NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated advanced or metastatic urothelial cancer

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Contents:

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

Pre-meeting briefing

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

This slide set is the pre-meeting 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

Common abbreviations			
AE	Adverse event	LYG	Life years gained
AIC	Akaike information criterion	mRECIST	modified RECIST
ASaT	All subjects as treated	NMA	Network meta-analysis
BIC	Bayesian information criterion	NR	Not reported
BICR	Blinded independent central review	ORR	Objective response rate
CDF	Cancer Drugs Fund	OS	Overall survival
CHMP	Committee for Medicinal Products for Human Use	PAS	Patient access agreement
CI	Confidence Interval	PD	Progressed disease
CPS	Combined proportion score	PD-L1	Programmed death-ligand 1
CR	Complete response	PFS	Progression-free survival
CS	Company submission	PH	Proportional hazards
CSR	Clinical study report	PR	Partial response
DCR	Disease control rate	PSA	Probabilistic sensitivity analysis
EAMS	Early Access to Medicines Scheme	PSS	Personal and Social Services
ECOG	Eastern Cooperative Oncology Group	Q3W	Every 3 weeks
EMA	European Medicines Agency	QALY	Quality adjusted life year
EORTC	European Organisation for the Treatment of Cancer	QLQ	Quality of life questionnaire
EQ-5D	European Quality of Life - 5 Dimensions Questionnaire	RCT	Randomised controlled trial
ERG	Evidence Review Group	RECIST	Response Evaluation Criteria In Solid Tumors
HR	Hazard ratio	RPSFT	Rank preserving structural failure time
HRQoL	Health-related quality of life	RR	Response rate
IA1	First interim analysis	SAE	Serious adverse event
IA2	Second interim analysis	sd	Standard deviation
ICER	Incremental cost effectiveness ratio	SD	Stable disease
Incr.	Incremental	SmPC	Summary of product characteristics
IPCW	Inverse Probability of Censoring Weighting	SOC	Standard of care
ITT	Intention-to-treat	TCC	transitional cell carcinoma
K-M	Kaplan-Meier	TPS	Tumour proportion score
KN045	KEYNOTE-045: Key trial that informs the clinical effectiveness and cost effectiveness evidence	UK SOC	UK standard of care (i.e. paclitaxel and docetaxel)
LS	Least squares		2

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 is low*

* The most plausible 5-year survival rate is a key issue which will be discussed in the economic section

Pembrolizumab (KEYTRUDA)

Merck Sharp & Dohme

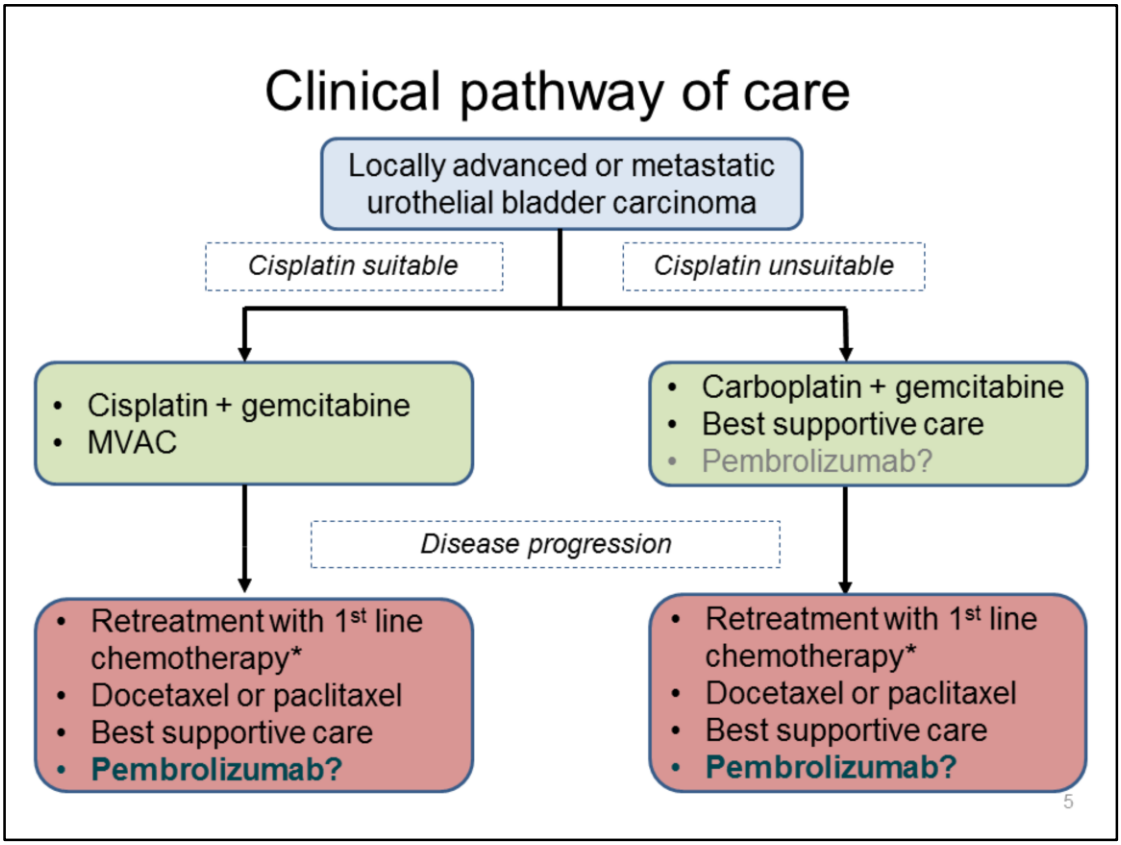
Marketing authorisation	Locally advanced or metastatic urothelial carcinoma in adults: • **who have received prior chemotherapy** • who are not eligible for cisplatin-containing chemotherapy*
Administration & dose	Intravenous infusion, 200mg every 3 weeks until disease progression or unacceptable toxicity
Mechanism of action	Humanised monoclonal antibody acts on the programmed cell death-1 (PD-1) receptor, part of the immune checkpoint pathway.
Cost	List price: 100mg vial = £2,630 Average length of treatment: 5.60 months (8.81 cycles) Average cost per course (at list price): £46,341 Presented analyses incorporate a simple discount PAS

*Due to a late change in expected marketing authorisation, final scope released by NICE and company decision problem only includes people who have progressed on or after **platinum-containing** chemotherapy, and **does not** include people who are ineligible for cisplatin-containing chemotherapy.

Results of KEYNOTE-052 (not reported) will inform the population who are ineligible for cisplatin-containing chemotherapy (estimated June 2018 primary completion date) – scoping proceeding separately

- Pembrolizumab has been appraised for several indications:
  - 'Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab' (ID760/TA357) – Committee A
  - 'Pembrolizumab for treating ipilimumab naive unresectable, metastatic melanoma' (ID801/TA366) – Committee A
  - 'Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy' (ID840/TA428) – Committee D
  - 'Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer' (ID990) – Committee D

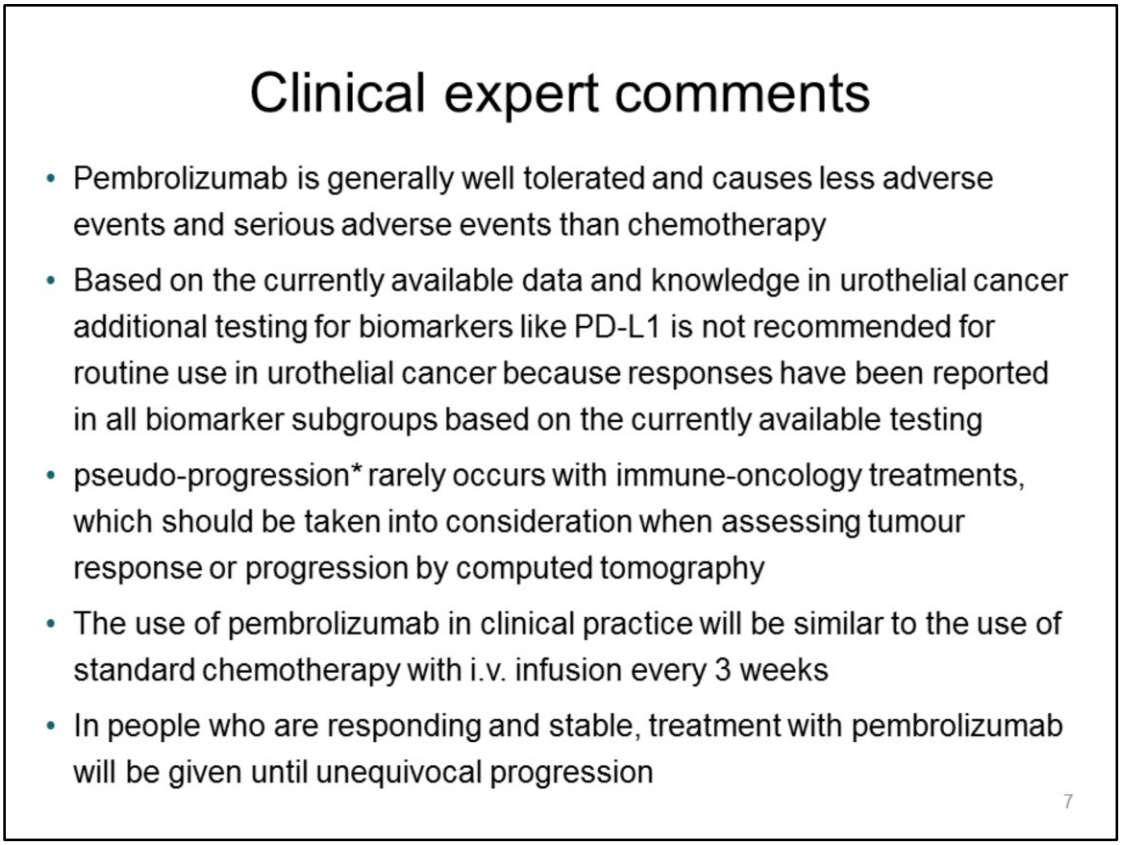
- Other PD-L1/PD-1 inhibitors have been appraised for this indication:
  - 'Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy' (ID939) – Committee D
  - 'Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy' (ID995) – Committee D



*Retreatment with 1st line platinum-based chemotherapy is a valid option only for people whose disease has had an adequate response. For this proportion of people the company are positioning pembrolizumab as a possible 3rd line treatment.
MVAC: high dose methotrexate, vinblastine, doxorubicin and cisplatin plus granulocyte-colony stimulating factor

Patient expert comments

- No new treatments for urothelial cancer for over 35 years
- Urothelial cancer has the highest recurrence rate of any cancer
- Treatments are invasive, have significant side effects and reduce Quality of Life
- Urothelial cancer comes bottom of NHS cancer patient experience survey
- The new immunotherapy treatments could see a step change in treating this much ignored cancer, and will possibly offer hope to many, extra time to many and possibly be curative for some.
- Further research/trials to optimise the treatment and develop biomarkers would be highly desirable
- Considerations should be given for research/trials for use of pembrolizumab earlier in the treatment pathway



In those centres where weekly instead of 3-weekly taxanes are standard of care, pembrolizumab use will be easier with less seating time, and concomitant treatment will be less with pembrolizumab (less with regards to antiemetics and corticosteroid pretreatment)

*Pseudo-progression: tumor growth from treatment effect (such as development of new lesions associated with oedema and infiltration of immune cells), or delayed clinical responses. This would be classified prematurely as progressive disease by RECIST 1.1 criteria.

NHS England comments

- Main clinical prognostic factors for locally advanced/metastatic disease are performance status and presence of visceral metastases (lung, liver, bone).
- Cisplatin-based combination chemotherapy inappropriate with any of:
  - impaired renal function
  - 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
- Carboplatin and gemcitabine is used in patients who are ineligible for cisplatin. If unfit for carboplatin unlikely any chemotherapy or immunotherapy can be used
- Taxanes and best supportive care are the relevant comparators. Re-treatment with a 1st line regimen is rare, and not an appropriate comparator
- Pembrolizumab NHSE treatment criteria likely to include ECOG 0 or 1 or 2, but treatment of people with performance status 2 should only proceed with caution

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If NICE recommends pembrolizumab for use, 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 SACT
- 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 or metastatic
- 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 AND who have relapsed 12 or less months since completing platinum-based chemotherapy are eligible but must satisfy all other criteria
- ECOG score of 0/1 /2 but treatment with performance status 2 should only proceed with caution
- To be treated until disease progression or excessive toxicity or for a maximum of 2 years, 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)

Pembrolizumab to be otherwise used as set out in its Summary of Product Characteristics

Decision problem
deviations from final scope

	Final Scope	Company submission and rationale
Comparator	• Retreatment with 1st line platinum-based chemotherapy* • Docetaxel • Paclitaxel • Best supportive care (BSC)	• Docetaxel • Paclitaxel No evidence exists for retreatment with 1st line platinum-based chemotherapy BSC not considered a relevant comparator, as alternative active treatments are available

Subgroups	• Cancer histology
	• Biological markers (PD-L1)
		• PD-L1 positive subgroups^
		  • Combined proportion score (CPS) ≥1%
		  • CPS ≥10%
		• Specific histology subgroups
		  • Predominant transitional cell carcinoma (TCC)
		  • Pure TCC
		90% of bladder cancer and 87% of ureter and renal pelvis cancer is TCC histology. 71% of the KEYNOTE-045 trial is TCC.

Source: table 1 (18-19), company submission

*Retreatment with 1st line platinum-based chemotherapy is a valid comparator only for people whose disease has had an adequate response

^CPS is defined as the percentage of tumour cells and mononuclear inflammatory cells (MIC) within the tumour nests and the adjacent supporting stroma expressing PD-L1 at any intensity. Previous appraisals have used tumour proportion score (TPS), which only includes the percentage of tumour cells. The cut-off of ≥1% for positivity was determined with the analyses of tumour specimens from the KEYNOTE-012 trial (a phase 1 study that included a cohort of people of advanced urothelial cancer) while the cut-off of ≥ 10% was based on a review of data from the first 100 subjects enrolled in KEYNOTE-052 (a phase 2 study in people with advanced/metastatic urothelial cancer who are ineligible for cisplatin-based therapy)

Clinical effectiveness evidence

Company submission section 4

Clinical evidence
KEYNOTE-045

Design	Multi-site (4 UK patients), Open-label randomised controlled trial
Recruitment	Planned n=470; recruited n=528; UK standard of care subgroup n=370
Population	• urothelial cancer of the renal pelvis, ureter, bladder, or urethra • progression or recurrence of urothelial cancer following first-line platinum-containing regimen (cisplatin or carboplatin) • no more than two prior lines of systemic chemotherapy • ECOG Performance status of 0, 1 or 2
Intervention	Pembrolizumab, 200 mg IV every 3 weeks (Q3W)
Comparator	Investigators choice of: Paclitaxel 175 mg/m2 Q3W; Docetaxel 75 mg/m^2 Q3W; Vinflunine 320 mg/m^2 Q3W*
Key Pre-defined subgroups	• Geographic region of enrolling site (EU vs. non-EU) • Prior platinum therapy (carboplatin vs. cisplatin) • PD-L1 positive (CPS ≥1%) and strongly positive (CPS ≥10%) • Cancer histology (pure transitional cell vs mixed histology)
Post-hoc subgroups	• UK Standard of care (UK SOC) – Comparator of paclitaxel and docetaxel only (removal of vinflunine data)

Source: table 7 (page 48); table 10 (page 66-69); of the company submission

- Population stratified (block size 2) by the following factor:
  - Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1vs. 2)
  - Presence or absence of liver metastases
  - Haemoglobin (≥ 10 g/dL vs. <10 g/dL)
  - Time from completion of most recent chemotherapy (<3 months or ≥3 months [90 days])

- Subjects with ECOG 2 could only be enrolled if liver metastases were absent, haemoglobin is ≥10 g/dL, and time from completion (last dose) of most recent chemotherapy is ≥ 3 months (90 days).

- The sample size and power calculation of PFS and OS was powered to account for the PD-L1 positive and strongly positive subgroup

KEYNOTE-045
Clinical outcomes

Primary	• **Progression-free survival (PFS) per RECIST 1.1 by Blinded Independent Central Review (BICR)** • **Overall Survival (OS)**
Secondary / exploratory outcomes	• Safety and tolerability profile • PFS per Modified RECIST (mRECIST) 1.1 by BICR • Objective response rate (ORR), either complete or partial, per RECIST or mRECIST 1.1 by BICR • Time to response (TTR) defined by time from randomisation to the first assessment of a complete or partial response • Response duration per RECIST 1.1 by BICR • PFS per RECIST 1.1 from randomisation to specific time-points by BICR; • Health related quality of life (HRQoL) using the EORTC and EQ-5D-3L questionnaires
Data-cut	All results from planned second interim analysis – September 2016 median pembrolizumab follow-up: 10.3 months (range: 0.2 to 20.8)

Source: section 4.3.1 (pages 57 – 60), company submission

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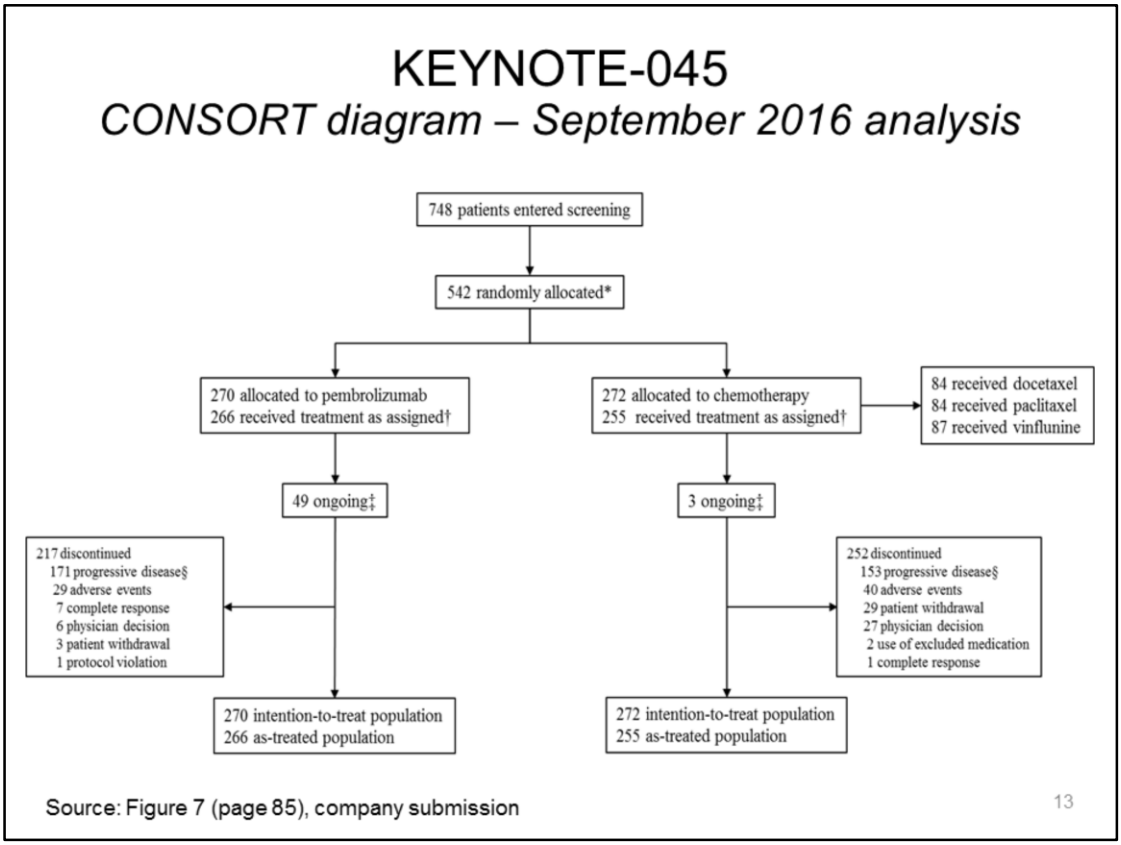
Tumour imaging was scheduled for week 9 followed by every 6 weeks during the first year and every 12 weeks thereafter

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0

PFS and ORR per modified RECIST (mRECIST) corresponds to RECIST 1.1 criteria with exception that a confirmation of PD (at least 4 weeks after the initial PD assessment) required for subjects who remain on treatment following a documented PD per RECIST 1.1.
RECIST 1.1 criteria

- Progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (includes baseline sum if that is the smallest). In addition, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: appearance of one or more new lesions also considered progression)
- OR: Complete Response (CR) - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

At September 2016 cut-off, 40% (108/270) of patients in the pembrolizumab group and 24.6% (67/272) in control group were continuing in trial, with 18.4% (49/266) in pembrolizumab group continuing to receive the drug on trial compared to 1.2% (3/255) in control group.

