the health home visit cost is referenced as Curtis 2016 but that publication does not report this cost. The ERG and NICE queried this with the company and in response the company described the error as typographical (clarification response B1). The company stated that the correct reference for the health home visit cost is the manufacturer's submission for vinflunine. Health state costs are slightly higher in the CS and the company explained further in their clarification that they have been inflated to 2015/16 costs.

Resource utilisation for health states is estimated on a per cycle basis in the CS, calculated from separately stated unit costs and frequency of use per month. In the CS, the pre-progression state costs amounted to £111.85, while the post-progression costs amounted to £146.79. despite the paucity of data, the company's approach is consistent with the reference case. The CS reports one-way sensitivity analysis for monthly atezolizumab off-treatment supportive care costs, and comparator off-treatment supportive care costs, varying between a lower value of half the base case and an upper value increased by 50% of the base case value. The ERG notes that the values used in these sensitivity analyses are arbitrary but in the absence of relevant data they are reasonable to capture the high uncertainty surrounding the cost inputs.

Table 32 Comparison of best supportive care results for the current submission and a previous submission on vinflunine

Comparator	Costs, £	Life years	QALYs
BSC (from vinflunine appraisal)	£8642	0.63	0.234
BSC (from atezolizumab appraisal)	*£4836*	0.75	0.55

BSC: best supportive care; QALY: quality-adjusted life year

4.3.9 Cost effectiveness Results

Results from the economic model (section 5.7 of the CS) are presented as the incremental cost per QALY gained for first-line atezolizumab compared with gemcitabine + carboplatin and for second-line comparisons with docetaxel, paclitaxel and best supportive care.

For the first-line base case an incremental cost per QALY gained of £44,158 per QALY is reported (see Table 33) for atezolizumab compared to gemcitabine + paclitaxel. For the second-line base case, the ICERs for atezolizumab compared to docetaxel, paclitaxel and best supportive care are £131,579, £104,850, £98,208 per QALY gained respectively.

Table 33 First-line base case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£77,211	3.74	2.69				
Gemcitabine + carboplatin	£18,106	1.84	1.35	£59,106	1.91	1.34	£44,158

ICER: incremental cost-effectiveness ratio; LYG: life years gained: QALYs: quality-adjusted life years

Table 34 Second-line base case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)[a]
Atezolizumab	£71,868	1.69	1.23				
Docetaxel	£9,439	1.04	0.76	£62,430	0.65	0.47	£131,579
Paclitaxel	£16,606	0.96	0.71	£55,262	0.73	0.53	£104,850
BSC	£4,836	0.75	0.55	£67,032	0.94	0.68	£98,208

ICER: incremental cost-effectiveness ratio; LYG: life years gained: QALYs: quality-adjusted life years
[a] Pairwise comparison with atezolizumab.

CONFIDENTIAL UNTIL PUBLISHED

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma: ERG critique of the company's Patient Access Scheme

Confidential appendix to the Evidence Review Group report

Produced by Southampton Health Technology Assessments Centre

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1 Introduction

This document is an appendix to the Evidence Review Group (ERG) report to NICE. It provides the ERG's critique of the company's base case cost-effectiveness analysis and sensitivity analysis, with the confidential patient access scheme (PAS) discount for atezolizumab applied.

2 ERG critique and update of the company's base case analyses

The company has submitted a PAS with a simple discount of [redacted]. The company states in their PAS template that the cost of atezolizumab changes from the proposed list price of £3807.69 per 1200 mg vial to a PAS price of [redacted] per 1200mg vial. However, the ERG notes that the proposed PAS discount produces a PAS price of [redacted]. This small calculation error means that the results presented in the PAS template contain a small discrepancy of about [redacted] and [redacted] for first-line and second-line respectively. The ERG has provided the corrected base case results for first-line and second-line treatments in Table 1 and Table 2.

Table 1: First-line base-case cost-effectiveness results with corrected PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	3.74	2.69				
Gemcitabine + carboplatin	£18,106	1.84	1.35	[redacted]	1.91	1.34	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 2: Second-line base-case cost-effectiveness results with corrected PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.69	1.23				
Docetaxel	£9,439	1.04	0.76	[redacted]	0.65	0.47	[redacted]
Paclitaxel	£16,606	0.96	0.71	[redacted]	0.73	0.53	[redacted]
BSC	£4,836	0.75	0.55	[redacted]	0.94	0.68	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

CONFIDENTIAL UNTIL PUBLISHED

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma: updated ERG base-case analyses using the company's Patient Access Scheme price

Confidential appendix to the Evidence Review Group report

Produced by Southampton Health Technology Assessments Centre

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1.1 Introduction

This document is an appendix to the Evidence Review Group (ERG) report to NICE. It provides updated ERG analyses with the confidential patient access scheme (PAS) discount for atezolizumab of [redacted] applied. Full details of the analysis approaches are given in the ERG report.