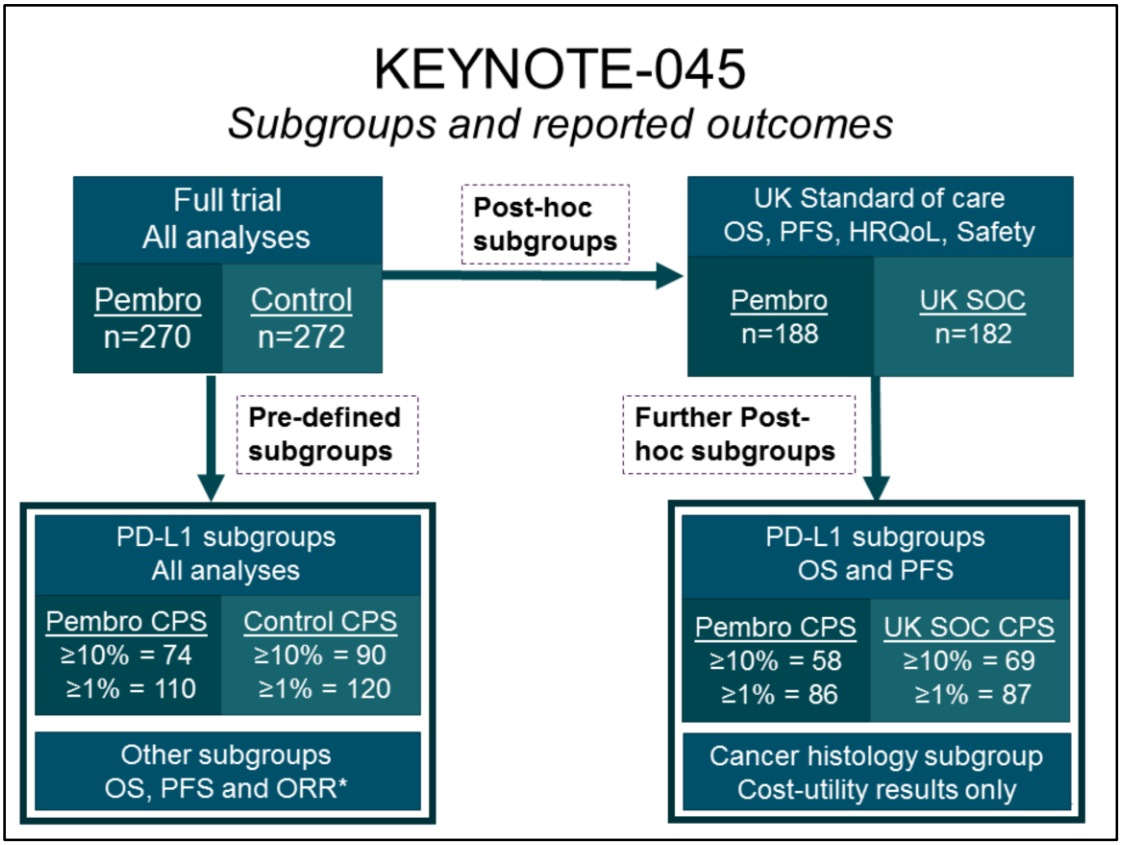


*Reasons for screen failure on page 85, company submission

†Reasons for not receiving study treatment were randomisation in error based on failure to meet all eligibility criteria (n=2) and fatal adverse events (n=2) in the pembrolizumab group and withdrawal of consent after randomisation (n=15), worsening physical condition (n=1), and a decrease in platelet count that precluded treatment (n=1) in the chemotherapy group.

‡Patients without a completed study medication discontinuation form.

§Includes patients with radiologic and clinical disease progression.



*ORR not included in company submission but reported in the Clinical Study Report (p398)

KEYNOTE-045

Key baseline characteristics

	UK SOC (n=182)	Pembrolizumab (n=188)
Mean age (sd)	65.1 (8.9)	66.0 (10.0)
% ECOG 0/1/2*	39.6 / 58.8 / 1.1	46.3 / 51.1 / 1.1
% prior platinum therapy cisplatin/carboplatin/other	79.1 / 19.8 / 1.1	73.9 / 25.0 / 0.5
% EU / Non-EU	26.9 / 73.6	29.3 / 70.7
% smoking: never / ex / current	30.2 / 59.3 / 9.3	41.0 / 49.5 / 9.0
% TCC histology pure / predominant	69.8 / 29.7	67.6 / 31.9
% PD-L1 <1% / ≥1% / missing	50.0 / 47.8 / 2.2	51.6 / 45.7 / 2.7
% PD-L1 <10% / ≥10% / missing	59.3 / 37.9 / 2.7	66.0 / 30.9 / 3.2
% at baseline lymph node / visceral	14.8 / 85.2	11.7 / 87.8

*Subjects with ECOG 2 could only be enrolled if liver metastases were absent, haemoglobin ≥10 g/dL, and time from completion (last dose) of most recent chemotherapy ≥ 3 months (90 days).
Source: adapted from table 9 (page 150), company appendix 9

People were allocated to investigators choice of comparator pre-randomisation. Patients who at pre-randomisation were allocated to vinflunine, but at randomisation then received pembrolizumab, are also excluded from subgroup analyses. Full trial recruited 542 patients (Control = 272; pembrolizumab = 270)

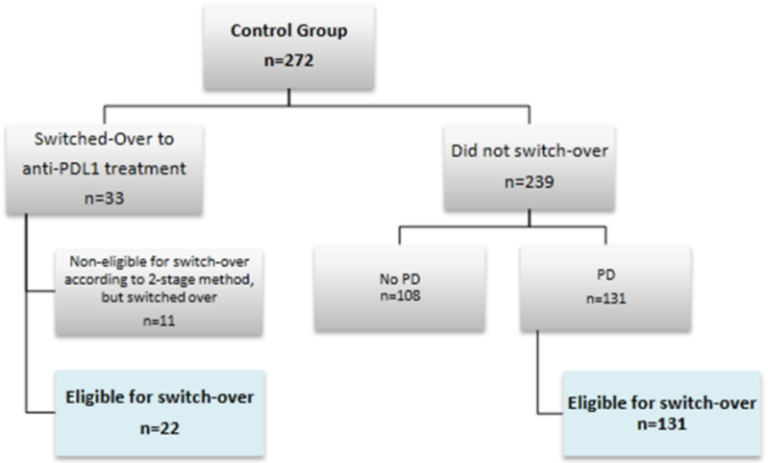
The majority of people treated have most recently received first-line therapy

% Neo adjuvant / adjuvant / 1st line / 2nd line / 3rd line	
UK SOC:	8.8 / 12.1 / 54.4 / 24.2 / 0.5
Pembrolizumab:	7.4 / 4.8 / 66.0 / 21.3 / 0.0

Company has not reported baseline characteristics of KEYNOTE-045 patients according to the investigator's choice before randomisation. Consequently, the ERG is unable to confirm the strict comparability of patients depending on investigator's choice before randomisation, and cannot exclude the absence of significant heterogeneity within the KEYNOTE-045 population.

KEYNOTE-045
Treatment switching

- People were allowed to receive anti PD-L1/PD-1 treatments* after disease progression
- Company preferred methodology was to adjust using the 2-stage method



Source: Figure 22 (page 118), company submission

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Please note that patients, who did not meet the eligibility criteria for switchover (8 in the UK SOC arm), were not included in the analysis.
*Subsequent treatments in the table below. Patients eligible for switch over in brackets

KEYNOTE-045	Trial control	Pembrolizumab
Subsequent anti PD-L1/anti PD-1 therapies received	33 (22)	2 (2)
anti-PDL1 monoclonal antibody (unspecified)	1 (1)	
atezolizumab	7 (4)	2 (2)
avelumab	2 (2)	-
durvalumab	3 (2)	-
nivolumab	4 (3)	-
pembrolizumab	16 (10)	-
Source: table 3 (page 6) company response to clarification (section A and C)		

Company states:
- The IPCW method is likely to be biased because of the small sample size
- For 2-stage method the assumptions required for it to be valid (i.e. potential to switch determined by disease progression and potential confounders measured until this point) were met.

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KEYNOTE-045

Primary outcomes

		Median months (95% CI)	HR (95% CI); p-value
PFS	Pembro#	2.1 (2.0, 2.2)	-
	Trial control	3.3 (2.3, 3.5)	0.98 (0.81, 1.19); p=0.41648*
	UK SOC	[redacted]	[redacted]
OS	Pembro#	10.3 (8.0, 11.8)	-
	Trial control	7.4 (6.1, 8.3)	0.73 (0.59, 0.91); p=0.00224*
	UK SOC	[redacted]	[redacted]
	UK SOC + RPSFT	[redacted]	[redacted]
	UK SOC + 2-stage	[redacted]	[redacted]
	UK SOC + IPCW	[redacted]	[redacted]

*One-sided p-value; ^Two-sided p-value; #Pembrolizumab median months from the full trial population
RPSFT - Rank Preserving Structural Failure Time; IPCW - Inverse Probability of Censoring Weights
Sources: table 24 (page 98) + table 47 (page 135) + table 68 (page 179), company submission; table 1 (page 5), company response to additional clarification request

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KEYNOTE-045

Progression-free survival – UK SOC

Source: Figure 1 (page 5), company response to additional clarification request

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KEYNOTE-045

Overall survival – UK SOC + 2-stage adjustment

Source: Figure 34 (page 181), company submission

KEYNOTE-045

Response rates

Outcome		Pembrolizumab (n=270)	Trial Control (n=272)
Objective response	No. of objective responses	57	31
	rate % (95% CI)	21.1 (16.4, 26.5)	11.4 (7.9, 15.8)
	difference (95% CI); p-value	9.6 (3.5,15.9); 0.00106	
time to response	mean (SD)	2.7 (1.2)	2.4 (0.8)
	median (range)	2.1 (1.4-6.3)	2.1 (1.7-4.9)
response duration	median (range)	Not reached (1.6+ - 15.6+)	4.3 (1.4+ - 15.4+)
% responders	Number at ≥ 6 Months (%)	41 (78)	7 (40)
	Number at ≥ 12 Months (%)	14 (68)	3 (35)

Source: adapted from table 4 (page 52), ERG report

- Exploratory analyses per mRECIST 1.1 by BICR were consistent with the results per RECIST 1.1 by BICR

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KEYNOTE-045

CPS <1% PD-L1 subgroup (I)

		Median months (95% CI)	HR (95% CI); p-value
PFS	Pembro#	[redacted]	[redacted]
	Trial control	[redacted]	[redacted]
	UK SOC	[redacted]	[redacted]
OS	Pembro	[redacted]	[redacted]
	Trial control	[redacted]	[redacted]
	UK SOC	[redacted]	[redacted]
	UK SOC + RPSFT	[redacted]	[redacted]
	UK SOC + 2-stage		[redacted]
	UK SOC + IPCW		[redacted]

*One-sided p-value; ^Two-sided p-value; #Pembrolizumab median months from the UK SOC population
RPSFT - Rank Preserving Structural Failure Time; IPCW - Inverse Probability of Censoring Weights
Sources: table 2-3 (page 8-10), company revised appendices; table 4 (page 8), company response to additional clarification request; table 9-10 (57-60)

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KEYNOTE-045

CPS <1% PD-L1 subgroup (II)

Outcome		Pembrolizumab (n=151)	Trial Control (n=147)
Objective response	No. of objective responses	[redacted]	[redacted]
	rate % (95% CI)	[redacted]	
	difference (95% CI); p-value	[redacted]	
time to response	mean (SD)	[redacted]	
	median (range)	[redacted]	
response duration	median (range)	[redacted]	
responders	Number at ≥ 6 Months (%)	[redacted]	
	Number at ≥ 12 Months (%)	[redacted]	

Source: adapted from table 11 (page 62-64) ERG report

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KEYNOTE-045

CPS ≥1% PD-L1 subgroup (I)

		Median months (95% CI)	HR (95% CI); p-value
PFS	Pembro#	2.1 (2.0, 2.4)	-
	Trial control	3.2 (2.2, 3.4)	0.91 (0.68, 1.24); p=0.26443*
	UK SOC	[redacted]	[redacted]
OS	Pembro	11.3 (7.7, 16.0)	-
	Trial control	6.9 (4.7, 8.8)	0.61 (0.43, 0.86); p=0.00239*
	UK SOC	[redacted]	[redacted]
	UK SOC + RPSFT	[redacted]	[redacted]
	UK SOC + 2-stage		[redacted]
	UK SOC + IPCW	[redacted]	[redacted]

*One-sided p-value; ^Two-sided p-value; #Pembrolizumab median months from the full trial population
RPSFT - Rank Preserving Structural Failure Time; IPCW - Inverse Probability of Censoring Weights
Sources: table 26 (page 101) + table 48 (page 137), company submission; table 2 (page 6), company response to additional clarification request

KEYNOTE-045

CPS ≥1% PD-L1 subgroup (II)

Outcome		Pembrolizumab (n=110)	Trial Control (n=120)
Objective response	No. of objective responses	26	10
	rate % (95% CI)	23.6 (16.1,32.7)	8.3 (4.1,14.8)
	difference (95% CI); p-value	16.9 (7.7,27.0); 0.00022	
time to response	mean (SD)	2.6 (1.0)	2.0 (0.1)
	median (range)	2.2 (1.4-5.3)	2.1 (1.9-2.2)
response duration	median (range)	Not reached (1.6+ - 15.6+)	Not reached (1.5+ - 15.4+)
responders	Number at ≥ 6 Months (%)	21 (88)	3 (56)
	Number at ≥ 12 Months (%)	7 (78)	2 (56)

Source: adapted from table 6 (page 53-54) ERG report

- Exploratory analyses per mRECIST 1.1 by BICR were consistent with the results per RECIST 1.1 by BICR

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KEYNOTE-045

CPS ≥10% PD-L1 subgroup (I)

		Median months (95% CI)	HR (95% CI); p-value
PFS	Pembro	2.1 (1.9, 2.1)	-
	Trial control	3.1 (2.2, 3.4)	0.89 (0.61, 1.28); p=0.23958*
	UK SOC	[redacted]	[redacted]
OS	Pembro	8.0 (5.0, 12.3)	-
	Trial control	5.2 (4.0, 7.4)	0.57 (0.37, 0.88); p=0.00483*
	UK SOC	[redacted]	[redacted]
	UK SOC + RPSFT	[redacted]	[redacted]
	UK SOC + 2-stage		[redacted]
	UK SOC + IPCW		[redacted]

*One-sided p-value; ^Two-sided p-value; #Pembrolizumab median months from the full trial population
RPSFT - Rank Preserving Structural Failure Time; IPCW - Inverse Probability of Censoring Weights
Sources: table 25 (page 99) + table 48 (page 137), company submission; table 3 (page 7), company response to additional clarification request

KEYNOTE-045

CPS ≥10% PD-L1 subgroup (II)

Outcome		Pembrolizumab (n=74)	Trial Control (n=90)
Objective response	No. of objective responses	16	6
	rate % (95% CI)	21.6 (12.9,32.7)	6.7 (2.5,13.9)
	difference (95% CI); p-value	19.3 (8.6,31.7); 0.00020	
time to response	mean (SD)	2.5 (1.0)	2.0 (0.1)
	median (range)	2.1 (1.4-5.3)	2.1 (1.9-2.2)
response duration	median (range)	Not reached (1.6+ - 15.4+)	4.4 (1.5+ - 10.8+)
responders	Number at ≥ 6 Months (%)	14 (93)	1 (40)
	Number at ≥ 12 Months (%)	3 (76)	0

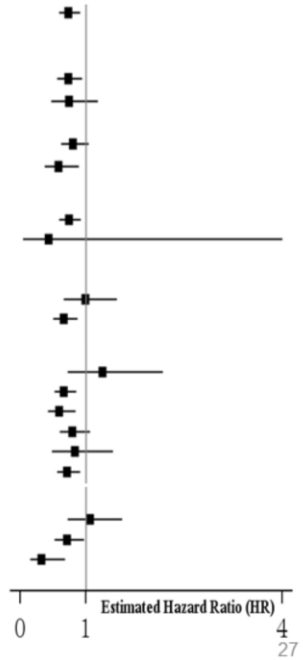
Source: adapted from table 8 (page 55-56) ERG report

- Exploratory analyses per mRECIST 1.1 by BICR were consistent with the results per RECIST 1.1 by BICR

KEYNOTE-045

Other subgroups (OS)

Overall	334/542	0.73	(0.59, 0.91)
Prior Platinum Therapy			
Cisplatin	248/411	0.73	(0.56, 0.94)
Carboplatin	82/126	0.74	(0.47, 1.18)
Histology			
Transitional Cell	240/383	0.80	(0.62, 1.04)
Mixed Transitional/non-transitional histology	93/155	0.58	(0.37, 0.89)
ECOG Status (0/1 vs 2)			
0 or 1	323/526	0.74	(0.59, 0.92)
2	5/6	0.43	(0.04, 4.20)
ECOG Status (0 vs 1/2)			
0	106/225	0.99	(0.66, 1.47)
1 or 2	222/307	0.66	(0.50, 0.87)
Geographic Region			
East-Asia	62/106	1.25	(0.72, 2.18)
Non-East Asia	272/436	0.66	(0.52, 0.85)
EU	137/223	0.59	(0.42, 0.84)
Non-EU	197/319	0.79	(0.60, 1.06)
US	61/106	0.83	(0.48, 1.41)
Non-US	273/436	0.71	(0.56, 0.91)
Smoking Status			
Never Smoker	118/187	1.06	(0.72, 1.55)
Former Smoker	170/284	0.71	(0.52, 0.97)
Current Smoker	43/67	0.32	(0.15, 0.68)

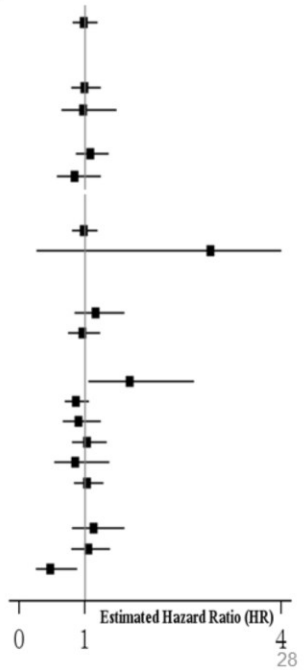


Source: adapted from Figure 28 (page 128-129), company submission

KEYNOTE-045

Other subgroups (PFS)

Overall	437/542	0.98	(0.81, 1.19)
Prior Platinum Therapy			
Cisplatin	324/411	0.99	(0.79, 1.24)
Carboplatin	109/126	0.97	(0.64, 1.48)
Histology			
Transitional Cell	315/383	1.08	(0.86, 1.36)
Mixed Transitional/non-transitional histology	119/155	0.84	(0.57, 1.24)
ECOG Status (0/1 vs 2)			
0 or 1	423/526	0.98	(0.80, 1.19)
2	5/6	2.92	(0.26, 32.93)
ECOG Status (0 vs 1/2)			
0	170/225	1.16	(0.84, 1.60)
1 or 2	258/307	0.96	(0.74, 1.23)
Geographic Region			
East-Asia	85/106	1.68	(1.05, 2.67)
Non-East Asia	352/436	0.86	(0.69, 1.06)
EU	178/223	0.90	(0.66, 1.24)
Non-EU	259/319	1.03	(0.80, 1.33)
US	80/106	0.85	(0.53, 1.37)
Non-US	357/436	1.03	(0.83, 1.28)
Smoking Status			
Never Smoker	149/187	1.13	(0.80, 1.60)
Former Smoker	229/284	1.05	(0.79, 1.38)
Current Smoker	56/67	0.47	(0.25, 0.88)



Source: adapted from Figure 29 (page 131-132), company submission

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Adverse events

- All-Patients-as-Treated (APaT) used for analysis of safety. APaT population consisted of all people who received at least 1 dose of study treatment.
- Adverse events considered by the investigator to have a reasonable possibility of being related to the technology were classified as drug-related adverse events
- Model includes disutility of all Grade 3+ adverse events with incidence over 5% (any grade) from the KEYNOTE-045 the UK standard of care population.

	Pembrolizumab	UK SOC
Grade 3+ adverse event included in model		
Anaemia	8.3%	11.9%
Febrile neutropenia	0.0%	4.76%
Neutropenia	0.0%	11.9%
Diarrhoea (including grade 2)	5.3%	5.36%
Fatigue	3.8%	5.95%
Neutrophil count decreased	0.4%	14.29%
White blood cell count decreased	0.4%	5.95%
Pneumonia	2.6%	4.17%
Hypophosphatemia	0.80%	3.57%

Sources: Table 72 (page 188), company submission; appendix 19, company appendices

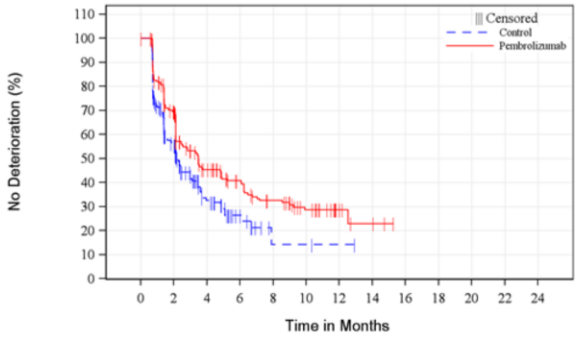
Febrile neutropenia (under 5% incidence) has been included as clinicians have suggested that this AE has significant impact on quality of life and costs.

Impact of AEs in the model was incorporated by estimating weighted average costs per patient, applied as a one-off cost, applied to the first cycle of the model for each treatment arm.

In the full trial population 93.2% of subjects in the pembrolizumab arm experienced at least 1 AE compared with 98.0% of subjects in the control arm. Fewer subjects in the pembrolizumab arm compared with the control arm experienced drug-related AEs (60.9% vs 90.2%), Grade 3 to 5 AEs (52.3 vs 62.7%), Grade 3 to 5 drug-related AEs (15.0% vs 49.4%) and drug-related AEs leading to treatment discontinuation (5.6% vs 11.0%)

Health-related quality of life (HRQoL)

- APaT population used for analysis of quality of life data.
- HRQoL in model was estimated using the EQ-5D-3L, collected every 3 weeks for the first 9 weeks, and then every 6 weeks subsequently up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further
- Pembrolizumab prolonged the time to deterioration measured by EORTC



Number of subject at risk

Control	243	101	34	12	2	2	1	0	0	0	0	0	0
Pembrolizumab	260	144	77	55	39	27	6	3	0	0	0	0	0

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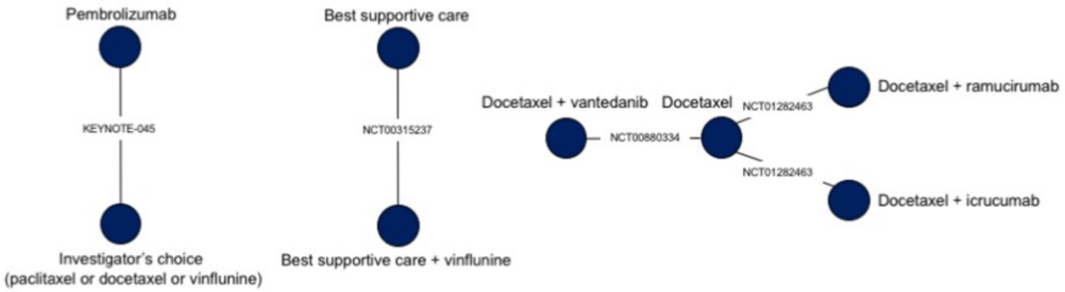
Source: Figure 27 (page 152), company submission

Indirect treatment comparison

Company raised the following issues with performing analysis:

- Differences at baseline across the trials
  - NCT00315237 only included Asian patients without EGFR mutation, and had highest proportion of ECOG 1 scores
- Adverse events and HRQoL inconsistently reported across trials
- Can't connect networks for comparison of interest



Source: Figure 30 (page 144), company submission

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NCT00315237: Pivotal vinflunine trail used in TA272 that compared vinflunine plus best supportive care with best supportive care alone in patients with advanced or metastatic transitional cell carcinoma of the urothelial tract whose disease had progressed after platinum-based chemotherapy.

ERG Comments
Treatment Switching

RPSFT least suitable because:

- censors patients prior to the time point at which they switched treatments and generates artificial survival times for those who switch
- assumes a common treatment effect for switchers to the experimental arm, and those who receive intervention in the full trial – but people in KEYNOTE-045 were able to switch to a range of anti PD-L1/PD-1 treatments*

IPCW:

- assumes there are no unobserved confounders, and weights patients according to their similarities to the censored switched patients – but the risk factors of bladder cancer and survival are uncertain

2-Stage:

- suitable as switching is linked to disease progression – but some subjects switched without progression which confounds analysis.

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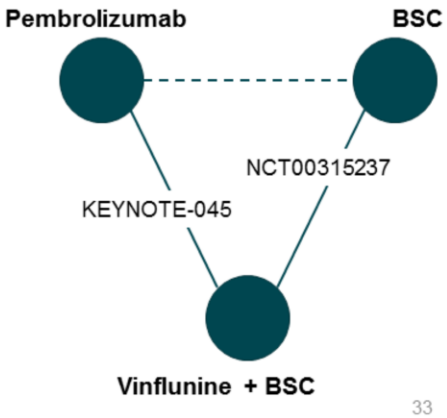
*Subsequent treatments in the table below. Patients eligible for switch over in brackets

KEYNOTE-045	Trial control	Pembrolizumab
Subsequent anti PD-L1/anti PD-1 therapies received	33 (22)	2 (2)
anti-PDL1 monoclonal antibody (unspecified)	1 (1)	
atezolizumab	7 (4)	2 (2)
avelumab	2 (2)	-
durvalumab	3 (2)	-
nivolumab	4 (3)	-
pembrolizumab	16 (10)	-
Source: table 3 (page 6) company response to clarification (section A and C)		

ERG Comments

Indirect treatment comparisons

- Disagree that NCT00315237 only included Asian patients, as not reported in publications and had 21 sites in North America or Europe
- ERG believe that the vinflunine arm in KEYNOTE-045 could be assumed to have also received BSC, and the network could be connected
- However BSC relevant for people with poor performance status (ECOG 3-4), who would not tolerate active treatment. Neither trial recruited this group, and the relevance would therefore be questionable
- The ERG did not conduct an indirect treatment comparison



ERG comments
Conclusions

- KEYNOTE-045 was of low risk of bias in most domains with the exception of blinding owing to open-label design
- Compared to UK standard of care both PD-L1 subgroups and full population, pembrolizumab reduces the risk of death but has a similar PFS - although the proportion of people progression-free is numerically higher in the pembrolizumab groups
- The subgroups show consistency with the overall findings
- Owing to open-label design it is difficult to draw reliable conclusions from the quality of life results
- Safety profile of pembrolizumab was more favourable than that of the trial control

Key issues for consideration

Clinical evidence

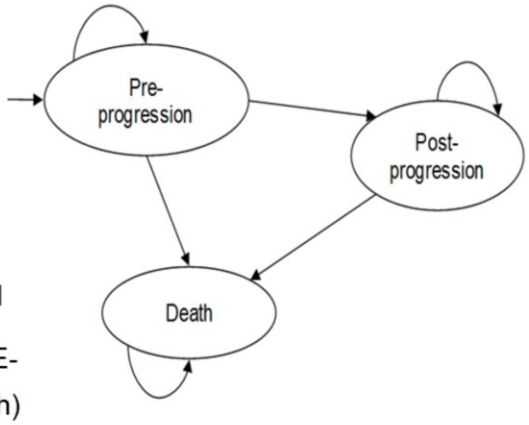
- Where will the technology be used in the treatment pathway?
- Is the KEYNOTE-045 clinical evidence generalisable to UK clinical practice?
- What is the most appropriate method of adjusting for treatment switching?
- Are PFS results using RECIST or mRECIST criteria more appropriate for decision making?
- Is the technology clinically effective:
  - In the whole population?
  - In the PD-L1 subgroups?
  - In the cancer histology subgroups?
  - Is the treatment effect maintained in the long-run?
- Is best supportive care an appropriate comparator?
- Is there value in an indirect treatment comparison between pembrolizumab and best supportive care

Cost effectiveness evidence

Company submission section 5

Model structure

- 3 state partitioned-survival model
- Time horizon: 35 years
- Starting age 65.5 years
- Cycle length: 1 week with half-cycle correction
- 1 line of subsequent therapy modelled
- 2-phase piecewise method (KEYNOTE-045 KM data plus parametric approach) to estimate PFS and OS
- Fully parametric curves fitted for time on treatment



Source: figure 33 (page 175), company submission

Resource use and costs

- Model includes separate acquisition and administration costs of pembrolizumab, docetaxel, paclitaxel^. An average cost is included for the cost of subsequent treatment#.
- Resource use for pre- and post-progression obtained from TA272 (vinflunine) and PSSRU 2015/16. Unit costs obtained from the NHS reference costs (2015-2016) and the PSSRU 2016 report
- Resource use associated with terminal care was based on the study by Brown et al (2013)
- Adverse event incidence based on KEYNOTE-045 (see slide 26). Unit costs taken from NHS Reference Costs 2015/16*
- The ERG did not modify resource use or costs in their preferred base case

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^docetaxel and paclitaxel treatment costs were estimated based on the KEYNOTE-045 trial docetaxel-paclitaxel administration ratio instead of the UK market administration ratio

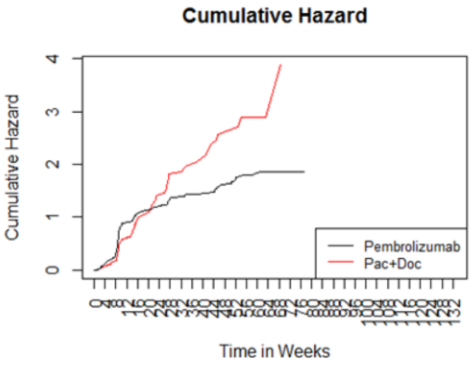
#average cost of subsequent treatment is calculated by weighting the proportions of patients receiving each subsequent treatment and the unit cost of each subsequent treatment, assuming an average duration of 2 cycles (based on NICE TA272). This weighted cost was applied during 2 cycles to patients who moved to the post-progression health state.

*when the codes were not similar, the unit costs were inflated to 2015/16 prices using the hospital and community health services (HCHS) index published by PSSRU for 2016

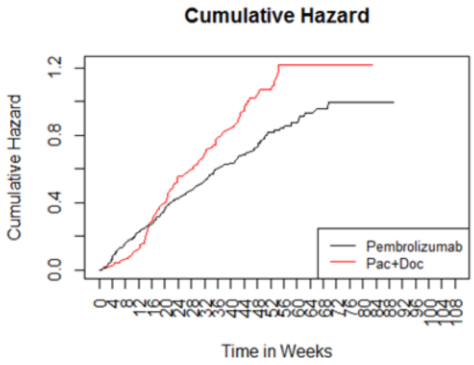
Survival curves

Proportional hazards assumption

Progression-free survival



Overall Survival

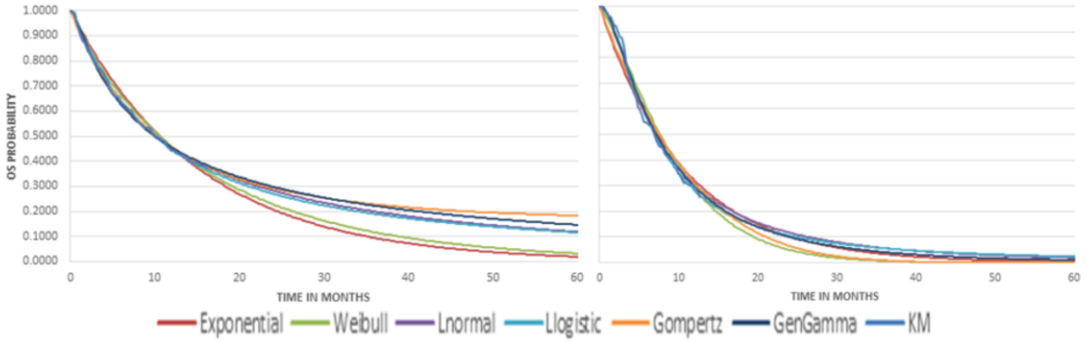


- The proportional hazards assumption does not hold
- Separate models were fitted based on the individual patient data from KEYNOTE-045

Source: Figure 36 and Figure 38 (page 183 and 185), company submission

Survival curves
Overall survival (III)

- Company explored fully-fitted parametric curves



- As the cumulative hazard plot is not constant over time, the company preferred using 2-phase piecewise models

Source: figure 35 (page 182), company submission

Survival curves
Overall survival (I)

- KM data until week 40, then fitted parametric curves
  - Justification: "OS curves start separating from week 24… clear change in the slope after around 40 weeks"

Fitted Function	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC
Exponential	339.1	342.1	165.1	167.1
Weibull	340.5	346.4	165	169.1
Gompertz	338.1	344	160.4	164.5
Log-logistic	339.4	345.3	163.7	167.7
Log-normal	337.5	343.4	161.8	165.9
GenGamma	338.5	347.3	160.2	166.3

AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: table 69*, page 184 of the company submission

- Curves with closest statistical fit regarded as clinically implausible - approximately 17% and up to 24% 5 year OS rate
- Company prefer Log-normal distribution, as projected 7.8% OS rate at 5 years is closest to available data (9-11%; CRUK)

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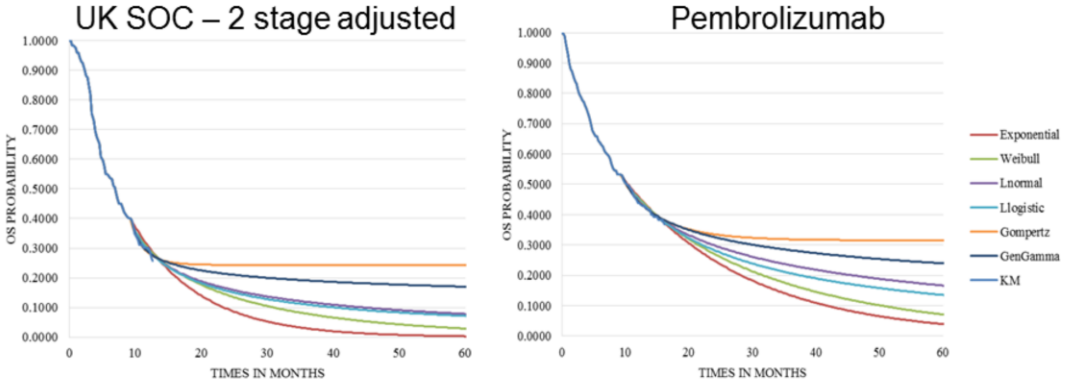
*Note: table 69 is labelled as the "fully fitted parametric approach for OS". The company have clarified that this is an error, and the table describes the results for the goodness-of-fit measures for OS with a cut-off of KM data at 40 weeks. See page 11 of the company clarification response (section B)

Survival curves
Overall survival (II)

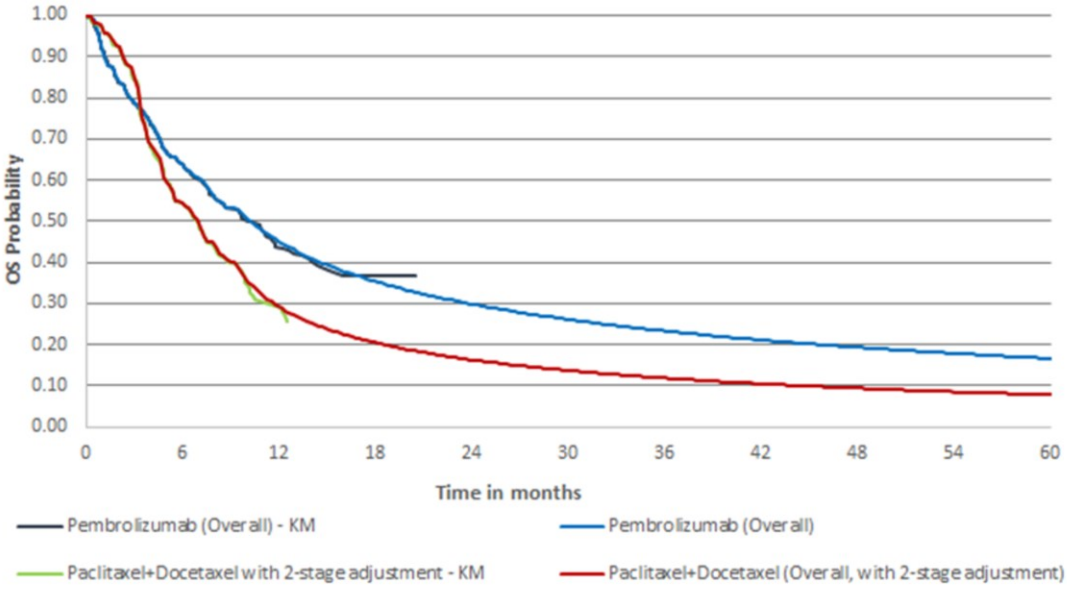
- Company base case used Log-normal curve (purple)



Source: adapted from figures 7 and 8 (page 85), ERG report

Survival curves

Overall survival (III)



Source: figure 37 (page 184), company submission

Survival curves
Progression-free survival (I)

- KM data until week 21 (3rd assessment), then parametric curves
  - Justification: "clear separation of the curves observed"

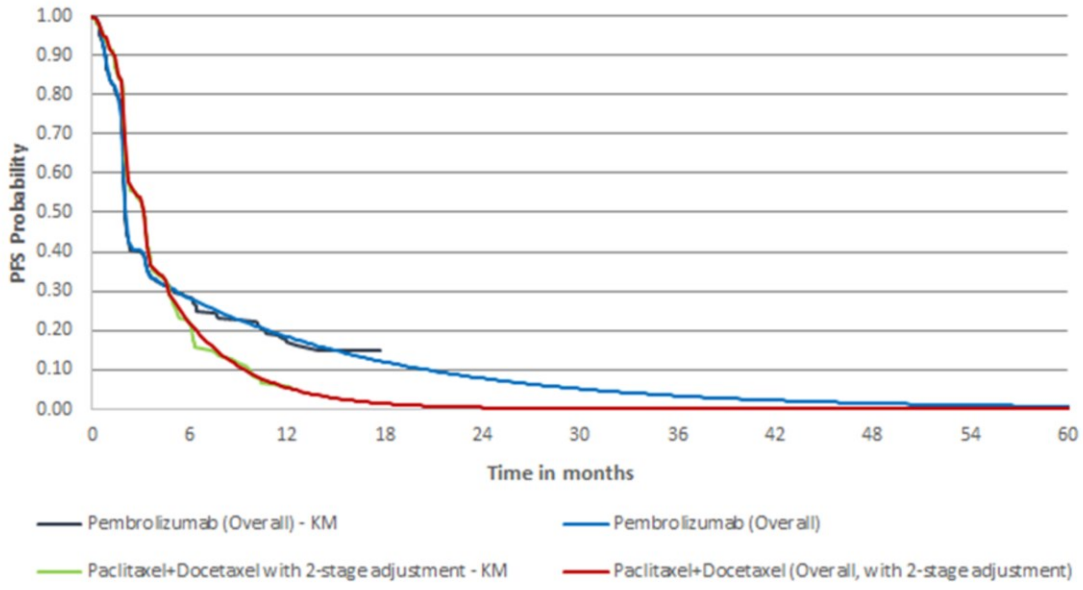
Fitted Function	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	339	341.4	154.1	155.4
Weibull	340.7	345.5	150.6	153.1
Gompertz	340.2	345	155.9	158.4
Llogistic	340.2	344.9	153.6	156.1
Lnormal	339.9	344.6	153.4	155.9
GenGamma	341.8	348.9	149.8	153.6

AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: table 71, page 184 of the company submission

- Exponential best statistical and visual fit for pembrolizumab
- No clear best statistical fit for UK SOC, and distributions very close visually
- Exponential curve selected for UK SOC to maintain consistency with pembrolizumab arm

Survival curves

Progression-free survival (II)



Source: figure 41 (page 187), company submission

Survival curves

Time-on-treatment (ToT) (I)

- Fully fitted parametric curves

Fitted Function	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	1923.8	1927.4	1133.1	1136.3
Weibull	1870.5	1877.7	1126.8	1133.1
Gompertz	1890.9	1898.1	1134.1	1140.4
Llogistic	1885	1892.2	1167.2	1173.5
Lnormal	1899.8	1906.9	1177.1	1183.3
GenGamma	1872.1	1882.8	1122.2	1131.6

AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: table 71 (page 184), company submission

- Stopping rules: 24 months pembrolizumab; 18 weeks UK SOC
  - 24 months for pembrolizumab reflects KEYNOTE-045 protocol
  - 18 weeks for UK SOC reflects UK clinical practice
- Curves selected were Weibull for pembrolizumab and GenGamma for UK SOC due to lowest AIC/BIC