1.2 Sensitivity analyses on the ERG base case

Table 1 lists the assumptions used for the ERG base case, along with their justifications (this is the same as Table 47 in the ERG report).

Table 1 Assumptions for the ERG base case analysis

Treatment line	Parameter	Value	Justification
First- and second-line	Utility	As shown in Table 4 below	Clinical expert advice to ERG
First-line	OS	K-M + exponential tail	Best fit for atezolizumab and gemcitabine + carboplatin
	TTD	Weibull	Best fit according to AIC and BIC
Second-line	OS	KM + Weibull tail	Best fit for atezolizumab and BSC
	TTD	Log-logistic	Best fit according to AIC and BIC

AIC Akaike information criterion; BIC Bayesian information criterion BSC: best supportive care; ICER: incremental cost-effectiveness ratio; K-M: Kaplan-Meier; OS: overall survival; QALY: quality-adjusted life year; TTD: time to treatment discontinuation;

Tables 2, 3 and 5 show the effects of changes in the parametric functions for extrapolating time to treatment discontinuation (TTD) and overall survival, and varying utility values, as used in the ERG base case.

i) Time to treatment discontinuation / overall survival extrapolation

The TTD was varied in the ERG base case using the Weibull distribution for first-line treatment and using the log-logistic distribution for second-line treatment. For overall survival, the ERG base case uses the Kaplan-Meier distribution with an exponential tail for first-line treatment and the Kaplan-Meier distribution with a Weibull tail for second-line treatment. The results are shown in

Table 2 and Table 3.

Table 2 ERG sensitivity analyses selecting different parametric functions for extrapolating TTD and overall survival for first-line treatment

First-line		
Parameter	**Value**	**ICER (£/QALY) vs gemcitabine + carboplatin**
TTD	Company base case (gamma)	[redacted]
	Weibull	[redacted]
OS	Company base case (cure generalised gamma)	[redacted]
	K-M + Exponential tail	[redacted]

ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; TTD: time to treatment discontinuation

Table 3 ERG sensitivity analyses selecting different parametric functions for extrapolating TTD and overall survival for second-line treatment

Second-line				
Parameter	**Value**	**ICER (£/QALY) vs docetaxel**	**ICER (£/QALY) vs paxlitaxel**	**ICER (£/QALY) vs BSC**
TTD	Company base case (gamma)	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]
OS	Company base case (cure generalised gamma)	[redacted]	[redacted]	[redacted]
	K-M + Weibull tail	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; TTD: time to treatment discontinuation

ii) Utility values

The ERG used the assumptions for utility values as shown in Table 4 (which is the same as Table 45 in the ERG report). The results of the sensitivity analyses using the ERG's assumptions for the utility values are shown in

Table **5**.

Table 4 Pre-progression utility values used in the CS and the ERG analysis

	CS Pre-progression utility		**ERG pre-progression utility values**	
	Atezolizumab	Comparators	Atezolizumab	Comparators
On-treatment	0.75	0.75	0.75	0.71
Off-treatment	0.71	0.75	0.75	0.75

Table 5 ERG sensitivity analyses with changes to the assumptions for pre-progression health state utility values

Parameter	First-line	ICER (£/QALY)		
		vs gemcitabine + carboplatin		
Utility values	Base case	[redacted]		
	ERG assumption	[redacted]		
	Second-line	**vs docetaxel**	**vs paxlitaxel**	**vs BSC**
	Base case	[redacted]	[redacted]	[redacted]
	ERG assumption	[redacted]	[redacted]	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

1.3 ERG base case analysis results

Using the assumptions for the ERG base case as listed in

Table **1** above, the ERG's base case cost-effectiveness results are shown in Table 6 for first-line treatment and in Table 7 for second-line treatment.

Table 6 ERG first-line base case analysis results

	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
Atezolizumab	[redacted]		1.32		
Gemcitabine + carboplatin	£12,469	[redacted]	0.81	0.51	[redacted]

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

The ERG base case ICER for first-line atezolizunab compared to gemcitabine + carboplatin is [redacted] per QALY gained.

Table 7 ERG second-line base case analysis results

	Costs	Incremental costs	QALYs	Incremental QALYs	ICER (£/QALY)
Atezolizumab	[redacted]		0.84		
Docetaxel	£8,196	[redacted]	0.64	0.20	[redacted]
Paclitaxel	£13,615	[redacted]	0.55	0.29	[redacted]
BSC	£4,090	[redacted]	0.47	0.37	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

The ERG base case ICERs for second-line atezolizumab compared to docetaxel, paclitaxel and best supportive care are [redacted], [redacted] and [redacted] per QALY gained respectively.