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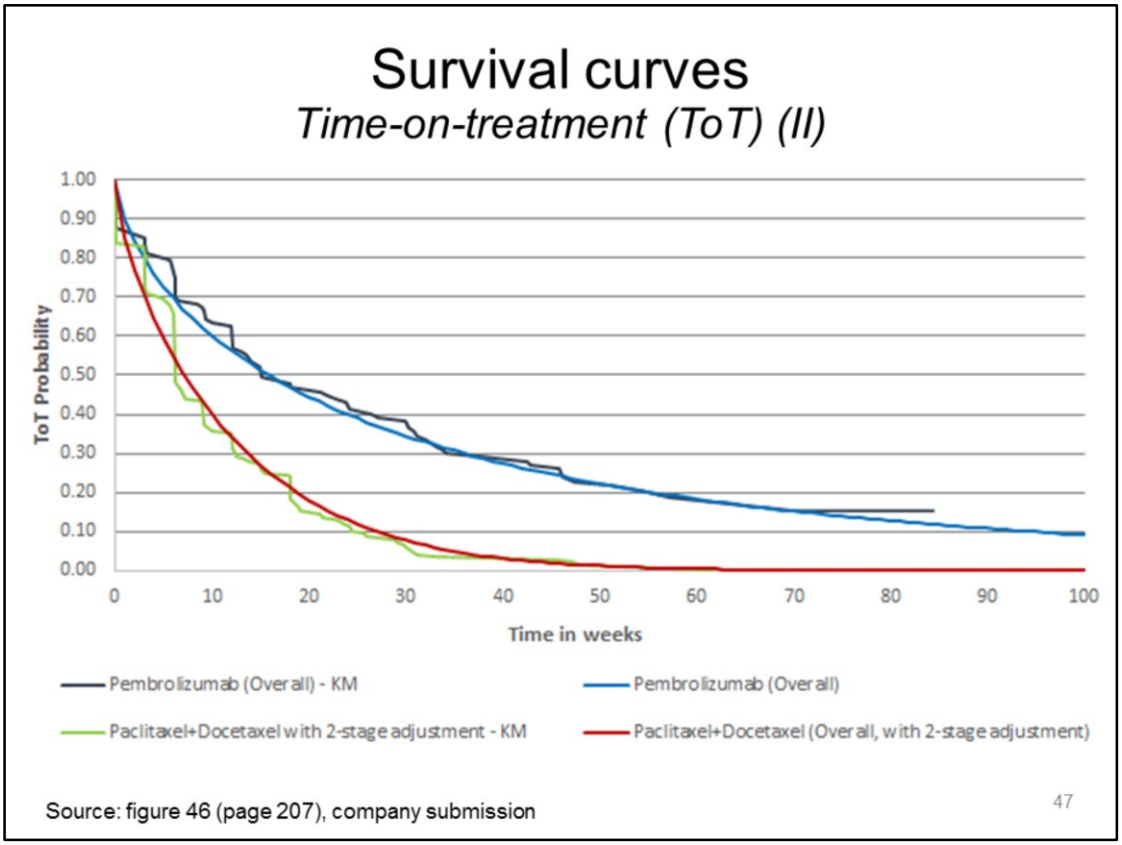
Note: 24 month stopping rule for pembrolizumab is not incorporated into the expected marketing authorisation



The average number of cycles received per patient in KEYNOTE-045 was 8.81 cycles (5.60 months) for pembrolizumab, 5.00 cycles (2.92 months) for paclitaxel and 3.90 cycles (2.21 months) for docetaxel

Utility values

- Company base case:
  - utilities based on time-to-death, as data for post-progression is very limited as it is usually collected directly after progression and more health states offers a better HRQoL data fit.
  - vinflunine data included to maximise the data for analysis
  - mean utility scores by health status were estimated per treatment arm (pembrolizumab and UK SOC arms) and pooled for both arms, as no statistical or clinically meaningful difference between arms
  - age-related utility decrement of 0.0045 is applied per year from the age of 65 until 75 as per *Kind et al*. No decrease after 75yrs of age
- Company explored several scenarios for incorporating the utility values in their analyses
- For scenarios using utilites based on progression-state, progression date was determined by RECIST 1.1 BICR progression date

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- Incorporation of utility values by time to death was also used in appraisals for pembrolizumab for melanoma (TA357/TA366). The committee did not discuss their preferred methodology, as it did not impact the decision-making for these appraisals.
- The appraisal of vinflunine (TA272) considered it appropriate that the utility value for vinflunine and BSC be pooled (pooled 0.65 pre-progression; pooled 0.25 post-progression
- there are statistically significant differences using the progression-based method but this is not the case for the utilities by time-to-death.

Base case results

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company – Deterministic					
UK SOC	£20,938	1.10	-	-	**-**
Pembro	£60,053	1.95	£39,115	0.85	**£45,833**
Company – Probabilistic					
UK SOC	£21,367	1.13	-	-	**-**
Pembro	£60,634	1.98	£39,267	0.85	**£46,194**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

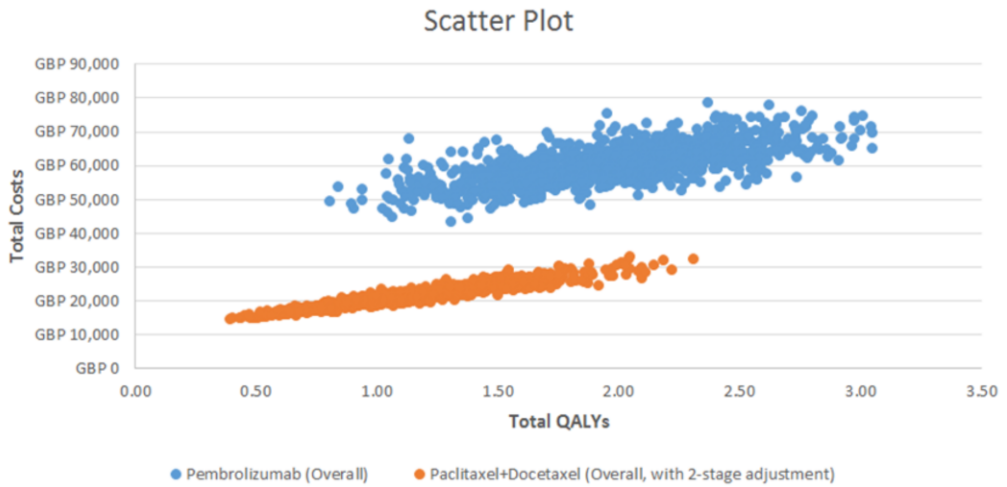
Source: Table 87 (page 24) and table 91 (page 91), addendum 1, company revised appendices

While updating the cost-effectiveness model for the clarification questions, some errors have been identified and corrected in the model. These increased the probabilistic ICER from £45,826 to £46,194 and decreased the deterministic ICER from £45,861 to £45,833

Sensitivity analyses

Probabilistic sensitivity analysis

- 1000 iterations; 10% coefficient of variation in cost and resource use parameters
- 57% probability pembrolizumab is cost-effective at £50,000 per QALY



Source: figure 49 (page 122), addendum 1, company revised appendices

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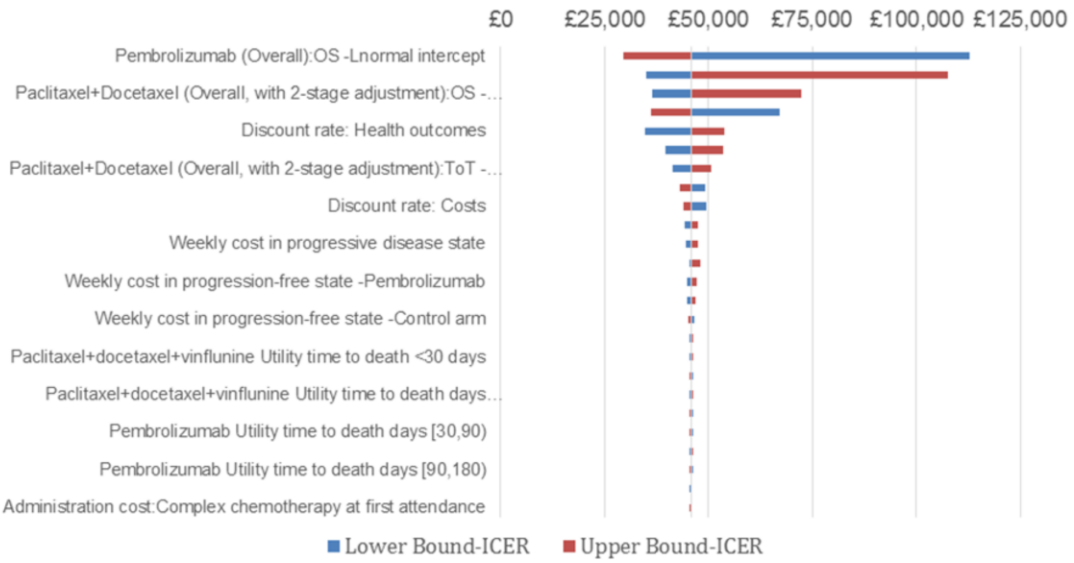
Deterministic ICER – £45,833
Probabilistic ICER – £46,194

Sensitivity analyses
Tornado diagram

- ICER sensitive to varying the overall survival extrapolation



Source: figure 26 (page 122), ERG report

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Deterministic ICER – £45,833
Probabilistic ICER – £46,194

Scenario analyses (I)

Scenario		Pembrolizumab vs UK SOC			
		Inc. costs	Inc. QALY	ICER	Δ ICER
	Base case	£39,115	0.85	£45,833	-
1.a	No switching adjustment	£34,296	0.54	£64,101	+£18,268
1.b	Switchover – RPSFT	£44,022	1.40	£31,509	-£14,324
1.c	Switchover – IPCW	£38,350	0.77	£49,874	+£4,041
2.a	OS cut-off – 24 weeks	£42,693	1.25	£34,168	-£11,665
2.b	OS cut-off – 32 week	£42,999	1.28	£33,613	-£12,220
3.a	PFS cut-off – 15 weeks	£39,099	0.85	£45,815	-£18
3.b	PFS cut-off – 27 weeks	£39,110	0.85	£45,827	-£6
4	UK SOC PFS extrapolation based on gen. gamma	£39,392	0.85	£46,158	+£325
5	No half cycle correction	£38,732	0.85	£45,374	-£459
6	UK SOC - UK market shares	£39,239	0.85	£45,978	+£145
7	Utilities - Progression (pooled)	£39,115	0.72	£54,665	+£8,832
8.a	Utilities – Time to death (per treatment arm)	£39,115	0.79	£49,555	+£3,722
8.b	Utilities – Progression (per treatment arm)	£39,115	0.92	£42,738	-£3,095
9	No age-related disutilities	£39,115	0.88	£44,418	-£1,415

Source: adapted from table 92 (page 34), addendum 1, company revised appendices

Scenario analyses (II)

- Economic model assumes people stop treatment at 2 years – which is not included in the expected marketing authorisation
- Extrapolated curves assume pembrolizumab remains effective irrespective of time or implementation of a stopping rule

	Lifetime treatment effect	10 year treatment effect	5 year treatment effect	3 year treatment effect
100% continue	£53,484	£55,801	£60,592	£65,656
25% continue	£48,238	£50,280	£54,502	£58,967
0% continue	£46,194	£48,129	£52,130	£56,360

Source: adapted from table 2 (page 38), company response to clarification (section B)

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Previous guidance for pembrolizumab and other PD-L1/PD-1 technologies have included a stopping rule as part of the recomednation. NHS England have previously responded to consultation that that it was confident that a 2-year stopping rule would be acceptable to both patients and clinicians and would be implementable.
The committee have previously noted there is evidence to support a continued benefit of pembrolizumab after stopping treatment and in the progressed state, but considered a lifetime treatment effect to be implausible (TA428 – Pembrolizumab NSCLC)

The average number of cycles received per patient in KEYNOTE-045 was 8.81 cycles (5.60 months) for pembrolizumab, 5.00 cycles (2.92 months) for paclitaxel and 3.90 cycles (2.21 months) for docetaxel

Subgroup analyses
Crossover adjustment

- Crossover adjustment not always possible due to low sample size

Population	Comparators	OS for comparator arm			
		ITT unadjusted	Two-stage	RPSFT	IPCW
Basecase	UK SOC	✓	✓	✓	✓
ITT – histology subgroup	UK SOC ▪ Predominant transitional cell carcinoma ▪ Pure transitional cell carcinoma	✓	✗	✗	✗
CPS<1%	UK SOC	✓	✗	✓	✗
CPS≥1%	UK SOC	✓	✗	✓	✓
CPS≥10%	UK SOC	✓	✗	✓	✗

Source: adapted from table 66, page 178 of the company submission

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Subgroup analyses

Cancer histology

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
Base case (deterministic)						
UK SOC	£20,938	1.10	-	-	-	
Pembro	£60,053	1.95	£39,115	0.85	£45,833	-
Predominantly transitional cell urothelial carcinoma (68.6% of trial)						
UK SOC	[redacted]					
Pembro	[redacted]					
Pure transitional cell urothelial carcinoma (31.9% of trial)						
UK SOC	[redacted]					
Pembro	[redacted]					

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: page 38, appendix 22, company revised appendices

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Subgroup analyses

PD-L1 CPS<1% subgroup (50.81% of trial)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
Basecase (deterministic)						
UK SOC	£20,938	1.10	-	-	-	
Pembro	£60,053	1.95	£39,115	0.85	£45,833	
PD-L1 negative (CPS<1%) – no adjustment						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 negative (CPS<1%) – RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: table 16 (page 34), company response to clarification (section B)

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Company used different preferred assumptions for the PD-L1 subgroup analyses:

For the subgroup of patients with PD-L1 status, a 32-week cut-off was selected as a point for extrapolation. Unlike company base-case, the 40-week cut-off point for the UK SOC with RPSFT adjustment had a small number of patients left at risk. Therefore, the extrapolation from this point would have been uncertain.

The exponential curve presented the closest statistical fit to the data for both pembrolizumab and the UK SOC. However, please note that the exponential curve might underestimate the UK SOC with only 0.4% OS rates at 5 years. Alternative scenario analysis is presented below applying a log-normal distribution, in line with our base-case, with 7.5% OS rate in UK SOC at 5 years which is closer to the estimates observed by Cancer research UK.

Separate parametric curves were fitted to the treatment duration data from KEYNOTE-045 based on the AIC/BIC measures for this subgroup of patients. The function with the lowest AIC/BIC is Weibull for pembrolizumab and exponential for the UK SOC.

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Subgroup analyses

PD-L1 CPS≥1% subgroup (46.8% of trial)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
Base case (deterministic)						
UK SOC	£20,938	1.10	-	-	-	
Pembro	£60,053	1.95	£39,115	0.85	£45,833	
Positive PD-L1 (CPS≥1%) – no adjustment						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Positive PD-L1 (CPS≥1%) – RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Positive PD-L1 (CPS≥1%) – IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: page 39, appendix 22, company revised appendices

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Subgroup analyses

PD-L1 CPS≥10% subgroup (34.3% of trial)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
Basecase (deterministic)						
UK SOC	£20,938	1.10	-	-	-	
Pembro	£60,053	1.95	£39,115	0.85	£45,833	
Strongly positive PD-L1 (CPS≥10%) – no adjustment						
UK SOC	[redacted]					
Pembro	[redacted]					
Strongly positive PD-L1 (CPS≥10%) – RPSFT						
UK SOC	[redacted]					
Pembro	[redacted]					

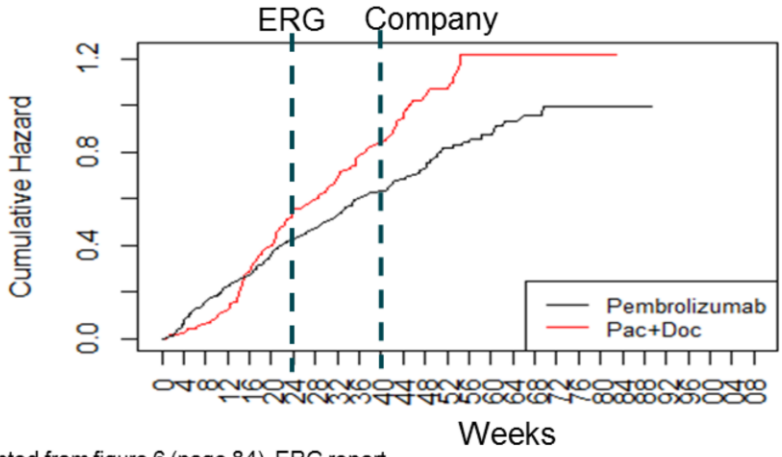
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: page 39, appendix 22, company revised appendices

ERG Comments

Survival curves (I)

- ERG agree that proportional hazard assumption does not hold
- Cumulative hazard plot looks consistent after week 16, and using this time-point would maximise the data available for extrapolation – but the closest time-point the model allows is week 24



Source: adapted from figure 6 (page 84), ERG report

ERG Comments
Survival curves (II)

- ERG consider 9-11% 5-year OS estimate from CRUK to be an overestimate
- Clinical expert and results from a systematic review indicate that 2-3% 5-year overall survival more consistent with current clinical practice
- Based on AIC/BIC Log-logistic is best fit, and clinically plausible

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
24-week cut-off – ERG base case						
1-year	30.2%	30.1%	29.3%	**28.9%**	30.1%	29.4%
3-year	3.5%	2%	6.9%	**6.5%**	9.1%	12.7%
5-year	0.4%	0.1%	2.9%	**3.2%**	5.9%	8.9%
10-year	0%	0%	0.7%	**1.2%**	4.6%	5.6%
40-week cut-off – Company base case						
1-year	30%	29.4%	**28.8%**	28.8%	28.1%	28.3%
3-year	2.9%	7.9%	**11.9%**	11%	24.3%	19.1%
5-year	0.3%	2.9%	**7.8%**	7.1%	24.3%	17%
10-year	0%	0.4%	**4.2%**	4%	24.3%	14.8%

Source: adapted from table 22 (page 93), ERG report; bolded red figures represent the base cases

- Von der Maase 2000:
  - first-line metastatic treatment
  - 5-year OS - 20.9% without / 6.8% with visceral metastases (85.7% KEYNOTE-045 patients have visceral metastases at recruitment)
- Bellmunt 2008:
  - Worse ECOG score, but fewer metastases or visceral involvement.
  - Must have progressed on platinum-containing chemotherapy at metastatic stage (KEYNOTE-045 could be at adjuvant/neoadjuvant stage)
  - 40-month OS - 2.3% (6/253)

Other concerns on Cancer Research UK (CRUK) data:

- People in KEYNOTE-045 were in a more advanced disease stage compared to CRUK population - people at diagnosis of metastatic disease, who would be at 1st line therapy. Around 80% of people in KEYNOTE SOC arm were likely to be either at 2nd or 3rd line of metastatic disease which makes this population at even greater risk
- Little else is known about the baseline characteristics of the patients who have generated the CRUK data, and so the ERG has reservations about using this data as a reference point.

ERG Comments

Survival curves (III)

- ERG note no validation past 1-year, despite follow-up data being available
- Company model estimates are relatively higher in the pembrolizumab arm than UK SOC when compared to the trial results

	Pembrolizumab			UK SOC		
Outcome	**Company**	**ERG**	**Trial**	**Company**	**ERG**	**Trial**
Median PFS*	2.3	2.3	2.1	3.4	3.4	3.2
6-month PFS	28.6%	28.6%	28.8%	22.8%	22.8%	22.7%
Median OS*	10.3	10.3	10.3	7.1	7.1	6.9
6-month OS	64.1%	64.4%	63.9%	54.8%	54.3%	54.5%
1-year OS	45.5%	45.7%	43.9%	29.6%	29.9%	30.2%
14.5 month OS	40.4%	40.7%	39.3%	24.8%	23.5%	25.7%
16.1 month OS	38.0%	38.0%	36.8%	22.6%	20.5%	25.7%
20 month OS	33.4%	32.7%	36.8%	18.9%	15.2%	25.7%
2-year OS	30.0%	28.7%	-	16.4%	11.8%	-
5-year OS	16.7%	13.5%	-	7.9%	3.2%	-
10-year OS	9.9%	7.1%	-	4.3%	1.2%	-

Sources: Table 88 (page 25), addendum 1, company revised appendices; ERG model; company model
*months

ERG Comments
Utility scores (I)

- Company use pooled utility by time to death (days), using trial control data (i.e. inclusion of people using vinflunine). The ERG note:
  - not common in practice – previously used in melanoma and NSCLC
  - groupings of time periods was not strongly justified
  - average scores were not weighted per person and were averaged across from all eligible questionnaires ^
- ERG prefer a pooled utility by progression-status, excl. vinflunine data
- ERG use newer algorithm to estimate age-related utility decrements
- Utility values are lower for pembrolizumab compared to UK SOC when measured based on time to death, but higher based on progression status. ERG unsure of cause for inconsistency, but suggest:
  - lack of accounting for treatment switching
  - survival of unhealthy participants in the pembrolizumab arm

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^The ERG feels that this could lead to overestimation of the utility values, due to a possible relationship between non-response and health status

Ara and Brazier (2010) estimates general population utility scores as a function of age and gender. This is more appropriate as: (a) the study by Kind et al. (1999) is outdated; and (b) the algorithm can provide age-related utility decrements for people beyond the age of 75.

ERG Comments

Utility scores (II)

	Pembro	Trial control	Pembro + trial control pooled	UK SOC	Pembro + UK SOC pooled	TA272
Time to death based (days) – Company base case						
≥360	0.765	0.804	**0.778**	0.823	0.780	-
180-360	0.686	0.699	**0.693**	0.673	0.680	-
90-180	0.566	0.612	**0.590**	0.595	0.578	-
30-90	0.457	0.446	**0.451**	0.414	0.435	-
<30	0.336	0.311	**0.325**	0.337	0.337	-
Progression based – ERG base case						
Pre-progress	0.757	0.698	0.731	0.709	**0.741**	0.65
Post-progress	0.680	0.565	0.641	0.554	**0.647**	0.25

Source: adapted from table 31 (page 108), ERG report; bolded red figures represent the base cases

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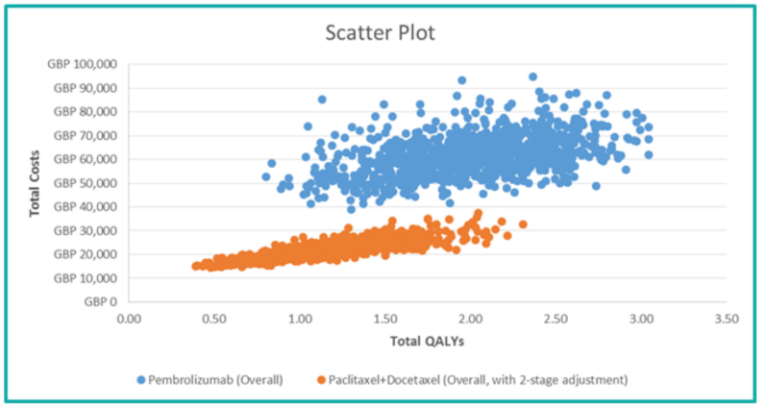
ERG notes estimating utility scores by time-to-death approach slightly overestimates life years in both pembrolizumab and UK SOC arms relative to life years based on progression status

ERG Comments
probabilistic sensitivity analysis

- Variation in costs appears to be considerably less than variation in QALYs
- ERG increased coefficient of variation in cost and resource use from 10% to 20%
- ICER increases from £46,194 to £46,898 and probability pembrolizumab is cost-effective at £50,000 per QALY threshold reduces from 57% to 55%



Source: figure 23 (page 116), ERG report

ERG Comments

Base case

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company – Deterministic					
UK SOC	£20,938	1.10	-	-	**-**
Pembro	£60,053	1.95	£39,115	0.85	**£45,833**
Company – Probabilistic					
UK SOC	£21,367	1.13	-	-	**-**
Pembro	£60,634	1.98	£39,267	0.85	**£46,194**
ERG – Deterministic					
UK SOC	£17,439	0.73	**-**	**-**	**-**
Pembro	£57,457	1.51	£40,017	0.78	**£51,235**
ERG – Probabilistic					
UK SOC	£17,689	0.75	-	-	-
Pembro	£57,986	1.54	£40,298	0.79	**£50,902**

Incr., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
ERG results source: table 1 (page 4), ERG appendix probabilistic basecase and subgroup analyses

During factual accuracy check of the ERG report, the ERG's deterministic base case changed from an ICER of £51,405 to £51,235. This was due to removal of an ERG assumption which removed the disutility associated with pneumonia, hyphosphataemia and fatigue. Following clarification with the company the ERG now leave the company's preferred assumption unchanged in their basecase.

ERG Comments

Individual impact of changes

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case model	**£39,115**	**0.85**	**£45,833**	**-**
ERG models				
Exclusion of vinflunine data from utilities	£39,115	0.86	£45,712	**-£121**
progression status utilities (pooled)	£39,115	0.72	£54,665	**+£8,832**
Ara and Brazier utility decrements	£39,115	0.84	£46,673	**+£840**
UK market share of docetaxel and paclitaxel	£39,239	0.85	£45,978	**+£145**
log-logistic OS modelling	£37,029	0.62	£59,246	**+£13,413**
cut-off point of 24 weeks for OS modelling	£42,693	1.25	£34,168	**-£11,665**

Source: table 59 (page 139), ERG report

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ERG Comments
Scenario analyses

- The ERG explored other scenarios which were not included in their base-case

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case model	**£39,115**	**0.85**	**£45,833**	**-**
ERG scenarios				
Treatment specific utilities, time-to death, exclusion of vinflunine data	**£39,115**	**0.78**	**£50,074**	**+£4,241**
Treatment specific utilities, progression based, excl. vinflunine	**£39,115**	**0.92**	**£42,301**	**-£3,532**
Pooled utilities, progression-based, utility values from TA272	**£39,115**	**0.34**	**£114,082**	**+£68,249**
Treatment specific adverse event disutility, time-to-death	**£39,115**	**0.64**	**£60,714**	**+£14,881**
Treatment specific adverse event disutility, progression-based	**£39,115**	**0.79**	**£49,652**	**+£3,819**
AE costs from alternative sources	**£38,376**	**0.85**	**£44,967**	**-£866**

Source: tables 45-51 (page 127-130), ERG report

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ERG Comments

Sensitivity analyses (I)

- At 35-year time horizon, the model yielded a 1.25 life year gain (LYG), 2.34 life years with pembrolizumab vs. 1.09 life years for UK SOC
- Given the availability of the data (median follow-up duration 14.1 months, range: 9.9 to 22.1), ERG considered two time points, 10 months and 22 months

Time-point	LYG		Incremental LYG	LYG from observed data	LYG from extrapolated survival
	UK SOC	Pembro			
10 months	0.60	0.56	0.04	3%	97%
22 months	0.98	0.78	0.20	16%	84%

- Majority of incremental benefit is from extrapolated data. ERG recommends review of appraisal within a short period using more mature KEYNOTE-045 data

ERG Comments

Sensitivity analyses (II)

- ERG explored choice of parametric distribution with different time-horizons

Scenario	Pembrolizumab vs UK SOC				
	Incr costs	Incr. LYG	Incr QALY	ICER	Δ ICER
Base case	£40,017	1.25	0.78	£51,235	-
2-year time horizon					
Exponential	£32,038	0.22	0.15	£209,686	+£158,281
Weibull	£31,848	0.23	0.16	£195,312	+£143,907
Gompertz	£31,872	0.22	0.15	£207,614	+£156,209
Log-logistic	£31,908	0.23	0.16	£196,744	+£145,339
Log-normal	£31,810	0.23	0.16	£195,344	+£143,939
Generalised gamma	£32,086	0.20	0.14	£225,655	+£174,250
35-year time horizon					
Exponential	£34,763	0.46	0.31	£111,108	+£59,703
Weibull	£36,043	0.64	0.43	£83,713	+£32,308
Gompertz	£47,961	2.38	1.45	£33,179	-£18,226
Log-logistic	£40,132	1.25	0.78	£51,405	£0
Log-normal	£42,931	1.65	1.02	£41,933	-£9,472
Generalised gamma	£32,357	0.10	0.11	£297,821	+£246,416

Source: table 56 and table 58 (page 134-136), ERG report

At 2-years:

- model not capturing all costs and benefits over this short duration and ICER increase.
- Very little difference between parametric distributions as results are mostly dependent on observed data and not extrapolations

At 35-years:

- model depends heavily on the parametric distributions in order to inform on the cost-effectiveness

ERG Comments

Sensitivity analyses (III)

- The 2 piecewise model is sensitive to the choice of cut-off for extrapolation

Scenario	Pembrolizumab vs UK SOC					
	5-year OS	Incr. costs	Incr. LYG	Incr. QALYs	ICER	Δ ICER
ERG base case	3.2%	£40,017	1.25	0.78	£51,235	-
Overall survival; ERG preferred assumptions; 40 week time-point						
Exponential	0.3%	£35,028	0.51	0.35	£100,765	+£49,530
Weibull	2.9%	£35,006	0.51	0.34	£101,593	+£50,358
Gompertz	24.3%	£39,432	1.15	0.72	£55,118	+£3,883
Log-logistic	7.1%	£37,153	0.82	0.53	£70,304	+£19,069
Log-normal	7.8%	£39,239	1.12	0.71	£55,407	+4,172
G. Gamma	17%	£38,116	0.96	0.61	£62,809	+11,574
Overall survival; ERG preferred assumptions; 24 week time-point						
Exponential	0.4%	£34,648	0.46	0.31	£110,621	+£59,386
Weibull	0.1%	£35,928	0.64	0.43	£83,381	+£32,146
Gompertz	5.9%	£47,846	2.38	1.45	£33,092	-£18,143
Log-logistic	3.2%	£40,017	1.25	0.78	£51,235	£0
Log-normal	2.9%	£42,816	1.65	1.02	£41,807	-£9,428
G. Gamma	8.9%	£32,242	0.10	0.11	£295,841	£244,606

Source: ERG addendum, cut-off extrapolation scenarios

ERG Comments
Sensitivity analyses (IV)

- A fully-fitted parametric model leads to a reduced 5-year survival for all curves

Scenario	Pembrolizumab vs UK SOC					
	5-year OS	Incr. costs	Incr. LYG	Incr. QALY	ICER	Δ ICER
ERG base case	3.2%	£40,017	1.25	0.78	£51,235	-
ERG preferred assumptions; 0 week time-point						
Exponential	0.34%	£34,142	0.37	0.26	£131,018	+£79,783
Weibull	0.01%	£35,213	0.54	0.37	£96,353	+£45,118
Gompertz	0.00%	£49,213	2.58	1.57	£31,360	-£19,875
Log-logistic	2.38%	£39,142	1.11	0.71	£55,486	+£4,251
Log-normal	1.87%	£38,956	1.08	0.69	£56,366	+£5,131
G. Gamma	0.98%	£41,903	1.52	0.95	£44,147	-£7,088
Source: ERG addendum, cut-off extrapolation scenarios						

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ERG comments

Cancer histology subgroup

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
ERG base case (deterministic)						
UK SOC	£17,439	0.73	-	-	-	
Pembro	£57,457	1.51	£40,017	0.78	**£51,235**	-
Predominantly transitional cell urothelial carcinoma (68.6% of trial)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pure transitional cell urothelial carcinoma (31.9% of trial)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: table 2 (page 4), appendix 22, ERG appendix probabilistic basecase and subgroup analyses

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ERG's used the same preferred assumptions as their base-case analysis for all subgroups, varying only the subgroup population on interest

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ERG comments

PD-L1 CPS<1% subgroup (50.81% of trial)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
ERG base case (deterministic)						
UK SOC	£17,439	0.73	-	-	-	
Pembro	£57,457	1.51	£40,017	0.78	**£51,235**	
PD-L1 negative (CPS<1%) – no adjustment						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 negative (CPS<1%) – RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: table 5 (page 6), ERG appendix probabilistic basecase and subgroup analyses

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ERG comments

PD-L1 CPS≥1% subgroup (46.8% of trial)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
ERG base case (deterministic)						
UK SOC	£17,439	0.73	-	-	-	
Pembro	£57,457	1.51	£40,017	0.78	**£51,235**	
Positive PD-L1 (CPS≥1%) – no adjustment						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Positive PD-L1 (CPS≥1%) – RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Positive PD-L1 (CPS≥1%) – IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: table 3 (page 5), ERG appendix probabilistic basecase and subgroup analyses

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ERG comments

PD-L1 CPS≥10% subgroup (34.3% of trial)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Change
Basecase (deterministic)						
UK SOC	£17,439	0.73	-	-	-	
Pembro	£57,457	1.51	£40,017	0.78	**£51,235**	
Strongly positive PD-L1 (CPS≥10%) – no adjustment						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Strongly positive PD-L1 (CPS≥10%) – RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: table 4 (page 5), ERG appendix probabilistic basecase and subgroup analyses

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Subgroup overview (I)

- Difference in estimates driven by the sensitivity of overall survival extrapolation

	Company			ERG		
	Incr. LYG	ICER	Δ ICER	Incr. LYG	ICER	Δ ICER
Base case	1.120	£45,833	-	1.250	£51,235	-
Cancer histology subgroup						
Predomin-antly TCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pure TCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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LYG, Life year gains; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Incr. LYGs are not reported in the company submission or ERG report, and have been calculated by the NICE technical team from LYGs reported per treatment arm

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Subgroup overview (II)

	Company			ERG		
	Incr. LYG	ICER	Δ ICER	Incr. LYG	ICER	Δ ICER
Base case	1.120	£45,833	-	1.250	£51,235	-
PD-L1 CPS<1% subgroup (50.81% of trial)						
no adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥1% subgroup (46.8% of trial)						
no adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥10% subgroup (34.3% of trial)						
no adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG, Life year gains; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Incr. LYGs are not reported in the company submission or ERG report, and have been calculated by the NICE technical team from LYGs reported per treatment arm

ERG Comments
Conclusions

- Company model appears to be logical and methodologically sound
- The model appeared to have captured the key features of people with advanced or metastatic urothelial cancer
- Model most sensitive to changes made to the overall survival extrapolation
  - ERG would liked to have seen greater consideration of other survival curves for both OS and PFS in the scenario analysis
- Other key area of uncertainty relates to method of estimating utility values
- The majority of the incremental life-year benefit derives from the extrapolated data rather than observed data
- For the estimation of the subgroups the company varied the survival modelling but used the same model parameters (such as age and gender)
- Unit costs and incidence of additional adverse events that cancer patients typically exhibit, such as dyspnoea, hypertension, and abdominal pain were not considered in the company model

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Innovation

- The company considered pembrolizumab to be innovative for the following reasons:
  - Pembrolizumab was been granted a Promising Innovative Medicines (PIM) and positive EAMS Scientific Opinion for the treatment of melanoma and NSCLC
  - platinum-based chemotherapy and taxane regimens remain the foundation of second-line treatment for the majority of patients with urothelial cancer, and have not significantly improved the 1-year and 5-year survival rates
  - Due to its distinct mechanism of action, pembrolizumab has demonstrated significant survival benefit and improved tolerability profile compared to chemotherapy regimens and is expected to provide a durable response for patients with advanced or metastatic urothelial cancer, following treatment with platinum-containing chemotherapy.

End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: Following treatment with platinum-based chemotherapy, people have a short life expectancy with median survival measured in only a few months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months	Pembrolizumab offers an extension to life of at least 3 months compared to UK SOC: • Median OS for pembrolizumab in trial was 10.3 (95% CI, 8.0, 11.8) months compared to 6.9 (95% CI, 5.3, 8.1) months for UK SOC (using 2-stage model for adjustment) • Economic model estimates mean number of months of life gained is 32.5 months compared to 19 months with UK SOC
ERG critique	Overall, the ERG agree that pembrolizumab fulfils end-of-life treatment

Key issues for consideration

Cost-effectiveness evidence (I)

- Appropriateness and plausibility of the cost-effectiveness evidence for:
  - The overall population (pembrolizumab versus UK standard of care)?
  - The PD-L1 negative, positive, and strongly positive subgroups?
  - The cancer histology subgroups?
- For the survival modelling:
  - most plausible 10-year overall survival estimate?
  - most appropriate week to switch from K-M data to parametric curves?
  - most appropriate parametric curves?
- Is it plausible that pembrolizumab has a lifetime treatment effect, irrespective of time or implementation of a stopping rule?

Key issues for consideration

Cost-effectiveness evidence (II)

- For incorporation of utility estimates:
  - use of time-to-death method versus the progression-based method?
  - use of pooled utilities versus individual utilities per treatment arm?
  - choice of algorithm to apply age-related disutility?
- For incorporation of adverse events:
  - use of pooled adverse event disutility versus disutility per treatment arm?
- Any significant health benefits not captured or equality issues to be taken into account?
- What are the most plausible ICERs?

Authors

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  - Rachel Elliott – cost lead
  - William Turner – clinical lead

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab for previously treated urothelial cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for treating locally advanced and unresectable or metastatic urothelial cancer in adults whose disease has progressed on or after prior platinum-containing chemotherapy.

Background

Urothelial carcinoma is cancer of the transitional cells (TCC) which form the inner lining of the bladder, urethra, ureter, or renal pelvis. Urothelial carcinoma is most common in the bladder and accounts for 90% of urothelial cancers. Most urothelial cell carcinomas of the bladder are TCCs, which 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[1, 2]. 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 younger people too[2, 3]. Smoking is a major factor in the cause of bladder cancer[3].

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

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, anti-programmed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Pembrolizumab does not currently have a marketing authorisation in the UK for treating locally advanced or metastatic urothelial bladder cancer after prior platinum-based chemotherapy. It is being studied in a phase III clinical trial as monotherapy in adults with locally advanced and unresectable or metastatic urothelial cancer that has progressed following a platinum-containing regimen, compared with vinflunine, paclitaxel, or docetaxel.

Intervention	Pembrolizumab
Population	Adults with locally advanced and unresectable or metastatic urothelial cancer that has progressed on or after platinum-containing chemotherapy.
Comparators	• Retreatment with 1st line platinum-based chemotherapy (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 (e.g. duration of response and disease control rate) • 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. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If the evidence allows, consideration will be given to subgroups based on cancer histology and biological markers (PD-1 or CD274 antigen). 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. Atezolizumab for treating metastatic urothelial bladder after platinum-based chemotherapy NICE technology appraisal ID939. Expected publication date: September 2017 **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	**National Service Frameworks** Cancer **Other policies** Department of Health (2016) NHS outcomes framework 2016 to 2017 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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for previously treated urothelial cancer [ID1019]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Merck Sharp & Dohme (pembrolizumab) Patient/carer groups • Action Bladder Cancer UK • Black Health Agency • 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 • Muslim Council of Britain • Pelican Cancer Foundation • Penny Brohn 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 • British Geriatrics Society • British Gynaecological Cancer Society • British Institute of Radiology • British Psychosocial Oncology Society	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 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) • Medac (docetaxel, gemcitabine, paclitaxel) • Peckforton Pharmaceuticals (paclitaxel) • Sanofi (docetaxel) • Seacross Pharmaceuticals (docetaxel) • Sun Pharmaceuticals UK (carboplatin, gemcitabine)

Consultees	**Commentators (no right to submit or appeal)**
• 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	<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

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Merck Sharp & Dohme

Evidence submission

File name	Version	Contains confidential information	Date
		Yes	16 February 2017

Contents

Tables and figures

Abbreviations

AE	Adverse Event
AEOSI	Adverse events of special interest
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ASaT	All Subjects as Treated
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central radiologists'
BOR	Best Overall Response
BSA	Body surface area
BSC	Best Supportive Care
BTD	Breakthrough Therapy Designation
CAA	Commercial access agreement
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CPS	Combined positive score
CR	Complete response
CSR	Clinical Study Report
CTA	Clinical Trial Assay
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DAEs	Discontinuations due to adverse-events
DCR	Disease control rate
DMC	Data Monitoring Committee
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECIs	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eDMC	External data monitoring committee
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMit	Electronic Market Information Tool
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	EuroQoL 5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FWER	Family-wise type 1 error rate
G-CSF	Granulocyte-colony stimulating factor
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSD	Hwang Shih DeCani
HTA	Health technology assessment
IA1	First Interim-Analysis

IA2	Second Interim-Analysis
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INV	Investigator evaluation
IPCW	Inverse probability censoring weighted
irAEs	Immune-related AEs
IRC	independent review committee
irRC	Immune-related response criteria
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
IVRS/IXRS	Interactive Voice Response System/ Interactive Voice and Web Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary of Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MK-3475	Pembrolizumab - *Keytruda*®
MRA	Market Ready Assay
MSD	Merck Sharp and Dohme Ltd
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PA	Prototype Assay
PAS	Patient Access Scheme
PbR	Payment by results
PD	Progressive Disease
PD-1	Programmed death 1 protein
PD-L1	Programmed cell death 1 ligand 1
PFR	Progression-free rate
PFS	Progression free survival
PH	Proportional hazards
PIM	Promising Innovative Medicines
PK	Pharmacokinetics
PPS	Post-progression state
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcomes
PS	Performance status
PSSRU	Personal and Personal and Social Services Research Unit
PTs	Preferred terms
PT-DC	Platinum-based doublet chemotherapy
QALY(s)	Quality-Adjusted Life Year(s)
Q3W	Every 3 weeks
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank-preserving structural failure time
RR	Response rate

SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable Disease
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SOC	Standard of Care
STA	Single technology assessment
TA	Technology Appraisal
TC	Tumour cells
TNM	Tumour, Node, and Metastases
TOT	Time on treatment
TRAEs	Treatment-related adverse
TTD	Time to death
TTO	Time trade off
UK	United Kingdom of Great Britain and Northern Ireland
US	United States of America
VAS	Visual Analogue Scale
VAT	Value-Added Tax

1. Executive summary

The term urothelial cancer encompasses cancer of the bladder, renal pelvis, ureter and urethra. Of these, bladder cancer is the predominant type of urothelial cancer, and is the 7th most commonly diagnosed cancer in the UK[1, 2] and when specifically considering incidence in men, it is the 4th most common cancer in the UK[1, 3]. Although smoking has been identified as a major contributing factor to the development of urothelial cancer[2, 4] in over 50% of cases the actual cause of the disease is unknown. Despite it being a common cancer, research into urothelial cancer has, until recently, lagged behind other cancer types. Consequently there have been no major advances in the systemic therapy for urothelial cancer in almost 25 years.[5]

The survival rate for patients diagnosed with stage IV advanced bladder cancer is low; currently, such patients face a poor prognosis, with an estimated 5-year survival rate of just 10%.[6] Consequently, there remains a critical unmet medical need for more effective therapy options for this patient population.

Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging with its ligands PD-L1 and PD-L2. The drug first received a marketing authorisation for use in patients with metastatic melanoma in 2015 and was subsequently recommended for use in the NHS by NICE for this patient population. In 2016, the marketing authorisation for pembrolizumab was expanded to authorise its use for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab. Use in the NHS for this patient population was recommended by NICE in January 2017 (TA428). A further licence indication was added to the marketing authorisation for pembrolizumab in January 2017, authorising its use as first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. A submission to NICE covering this patient population is currently under review (ID990), with final guidance due in June 2017.

With this submission, pembrolizumab is proposed to be used as a treatment option for adult patients with locally advanced/unresectable or metastatic urothelial cancer that has progressed on or after platinum-containing chemotherapy. KEYNOTE-045 is a phase III randomised controlled trial (RCT) (median follow up in the pembrolizumab arm of 10.3 months; range 0.2 to 20.8 months) which serves as the evidence base for the efficacy of

pembrolizumab in the patient population of relevance to this submission. The results from the second interim analysis (IA2) of KEYNOTE-045 demonstrate both statistically significant and clinically meaningful overall survival (OS) benefit for all patients, regardless of level of PD-L1 expression on tumour cells (see section 4.7).

On the basis of the results from IA2 of KEYNOTE-045, the Data Monitoring Committee (DMC) recommended that KEYNOTE-045 be stopped early to allow a formal within study crossover phase to be implemented in the protocol, in order to give the patients who were receiving SOC the opportunity to receive pembrolizumab.

The results from IA2 of KEYNOTE-045 demonstrate that therapy with pembrolizumab 200mg Q3W significantly prolongs OS (HR 0.73; 95% CI: 0.59, 0.91; p=0.002) compared with SOC (which in the trial comprised of Investigator's choice of docetaxel, paclitaxel or vinflunine). The significant OS improvement associated with pembrolizumab 200mg Q3W was also demonstrated after applying statistical methods to adjust for any treatment switching in the control arm, which may have occurred following the end of trial assigned treatment. Additionally, compared to SOC, pembrolizumab 200mg Q3W was associated with both a higher response rate (21.1% vs. 11.4%), and a longer median duration of response (not reached [range, 1.6+ to 15.6+ months] vs. 4.3 months [range, 1.4+ to 15.4+]).

Survival benefit favouring pembrolizumab was demonstrated across subgroups such as Eastern Cooperative Oncology Group performance status (ECOG PS), liver metastasis, baseline haemoglobin and time from prior chemotherapy. As KEYNOTE-045 utilised a therapy as part of the SOC arm (vinflunine) which has not been recommended by NICE, subgroup-analyses have been presented for the comparison of pembrolizumab versus the comparators of relevance to the UK (UK SOC: docetaxel and paclitaxel). The results of these subgroup analyses have demonstrated the enhanced efficacy of pembrolizumab and form the basis of the clinical efficacy inputs for the economic model (see section 5).

Results for subgroups based on PD-L1 expression level and histology have been presented as these were pre-specified subgroups in KEYNOTE-045. However given the small sample sizes in these subgroups, results should be interpreted with caution. In urothelial cancer, PD-L1 tumour expression level is measured by the combined proportion score (CPS) which consists of the percentage of PD-L1–positive tumour cells (TCs) and infiltrating immune cells relative to the total number of TCs as measured using the PD-L1 IHC 22C3 pharmDx assay on samples collected by core needle or excisional biopsies or in resected tissue. The PD-L1 positive population is defined as those with CPS ≥ 1%, while CPS ≥ 10% defines the PD-L1 strongly positive population. The assay used in the determination of CPS PD-L1 expression

level in urothelial cancer patients is the same assay used for the determination of TPS level in NSCLC patients.

The base-case analyses cover the all-comers population, given that KEYNOTE-045 demonstrated efficacy in patients regardless of the aforementioned subgroup factors. Also, the current treatment pathway for urothelial cancer is not based on tumour histology, as the majority of urothelial cancers are of transitional cell histology.

In KEYNOTE-045, AEs of grade 3-5 severity attributed to treatment occurred in over three times as many patients treated with SOC compared with pembrolizumab (49.4% vs. 15.0%); and fewer discontinuations due to drug-related AEs occurred among patients in the pembrolizumab 200 mg Q3W arm compared to the SOC arm. Overall, the safety profile of pembrolizumab remains consistent with previously reported findings in patients other tumour types.[7-13] The enhanced efficacy and safety profile of pembrolizumab versus SOC demonstrated in KEYNOTE-045 is corroborated by improvements in HRQoL.

As per the submission to NICE which is currently under review for first-line treatment of NSCLC (ID990), this submission utilises the 200mg fixed dose in a Q3W dosing regimen for patients with previously-treated urothelial cancer. A fixed dosing scheme reduces complexity in the logistical chain at treatment facilities and reduces wastage.

The cost-effectiveness of pembrolizumab was evaluated through the development of a three-state partitioned survival model, with the three states being PFS, post-progression and death, in line with the modelling approach taken in previous oncology HTA submissions to NICE (see section 5.2). The model projected health outcomes (i.e. OS and PFS) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were estimated by considering time-to-death utilities derived from EQ-5D data collected in KEYNOTE-045 trial. Clinical and economic outcomes were projected over a 35-year time horizon to cover the anticipated lifetime of the population initiating second-line therapy and assessed as part of this submission.

A two-part piecewise approach was used on the basis of KEYNOTE-045 data, following NICE DSU guidance and recent NICE submissions. The results demonstrate that pembrolizumab, as an end of life therapy, meets the NICE criteria to be considered a cost-effective use of NHS resources. The model estimates that patients treated with pembrolizumab gain 0.86 additional QALYS compared to UK SOC. The incremental cost-effectiveness ratio (ICER) when comparing pembrolizumab to UK SOC is £45,861. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per QALY gained is therefore 58%.

Results from multiple sensitivity analyses showed the ICER to be consistently below £50,000 per QALY (discounted, with the PAS). The inputs that mostly affect of the cost-effectiveness analyses results were the extrapolation of OS, the dose intensity, the discount rates and the utilities for long-term survivors. The sensitivity analyses conducted demonstrated that the cost-effectiveness of pembrolizumab is resilient to the different sources of uncertainty assessed.

The availability of pembrolizumab as a treatment option in England, for patients with urothelial cancer following treatment with platinum-based chemotherapy, will represent a step-change in the treatment options available and will provide patients and clinicians with a long-overdue, transformative new treatment alternative.

1.1 Statement of decision problem

The decision problem addressed in the submission is presented in the Table 1 below.

Table 1: 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 and unresectable or metastatic urothelial cancer that has progressed on or after platinum-containing chemotherapy.	Adults with locally advanced/unresectable or metastatic urothelial cancer that has progressed on or after platinum-containing chemotherapy	Our submission reflects the population covered by the clinical trial supporting this submission, although we anticipate a broader label (i.e. our anticipated label covers the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy, rather than prior platinum-based chemotherapy).
Intervention	Pembrolizumab	Pembrolizumab 200 mg Q3W	In line with the anticipated licence and with the final NICE scope.
Comparator (s)	• Retreatment with 1st line platinum-based chemotherapy (only for people whose disease has had an adequate response) • Docetaxel • Paclitaxel • Best supportive care (BSC)	• Docetaxel • Paclitaxel	No evidence exists for a comparison between pembrolizumab and retreatment with 1st line platinum-based chemotherapy; therefore the latter has not been considered as a comparator in this submission. Although re-treatment with platinum-based chemotherapy is included in the NICE clinical guideline on bladder cancer, some of these treatment regimens are used off-label and there is limited evidence on the value of their use in this setting. BSC has not been considered as a relevant comparator in the population of interest, as alternative active treatments (e.g. docetaxel and paclitaxel) are available.
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS)	The outcome measures considered include: • OS • PFS	In line with NICE final scope

	• response rates (RRs) • adverse effects (AEs) of treatment • health-related quality of life (HRQoL)	• RRs • AEs of treatment • HRQoL	
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 the intervention or comparator technologies will be taken into account.	The cost-effectiveness is expressed in terms of an incremental cost per quality-adjusted life year (QALY). The time horizon considered is 35 years. Costs are considered from an NHS and PSS perspective.	In line with NICE final scope

Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on cancer histology and biological markers (PD-1 or CD274 antigen).	The following subgroups have been considered:
		• Histology subgroups
		  ○ Predominant transitional cell carcinoma
		  ○ Pure transitional cell carcinoma
		• PD-L1 positive (CPS≥1%)
		• PD-L1 strongly positive
		• (CPS≥10%)
			Although subgroup analyses have been presented for the various subgroups listed, the base-case analysis covers the all-comers population.
			
			90% of bladder cancer (which is the most common type of urothelial cancer) is of transitional cell histology[14], and 87% of ureter and renal pelvis cancers are transitional cell histology.[15] In KEYNOTE-045, 71% of the population were of transitional cell histology. The current treatment pathway for urothelial cancer is not based on tumour histology, and therefore the all-comers population should be considered the population of relevance to this submission.

Special considerations including issues related to equity or equality	N/A	N/A	N/A

1.2 Description of the technology being appraised

The technology being appraised is described in Table 2 below:

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Marketing authorisation/CE mark status	Pembrolizumab currently has a marketing authorisation covering the following indications: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.
Indications and any restriction(s) as described in the summary of product characteristics	Indication to which this submission relates: • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy. Please note that in a late change to the regulatory strategy, the regulatory submission filed also included an indication for first-line treatment, as specified below: • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy. However this submission only covers pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy, as specified above, and as previously covered by the NICE scoping process and decision problem meeting.
Method of administration and dosage	200 mg every three weeks (Q3W); intravenous (IV) infusion.

Pembrolizumab is a highly selective humanised monoclonal antibody against programmed death-1 (PD-1) receptor, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab activates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates antitumour immunity (see section 2.1).

The route of administration for pembrolizumab is IV infusion, over a 30-minute period. The anticipated licensed dosing regimen for patients with locally advanced and unresectable or metastatic urothelial cancer that has progressed on or after platinum-containing chemotherapy is 200mg Q3W.Treatment with pembrolizumab continues until disease progression or unacceptable toxicity, whichever occurs first. The list price of pembrolizumab is £2,630 per 100mg vial [redacted]

A regulatory variation to the product licence for pembrolizumab is currently under review by the EMA, to broaden the eligible population for this drug. The anticipated approval date for this variation is Q3 2017, and the anticipated licence indication is "KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy".

The innovative nature of pembrolizumab has been recognised on a number of occasions. Most recently in February 2017 the United States (US) Food and Drug Administration (FDA) granted the drug Breakthrough Therapy Designation (BTD) and priority review for the first-line treatment of patients with advanced or metastatic urothelial cancer who are ineligible for cisplatin-containing therapy; and for patients with patients with advanced or metastatic urothelial cancer at disease progression on or after platinum-containing chemotherapy. The FDA's Breakthrough Therapy Designation is intended to expedite the availability of promising new therapies that are planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates substantial improvement over existing therapies on one or more clinically significant endpoints.

1.3 Summary of the clinical effectiveness analysis

A systematic literature review was conducted to identify relevant clinical trials from the published literature (see section 4.1).

The clinical evidence presented in this submission is derived from the second interim analysis (IA2) of KEYNOTE-045[16, 17]; a suitably powered phase III randomised controlled trial (RCT) of pembrolizumab 200 mg Q3W (anticipated licence dose and schedule, relevant to this submission) versus investigator's choice standard of care (SOC) chemotherapy regimens (docetaxel, paclitaxel or vinflunine), in a patient population relevant to the anticipated label: patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy (see section 4.7).

The baseline characteristics of the patients included in KEYNOTE-045 were as expected for patients with advanced urothelial cancer, and representative of the patients who are anticipated to receive pembrolizumab in UK clinical practice (see section 4.5).

The efficacy results from IA2 of KEYNOTE-045[16, 17] demonstrate the substantial benefit of pembrolizumab in subjects with urothelial carcinoma who have received platinum-containing chemotherapy, in the overall population, regardless of PD-L1 level of expression.

In this study, pembrolizumab was associated with a statistically significant and clinically meaningful improvement in the primary endpoint of OS (HR = 0.73; p=0.0022) versus treatment with SOC chemotherapy in the overall population. Subgroup analysis was remarkably consistent with the primary findings, providing further evidence of the survival benefit of pembrolizumab over SOC chemotherapy among important subgroups such as ECOG-PS, liver metastasis, haemoglobin, time from prior chemotherapy, prior platinum (cisplatin vs carboplatin), Investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine), and Bellmunt risk scores.

Three alternative treatment switching adjustment methods were applied to adjust for the switching observed in KEYNOTE-045 (see section 4.7). All methods adjusting for treatment switching in the control arm provide treatment estimates that are larger (HR in a range of 0.68 to 0.70) than the ITT estimate (HR=0.73). Survival improvement was observed across all key subgroups. In addition, pembrolizumab was associated with both a higher response rate compared to control group (21.1% vs. 11.4% respectively), and a longer median duration of response (not reached [range, 1.6+ - 15.6+months] vs. 4.3 months [range, 1.4+ - 15.4+]).

Although treatment with pembrolizumab was not associated with a statistically significant improvement in PFS versus treatment with SOC chemotherapy (HR = 0.98; *p*=0.416) in the overall population at the time of database cut-off, Kaplan-Meier estimates show a separation in favour of pembrolizumab after the 6-month time point and a plateau in the tail of the curve, suggesting a meaningful benefit for some subjects.

Treatment with pembrolizumab was shown to be associated with a statistically significant and clinically meaningful improvement in ORR versus treatment with chemotherapy (21.1% vs 11.4%, *p*=0.0011) in the overall population.

Responses to pembrolizumab typically occurred within 2 months and were durable, with the median DOR not reached in the pembrolizumab arm at the time of database cut-off (range: 1.6+ to 15.6+ months), whereas the median DOR for chemotherapy was 4.3 months.

The improved benefit in OS, ORR, and response duration for pembrolizumab as compared to SOC chemotherapy is corroborated by improvements in health-related status/QoL scores. Subjects treated with pembrolizumab had significantly better health status/QoL compared with subjects treated with chemotherapy (as demonstrated by the higher EORTC QLQ-C30 global health status/QoL score over time) and a longer time to deterioration in the pembrolizumab arm compared with control (see section 4.7).

The observed safety profile of the pembrolizumab arm was consistent with the safety profile for pembrolizumab established to date, and demonstrates that pembrolizumab is well tolerated in the target population, offering favourable tolerability compared to SOC chemotherapy regimens. Fewer subjects in the pembrolizumab arm experienced AEs, drug-related AEs, grade 3-5 AEs and grade 3-5 drug related AEs compared to those in the SOC chemotherapy arm (see section 4.12). Additionally, there was a lower frequency of drug-related AEs leading to treatment discontinuation in the pembrolizumab arm (5.6%) compared with the control arm (11.0%). In general, the frequency and severity of each adverse event of special interest (AEOSI) observed during the trial were similar to the previously described characterisation of the safety profile of pembrolizumab. No new safety risk was observed in association with pembrolizumab in the target population

As the comparator arm in KEYNOTE-045 comprised a mix of three different SOC chemotherapy regimens, a systematic search of the literature was conducted in order to assess the feasibility of conducting an indirect and mixed treatment comparison through a

Network Meta-Analysis (NMA), to estimate the efficacy of pembrolizumab versus specific chemotherapy regimens. The systematic search resulted in trials that did not form a connected network; hence an NMA was not feasible. However post-hoc subgroup analyses of the data from KEYNOTE-045 was conducted, to focus only on the data concerning comparators of relevance to England (i.e. paclitaxel and docetaxel, excluding the NICE non- recommended comparator vinflunine). The results of these analyses are presented in Section 4.8, and demonstrate the enhanced efficacy of pembrolizumab versus the individual chemotherapy regimens of relevance to UK practice.

The evidence provided is robust and consistently demonstrates both a statistically significant and clinically meaningful benefit of pembrolizumab compared to SOC for adults with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy. These data underscore the substantial benefit of pembrolizumab as a treatment option for this patient group, who currently face a very poor prognosis.

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness of pembrolizumab was assessed against UK SOC, i.e. docetaxel and paclitaxel, in patients with advanced or metastatic urothelial cancer following treatment with platinum-containing chemotherapy.

In line with the modelling approach taken in previous HTAs, cost-effectiveness was evaluated through the development of a three-state partitioned survival model, with the three states being PFS, post-progression and death (see section 5.2). The analysis was conducted in line with the NICE reference case. A discount rate of 3.5% per annum was applied to both costs and benefits. Clinical and economic outcomes were projected over a 35-year time horizon to cover the anticipated lifetime of the population here assessed. The analysis was run using 1-week model cycle. The model projected health outcomes (i.e. OS and PFS) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were estimated by using time-to-death utilities derived from EQ-5D data collected in KEYNOTE-045 trial.

In order to exclude the vinflunine comparator arm which is not recommended by NICE, the clinical evidence used to populate the UK SOC arm was derived from post-hoc analyses of the KEYNOTE-045 trial. For the UK SOC, OS was estimated by adjusting for treatment switching using a two-stage adjustment method.

PFS and OS for pembrolizumab and UK SOC were modelled using a piecewise approach:

- For OS, KEYNOTE-045 KM data was used for the initial period of 40 weeks, on the basis of the changes to cumulative hazards, and a log-normal distribution was fitted afterwards following standard parametric approaches.
- For PFS, KEYNOTE-045 KM data was used for the first 21 weeks, at which point the third radiologic assessment occurred. This was followed by extrapolating using an exponential distribution.

Section 5 details the development of the de novo economic model for pembrolizumab, with Table 3 below presenting the results for the main population of patients with advanced or metastatic urothelial cancer considered in this submission.

The model estimates that patients treated with pembrolizumab gain 0.86 additional QALYS compared to UK SOC. The incremental cost-effectiveness ratio (ICER) when comparing

pembrolizumab to UK SOC is £45,861. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 58%.

Results from multiple sensitivity analyses showed the ICER to be consistently below £50,000 per QALY (discounted, with the PAS). The inputs that mostly affect the cost-effectiveness results relate to the extrapolation of OS, utilities for long-term survivors, discount rates and dose intensity. The sensitivity analyses conducted demonstrated that the cost-effectiveness of pembrolizumab is resilient to the different sources of uncertainty assessed.

Table 3: Incremental cost-effectiveness results – Base case, main population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£20,820	1.59	1.09	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,233	0.86	£45,861

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: KEYTRUDA®

Generic name: pembrolizumab

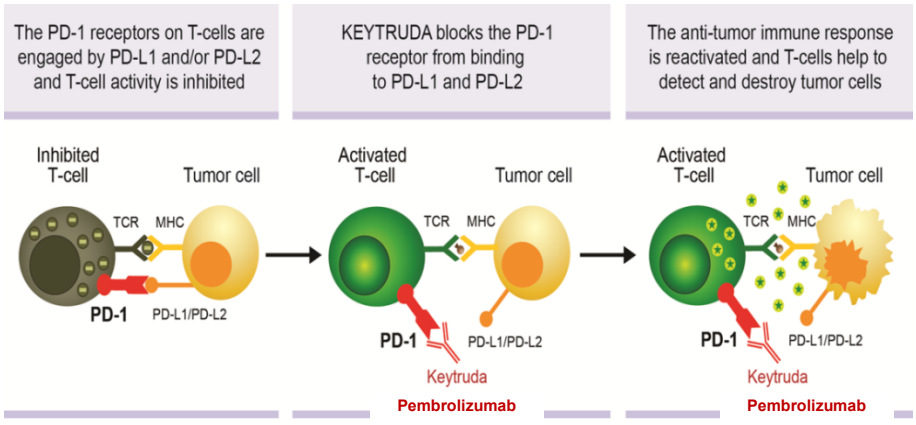
Therapeutic class: BNF Category "Other immunomodulating drugs" (08.02.04).[18]

Brief overview of mechanism of action:

Programmed death 1 protein (PD-1) is an immune-checkpoint receptor that is expressed on antigen-presenting T cells. PD-1 acts to initiate downstream signalling, which in turn inhibits the proliferation of T cells as well as cytokine release and cytotoxicity.[19] The PD-1 ligands, PD-L1 and PD-L2, are frequently upregulated on the surface of many tumour cell surfaces.[20]

Pembrolizumab (Keytruda®) is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype[19] designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells (Figure 1). By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity (Figure 1).

Figure 1: Pembrolizumab – mechanism of action



Source: MSD data on file.

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1: Current UK regulatory status

- Application submitted [redacted]
- CHMP Opinion expected: [redacted]
- Estimated date of Marketing Authorisation: [redacted]

2.2.2: Anticipated indication in the UK

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

Please note, as described in section 1.2, this submission only focuses on the first of the above mentioned populations (adults with urothelial carcinoma who have received prior chemotherapy)

2.2.3: Anticipated restrictions or contraindications that are likely to be included in the draft summary of product characteristics (SmPC)

Please see Appendix 1.

2.2.4: Draft SmPC

The draft SmPC has been included as an appendix – see Appendix 1. Please note this draft SmPC includes provisional indication wording which will be subject to change as the regulatory review progresses. Therefore the final approved indication wording, as well as other sections of the SmPC, may differ compared to the one presented in Appendix 1.

2.2.5 Draft EMA assessment report

The draft EMA assessment report is currently unavailable.

2.2.6: Summary of the main issues discussed by the regulatory authorities

Not applicable – public assessment report currently unavailable

2.2.7: Anticipated date of availability in the UK

The anticipated commercial launch date following regulatory approval is [redacted]

2.2.8: Details of regulatory approval outside of the UK

Not applicable

2.2.9: Other health technology assessments in the UK

MSD will be making a submission to the Scottish Medicines Consortium (SMC) in [redacted] for the anticipated licence indication.

2.3 Administration and costs of the technology

Table 4: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion	Draft SmPC (see Appendix 1)
Acquisition cost (excluding VAT) *	List price: 100mg vial = £2,630. A PAS is already in place with the Department of Health in a form of a simple discount ([redacted] to the list price of pembrolizumab. The NHS acquisition cost (excl. VAT) is: 100mg vial = [redacted]	Department of Health
Method of administration	Intravenous infusion	Draft SmPC (see Appendix 1)
Doses	Induction dose: 200mg	Draft SmPC (see Appendix 1)
Dosing frequency	200mg every 3 weeks until disease progression or unacceptable toxicity	Draft SmPC (see Appendix 1)
Average length of a course of treatment	Based on KEYNOTE-045 trial, the average time on therapy per patient is 5.60 months, equivalent to 8.81 cycles received per patient treated with pembrolizumab 200mg Q3W during a course of treatment	CSR KEYNOTE-045 [16]
Average cost of a course of treatment	The average cost per treatment course is: £46,341 at list price	KEYNOTE-045 [16]
Anticipated average interval between courses of treatments	Treatment is continued until disease progression or unacceptable toxicity leading to discontinuation	Draft SmPC (see Appendix 1)
Anticipated number of repeat courses of treatments	Repeated treatment is not anticipated	Draft SmPC (see Appendix 1)
Dose adjustments	No dose adjustment is expected	Draft SmPC (see Appendix 1)
Anticipated care setting	Pembrolizumab is anticipated to be administered in a hospital setting	
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

2.4 Changes in service provision and management

2.4.1 Additional tests or investigations needed

No additional tests or investigations are required further to the usual tests undertaken in current clinical practice. No diagnostic test is required to identify the population for whom pembrolizumab is indicated and no particular administration for the technology is required.

2.4.2 Main resource use to the NHS associated with the technology being appraised

Pembrolizumab is administered until disease progression or unacceptable toxicity. The main resource use to the NHS associated with the use of pembrolizumab is therefore expected to be related to the management of patients in the pre-progression period.

The administration of pembrolizumab will take place in secondary care (i.e. hospital setting) with no inpatient stay required. Patients will receive pembrolizumab as an outpatient on a 3-weekly cycle, with a duration of administration of 30 minutes per infusion.

2.4.3 Additional infrastructure in the NHS

Pembrolizumab is not anticipated to require any additional infrastructure in the NHS to be put in place.

2.4.4 Extent that the technology will affect patient monitoring compared with established clinical practice in England

Pembrolizumab is expected to provide durable benefit for a proportion of patients treated. These patients can be anticipated to receive ongoing follow-up including scanning.

2.4.5 Concomitant therapies administered with the technology

No concomitant therapies are required.

2.5 Innovation

2.5.1 State whether and how the technology is a 'step-change' in the management of the condition

Unlike the treatment of other more common cancers, customising therapy based on histology is not the standard approach in the treatment of urothelial cancer. Over the last decade, platinum-based chemotherapy and taxane regimens have remained the foundation of second-line treatment for the majority of patients with urothelial cancer, and have not significantly improved the 1-year and 5-year survival rates.[21]

There is currently a high unmet need for urothelial cancer therapies that prolong survival without greatly increasing toxicity or significantly compromising patients' quality of life. Due to its distinct mechanism of action, pembrolizumab has demonstrated significant survival benefit and improved tolerability profile compared to chemotherapy regimens and is expected to provide a durable response for patients with advanced or metastatic urothelial cancer, following treatment with platinum-containing chemotherapy.[16, 17]

The innovative nature of pembrolizumab was first recognised by the US Food and Drug Administration (FDA) in January 2013 by granting it Breakthrough Therapy Designation (BTD) for advanced melanoma.[22]. The FDA's BTD is intended to expedite the development and review of a drug that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoint.[23] In October 2014 the FDA granted pembrolizumab BTD for the treatment of patients with advanced (metastatic) NSCLC whose disease has progressed after other treatments. [23] In October 2015 pembrolizumab was granted accelerated approval for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. [23] In September 2016, the FDA granted BTD and priority review for the first-line treatment of patients with advanced non–small cell lung cancer whose tumours express PD-L1.[24] The innovative nature of pembrolizumab was most recently recognized when the FDA granted BTD for the second-line treatment of patients with locally advanced or metastatic urothelial cancer with disease progression on or after platinum-containing chemotherapy.

In the UK, in March 2015 pembrolizumab became the first medicine to be granted positive scientific opinion under the MHRA's Early Access to Medicines Scheme (EAMS) for the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care. [25] Pembrolizumab received Promising Innovative Medicines (PIM) designation (EAMS Step 1) in November 2015, and in March 2016 a positive Scientific Opinion was granted (MHRA EAMS number 00025/0001) for "*the treatment as monotherapy of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation or whose disease has progressed on or after platinum-containing chemotherapy. Patients who have an EGFR sensitising mutation or an ALK translocation should also have had disease progression on approved therapies for these aberrations prior to receiving pembrolizumab*".[26] EAMS aims to give earlier access to promising new unlicensed or 'off label' medicines to UK patients that have a high unmet clinical need. This validates MSD's position that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits in an area of high unmet need.

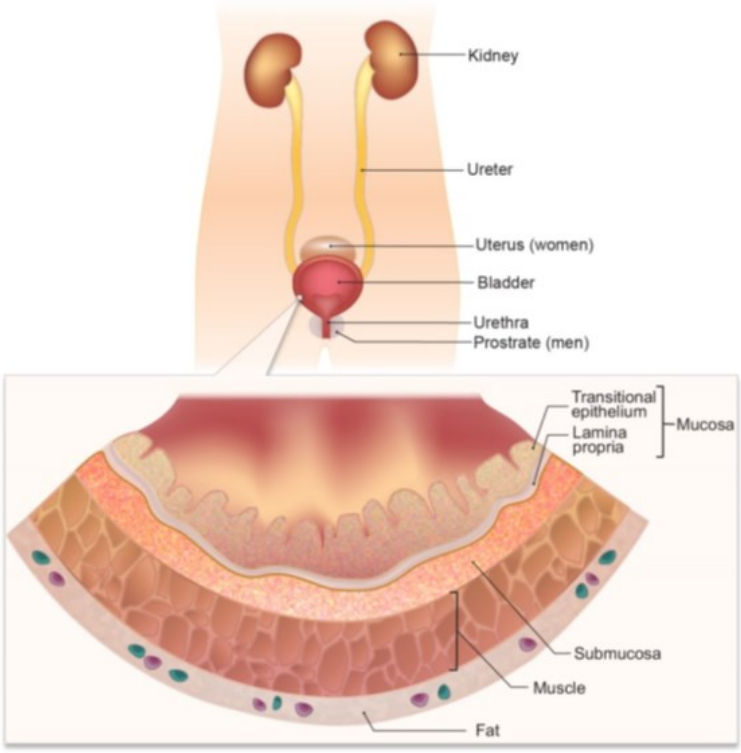
3. Health condition and position of the technology in the treatment pathway

3.1: Brief overview of the disease/condition for which the technology is being used

The term urothelial cancer describes cancers which may arise from the transitional cells in the endothelium of the bladder, renal pelvis, ureter and urethra.[27] Transitional cells are cells that can stretch as the organ expands and are most commonly found in the urinary system (Figure 2). For this reason, urothelial cancer is the predominant histologic type of urinary tract cancer in the UK accounting for approximately 90% of bladder, renal pelvis, ureter and urethra cancers.[27]

Whilst bladder is the 7th most commonly diagnosed cancer in the UK[1], urothelial cancer of the renal pelvis is significantly less common, accounting for 7% of all diagnosed kidney cancers, and urothelial cancer of the ureter is 4 times less likely to occur than in the kidney[28-30] Urothelial cancers are most prevalent in the male population, occurring at approximately a 3:1 ratio.[31]

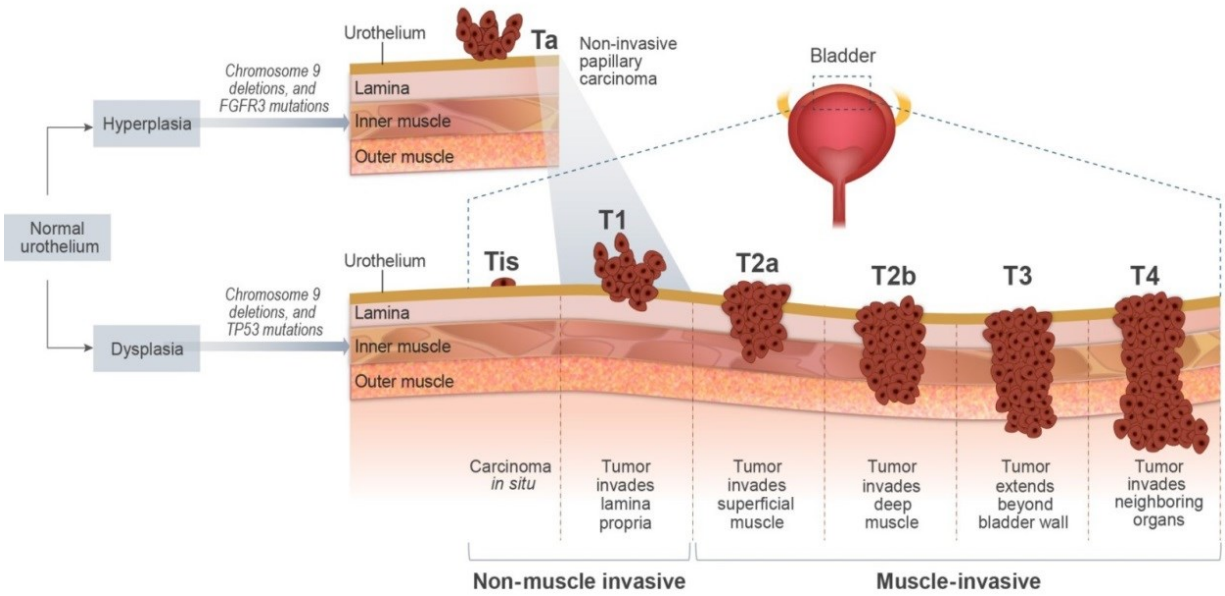
Figure 2: Cross sectional view of the bladder[32]



Most urothelial cancers of the bladder can be divided into two predominant histologies; flat carcinomas and papillary carcinomas. Flat carcinomas are non-invasive, as they remain in the inner layers of the bladder wall and do not grow toward the hollow part of the bladder. Papillary carcinomas grow towards the centre of the bladder, they can be non-invasive however they often grow deeper into the bladder wall and become invasive. Other types of bladder cancers include squamous cell carcinoma, which begins in thin flat cells and adenocarcinoma which begins in the mucus producing cells. These types of bladder cancer arise as a result of chronic irritation and inflammation [33]

Urothelial carcinoma is staged according to the Tumour-Node-Metastasis classification, based on the primary tumour size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M)[34]. This information is combined to assign an overall stage of 0, I, II, III or IV: In stage 0 the cancer is in the innermost layer of the epithelial lining. In stages I and II the cancer starts to grow in through the connective tissue and into the muscle layer of the bladder/renal pelvis/urethra wall. Around 75% of newly diagnosed urothelial bladder cancers are non-muscle invasive, which has a high rate of recurrence (70% and progression into muscle invasive disease (10-25%)[35, 36]. In stage III the cancer has grown through the muscle into the fat layer. In stage IV the cancer has spread to the wall of the abdomen or pelvis, the distant lymph nodes or on to other organs such as the liver, bone or brain (Figure 3).

Figure 3: Staging system – bladder cancer[32]



Urothelial carcinomas are associated with a variety of risk factors, the most important being smoking [4]. Tobacco smoke contains aromatic amines which when renally excreted exert a carcinogenic effect on the entire urinary system. For this reason, the risk of developing bladder cancer is 2-6 times greater in smokers than in non-smokers[37]. A study by Jensen et al. found that the risk from smoking appears to be higher still for ureteral and renal pelvic cancers than for bladder cancer.[38] Following smoking, occupational exposure to carcinogens such as processing paint, dye, metal and petroleum products in industrial areas has been attributed to a large proportion of urothelial carcinomas.[4]

Urothelial carcinoma harbors multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions and translocations. In cancers of other sites, molecular aberrations are important markers of prognosis and response to treatment; however targeted therapeutic treatment options for bladder cancer are currently limited.[39, 40]

3.2: Effects of the disease/condition on patients, carers and society

Urothelial bladder cancer can sometimes be detected early due to recognisable symptoms such as blood in the urine (haematuria). Other symptoms include burning when passing urine, increased urinary frequency or urgency, and pain in the lower abdomen or back. However in women, these symptoms are commonly mistaken for a urinary tract infection (UTI), which may lead to a delay in diagnosis.[2] Due to the intermittent nature of bladder cancer, it can appear that treatment with antibiotics has “cured” the symptoms, potentially delaying the route to diagnosis.[41]

Around a third (36.7%) of bladder cancer cases occur as a result of tobacco smoking and 6% occur as a result of occupational exposure, reduction in exposure to both is reflected in declining bladder cancer rates of 0.76% annually.[42, 43]

There is a lack of data for survival statistics in urothelial cancer; however survival rates in bladder cancer, which accounts for a large proportion of urothelial cancers, is strongly correlated to the stage of disease at diagnosis. Survival at 5 years is as high as 86-89% when diagnosed at Stage I but drops to as low as 9-11% when diagnosed at stage IV.[44]

There has been little change in survival rates in recent years, particularly for those diagnosed with transitional cell carcinoma of the renal pelvis where prognosis is lower than those with other types of kidney cancer. In part, this is a consequence of the differing biology of the disease with it being less easy to detect at an earlier disease stage, whilst there have also been fewer advances in development of successful systemic therapies.[45]

The majority of patients who are diagnosed with muscle invasive urothelial cancer will be offered radical treatment, such as a full cystectomy.[46] This can present a difficult emotional issue and lifestyle adjustment for both patients and carers, as post-operative quality of life is consistently and significantly lower than the general population, due to poor urinary and sexual function.[47, 48]

Urothelial cancer, like all cancers, imposes a burden to society, not only in terms of years of life lost (YLL) due to premature death, but also due to the corresponding loss of contribution to the economy and the substantial health care costs associated with its management. A study by Leal et al. estimated that informal care and productivity losses due to mortality and morbidity account for 18% and 29% whilst healthcare costs account for 53% of the total cost of bladder cancer.[49] In 2001-2002, the total cost for bladder cancer in the UK was £55.39 million, of which superficial disease cost £35.25 million.[50]

3.3: Clinical pathway of care showing the context of the proposed use of the technology

The clinical care pathway (Figure 4) for patients with locally advanced or metastatic urothelial cancer is determined by the performance status and level of renal function of the patient. According to the current NICE guideline for the diagnosis and treatment of bladder cancer (NG2)[46], published in February 2015, if a patient has progressed after first-line chemotherapy, but they have adequate renal function (typically defined as a GFR of 60 ml/min/1.73m^2 or more) and they are otherwise physically fit (have an ECOG performance status of 0 or 1), they should be considered for second-line chemotherapy with gemcitabine in combination with cisplatin, or accelerated (high-dose) MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) in combination with granulocyte-colony stimulating factor (G-CSF) .

People with incurable locally advanced or metastatic urothelial bladder cancer who have progressed after first-line chemotherapy, but who are unsuitable candidates to receive cisplatin-based chemotherapy, or who choose not to have it, should be considered for second-line chemotherapy with carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel. Although both of these regimens are common in UK clinical practice, at the time of NICE guideline publication,[46] neither carboplatin in combination with paclitaxel nor gemcitabine in combination with paclitaxel had a UK marketing authorisation for this indication. The NICE guideline states that the prescriber should follow relevant

professional guidance, taking full responsibility for the decision and informed consent should be obtained and documented.

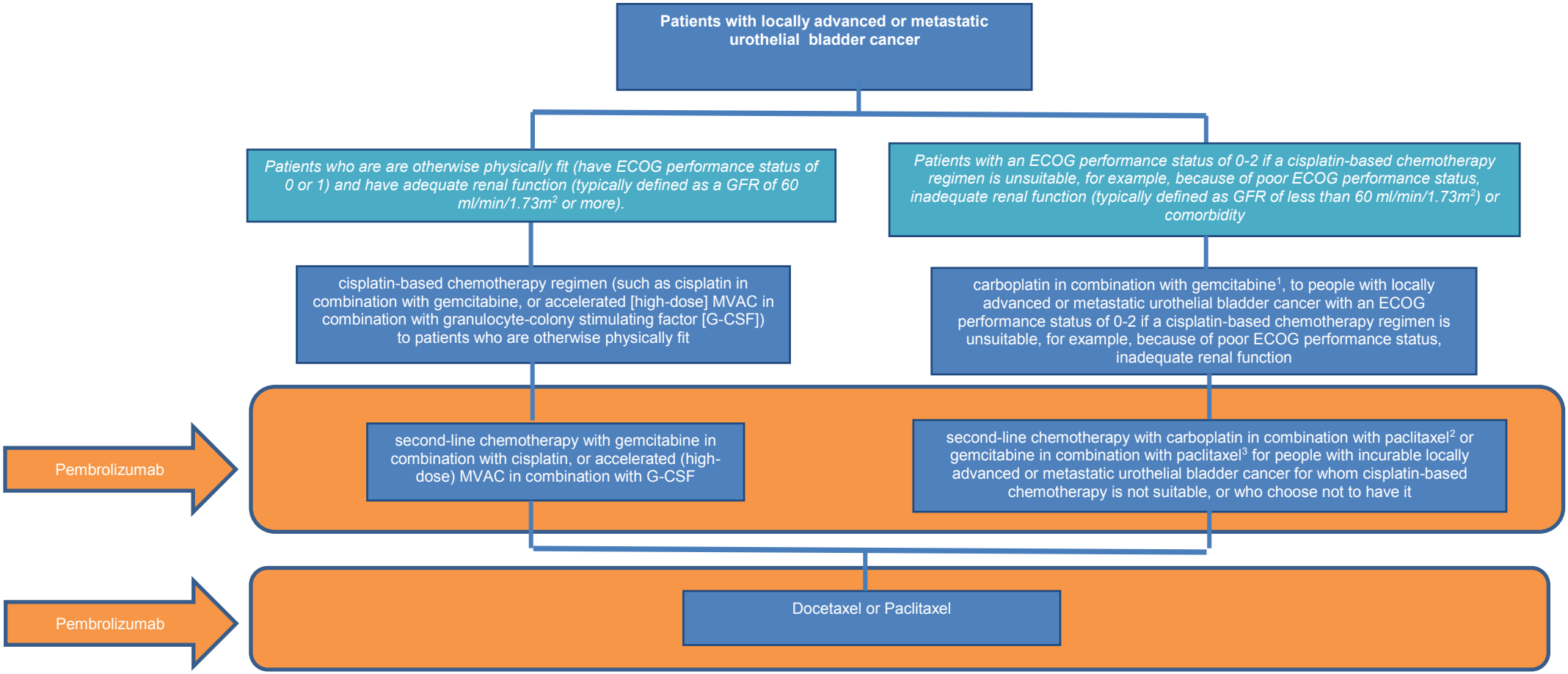
The NICE Final scope for this appraisal confirms that for people whose disease has progressed after platinum-based chemotherapy, a taxane such as docetaxel or paclitaxel may be given.

In the UK, vinflunine is not recommended within its marketing authorisation for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy.[51]

With this submission, pembrolizumab is proposed to be used as a second-line treatment option for adult patients with locally advanced or metastatic urothelial cancer.

The proposed positioning of pembrolizumab in the treatment pathway (Figure 4) is expected to displace the use of platinum-doublet chemotherapy, or gemcitabine in combination with paclitaxel as a second-line treatment option for patients with locally advanced or metastatic urothelial cancer, as well as displacing docetaxel or paclitaxel as a third-line treatment option for patients with locally advanced or metastatic urothelial cancer.

Figure 4: Treatment algorithm for locally advanced or metastatic urothelial bladder cancer with proposed positioning of pembrolizumab



[1]Although this use is common in UK clinical practice, at the time of publication (February 2015), carboplatin in combination with gemcitabine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

[2]Although this use is common in UK clinical practice, at the time of publication (February 2015), carboplatin in combination with paclitaxel did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[3]Although this use is common in UK clinical practice, at the time of publication (February 2015), gemcitabine in combination with paclitaxel did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

3.4: Information about the life expectancy of people with the disease or condition in England and the source of the data

Urothelial cancer is the predominant histologic type of urinary tract cancer in the UK accounting for approximately 90% of bladder, renal pelvis, ureter and urethra cancers.[27]Whilst bladder is the 7th most commonly diagnosed cancer in the UK,[1] urothelial cancer of the renal pelvis is significantly less common, accounting for 7% of all diagnosed kidney cancers, and urothelial cancer of the ureter is 4 times less likely to occur than in the kidney.[28-30]

Urothelial cancer is potentially curable when diagnosed at an early stage; however approximately 14% of those diagnosed with bladder cancer present at stage IV displaying metastases, which is associated with a poor prognosis. In England alone there were 4,504 deaths from bladder cancer in 2014.[31]

An unusual attribute of bladder cancer is that there is a significant difference (approximately 11%) between the percentage of men and women surviving at 1 year following diagnosis; this phenomenon has been reported worldwide with a number of potential rationales, such as sex hormones, tumour biology and earlier diagnosis in men, postulated to explain the difference.[52]

Survival at 1 year is as high as 94% when diagnosed with stage I disease, but this drops to 33% for those diagnosed with stage IV disease. In contrast to the 1-year survival statistics, 5-year survival statistics show that for those diagnosed with stage I disease, estimated 5-year survival drops to 86-89%, whereas for those diagnosed with stage IV disease, estimated 5-year survival is only 9-11%, which is reflective of the poor prognosis for those with late stage bladder cancer.[44]

The number of expected cases of cancers of the urinary system for 2017 in England is 10,205; of which 90% are expected to be transitional in histology and 14% are stage IV at time of diagnosis. In total, 502 patients are expected to be eligible for treatment with pembrolizumab in the second line setting (see Table 5 and section 6.2).

Table 5: Estimated patient numbers for England, 2017-2021

Year	2017	2018	2019	2020	2021
Total urothelial cancer cases	10,205	10,352	10,501	10,653	10,806
Total stage IV urothelial cancer cases	1,286	1,304	1,323	1,342	1,362
Total 2L stage IV patients with urothelial cancer	502	510	517	524	532

3.5: Details of relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used

The clinical pathway of care for patients with locally advanced or metastatic bladder cancer, according to the NICE guideline for the diagnosis and treatment of bladder cancer (NG2)[46] has been described in Section 3.3.

In January 2013, NICE issued technology appraisal guidance (TA272)[51] confirming that vinflunine is not recommended within its marketing authorisation for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy.

In December 2015, NICE published Quality Standards (NICE QS106)[53] that define clinical best practice regarding the diagnosis and management of bladder cancer in adults.

3.6: Details of other clinical guidelines and national policies

Details of other clinical guidelines and national policies are summarised below:

European Association of Urology (EAU) (2016)[54]

EAU published clinical practice guidelines in 2016 to provide evidence-based advice to support urologists in the management of patients with muscle invasive and metastatic bladder cancer.

The guidelines recommended that for patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.

European Society for Medical Oncology (ESMO)[55]

ESMO has recently published updated clinical practice guidelines concerning the diagnosis, treatment and follow-up of bladder cancer.

The guideline finds the data for second line treatment of metastatic bladder cancer highly variable. It recommends that patients with poor comorbid status or impaired renal function receiving second line treatment, who have disease progression less than 12 months from the initial treatment, should be given the option of either vinflunine or a taxane based chemotherapy. Patients with poor comorbid status or impaired renal function who have disease progression more than 12 months from the initial treatment should be given the option of platinum based re-challenge.

Patients with progressed metastatic disease who have poor renal function but are physically fit (ECOG status of ≤2) may receive best supportive care or seek novel treatments through enrollment in a clinical trial.

National Comprehensive Cancer Network (NCCN) [56]

The National Comprehensive Cancer Network state in their guidelines for the treatment of bladder cancer that, although no standard therapy exists in the second line treatment of urothelial carcinoma, single-agent taxane or gemcitabine are among the preferred agents.

Scottish Intercollegiate Guidelines Network[57]

In 2005, SIGN produced a guideline for the Management of transitional cell carcinoma of the bladder; however as it is over ten years old, it has been withdrawn from the public domain.

3.7: Issues relating to current clinical practice, including variations or uncertainty about established practice

We are not aware of any issues relating to current clinical practice. A comprehensive NICE guideline regarding the diagnosis and treatment of bladder cancer is available (see section 3.5 above) and provides clear recommendations.

3.8: Equality issues

We do not anticipate any equity or equality issues.

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1: Systematic review

A systematic literature review was conducted according to a previously prepared protocol, to identify relevant studies to inform both direct and indirect comparisons between the interventions included in this submission. Further details are provided below.

4.1.2: Search strategy description

A systematic literature search was conducted June 08, 2016 in Medline, EMBASE, and Cochrane Central Register of Controlled Trials databases, from inception to present. The database searches were supplemented with searches of the clinical trial registries (US National Institute of Health's (NIH) ClinicalTrials.gov and the EU Clinical Trials register) and manual searches of conference proceedings from the American Society of Clinical Oncology (ASCO), European Association of Urology (EAU), and the European Society for Medical Oncology (ESMO) (for the past two years). Additionally, the company's own records were checked to identify additional study information that had not yet been published in a peer-reviewed journal.

The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design (PICOS criteria presented in Table 6), and also incorporated a study design filter to identify randomised controlled trials (RCTs) (see Appendix 2 for full details of the search strategy by database). To meet the requirements of different regulatory authorities, all the comparators recommended for treatment of advanced/unresectable or metastatic urothelial carcinoma with progression after treatment with a platinum-based chemotherapy were included in the search strategy (see Appendix 2). However, to address the decision problem set by NICE, only studies with comparators relevant to the UK setting have been included (see PICOS eligibility criteria in Table 6). Cispatin+gemcitabine and MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) were added as interventions after the original search was run, so a separate search was conducted on February 08, 2017, in all three databases for these interventions, with all population and study design terms identical to the original search. Appendix 2 provides full details of the search strategy utilised.

4.1.3: Study selection

Description of the inclusion and exclusion selection criteria, language restrictions, and the study selection process

Two investigators working independently reviewed all abstracts and proceedings identified by the search. All citations identified as potentially relevant during abstract screening were then screened as full texts by the same two reviewers. Following reconciliation between the two investigators, a third investigator was included to reach consensus for any remaining discrepancies. Full articles were retrieved for further detailed assessment by the same reviewers. Discrepancies occurring between the two investigators were resolved by involving a third investigator and reaching consensus.

For selection of pembrolizumab specific studies, only the RCTs comparing pembrolizumab with any of the relevant comparators were included (see Table 6). For selection of studies which could be relevant for indirect and mixed treatment comparisons, those RCTs with comparisons between any of the interventions of interest were included (see section 4.10.1).

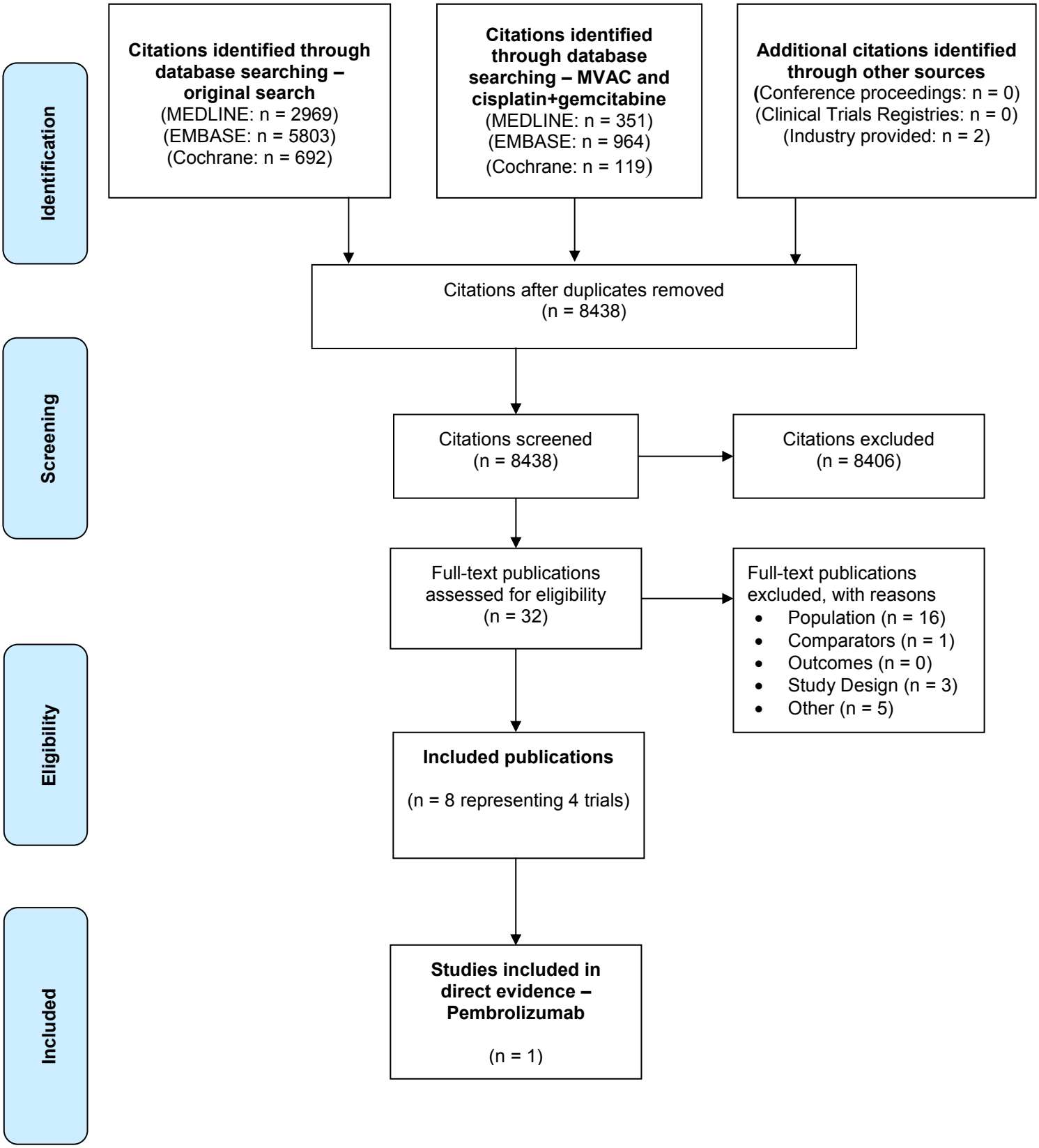
Table 6: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with advanced/unresectable or metastatic urothelial carcinoma recurring or progressing following platinum-based chemotherapy (2L)	
Intervention	Pembrolizumab / MK-3475	Any other intervention
Comparators	• Paclitaxel/Gemcitabine • Carboplatin/Paclitaxel • Cisplatin+gemcitabine • MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) • Docetaxel • Paclitaxel	Any other comparison
Outcomes	At least one of the following outcomes: • Overall survival (OS) • Progression-free survival (PFS) • Overall response rate • Time to Progression (TTP) • Duration of Response (DOR) • Serious (grade 3 and above) adverse events (not used for study selection) • Immune-related toxicity (regardless of grade) • Health Related Quality of Life (HRQoL)*	Other efficacy and safety outcomes to be considered for analysis, but each study must include at least one of those presented to the left
Study design	Randomised controlled trials (RCTs)	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	English	Any other language
*Note: Studies were not to be included based on reporting of adverse events; * – HRQoL scales were not limited during the screening process*		

4.1.4: Flow diagram of the numbers of studies included and excluded at each stage

The electronic searches yielded 10,898 citations (Medline: n = 3,320; EMBASE: n = 6,767; Cochrane Clinical Trial Registry: n = 1,503) through the database searches. No additional citations were identified through searches of conference proceedings or clinical trial registries. Of the 10,898 citations identified, 31 were selected for full text review. Of these, 25 were excluded for not meeting the PICOS criteria. Two company records were added at this stage (KEYNOTE 045 conference proceeding and clinical study report)[16, 17] giving rise to four studies (three primary and three secondary publications, plus one CSR and one conference proceeding) that were included in the evidence base for the potential network of indirect evidence (see section 4.10). As shown in the PRISMA flow diagram (Figure 5) one study, KEYNOTE-045 (reported in one conference proceeding and one clinical study report [CSR][16, 17] which met the inclusion/exclusion criteria of the systematic review (Table 6), provides the evidence base for the direct evidence of pembrolizumab in the population covered by the decision problem. A complete reference list of the included studies has been provided in Appendix 3.

Figure 5: PRISMA flow diagram of the systematic review process



4.1.5: Single study data drawn from multiple sources

A list of studies relevant to the decision problem is given in Table 7.

KEYNOTE-045 data consists of one conference proceeding[17] and one CSR[16] (in addition to an entry in clinicaltrials.gov[58])

4.1.6: Complete reference list for excluded studies

A complete reference list for excluded studies (and the reason for exclusion) has been provided in Appendix 3.

4.2 List of relevant randomised controlled trials

4.2.1: List of relevant RCTs involving the intervention of interest

Table 7: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
KEYNOTE-045	• Histologically or cytologically-confirmed diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra. • Experienced progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (cisplatin or carboplatin) • Received no more than two prior lines of systemic chemotherapy for metastatic urothelial cancer. • Measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. • ECOG Performance status of 0, 1 or 2	Pembrolizumab 200 mg IV Q3W	SOC (comprised of one of the following): • Paclitaxel 175 mg/m2 Q3W • Docetaxel 75 mg/m2 Q3W • Vinflunine 320 mg/m2 Q3W	• ClinicalTrials.gov reference: NCT02256436[58] • KEYNOTE-045 Clinical Study Report[16] • KEYNOTE-045 conference proceeding[17]

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1: Key aspects of listed RCTs

KEYNOTE-045[16, 17]

Trial design:

KEYNOTE-045 was a randomised, active-controlled, multi-site, open-label phase III trial of intravenous (IV) pembrolizumab monotherapy versus investigator's choice of either paclitaxel, docetaxel or vinflunine, in patients with metastatic or locally advanced/unresectable urothelial cancer that had recurred or progressed following platinum-containing chemotherapy.

After a screening phase of 42 days, patients were randomised in a 1:1 ratio to receive pembrolizumab 200 mg IV every 3 weeks (Q3W) or the control, which comprised of the investigator's choice of one of the following standard of care (SOC) chemotherapy regimens listed below:

- Paclitaxel 175 mg/m^2 Q3W
- Docetaxel 75 mg/m^2 Q3W
- Vinflunine 320 mg/m^2 Q3W

Investigators had to select one treatment among the control arm options before randomisation occurred, to use in the event that the subject was randomised to the control arm.

Randomisation occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS), and was stratified according to the following factors:

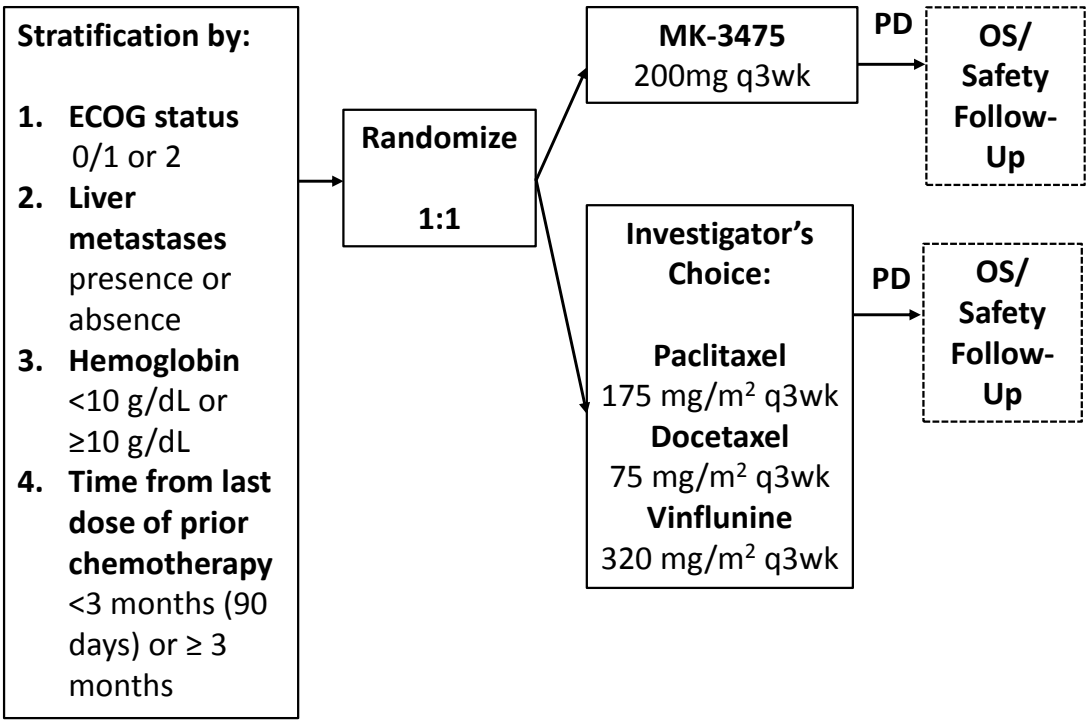
- Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1vs. 2)
- Presence or absence of liver metastases
- Haemoglobin (≥ 10 g/dL vs. <10 g/dL)
- Time from completion of most recent chemotherapy (<3 months or ≥3 months [90 days])

Subjects with ECOG 2 could only be enrolled if liver metastases were absent, haemoglobin is ≥10 g/dL, and time from completion (last dose) of most recent

chemotherapy is ≥ 3 months (90 days).

The design of KEYNOTE-045 is depicted in Figure 6 below:

Figure 6: Study design of KEYNOTE-045



Note: The overall proportion of subjects receiving vinflunine in the control arm was initially planned to be capped at approximately 35%, however, the cap was never implemented Vinflunine was a comparator option only in countries in which vinflunine was approved for the treatment of metastatic urothelial carcinoma. Docetaxel was a comparator option only for subjects with a total bilirubin ≤1 × upper limit of normal (ULN), and an aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤1.5 × ULN if alkaline phosphatase was also >2.5 × ULN.
MK3475 = pembrolizumab
Q3W = every 3 weeks

KEYNOTE-045 was an open-label trial; therefore, the study Sponsor, investigator and patients were aware of the treatment administered.

Although the trial was open label, analyses or summaries generated by randomised treatment assignment, actual treatment received, and/or PD-L1 biomarker status was limited and documented. Access to the allocation schedule for summaries or analyses was restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who had no other responsibilities associated with the study.

In addition, imaging data for the primary analysis were centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment, in order to minimise bias in the response assessments.

Further details concerning the dose selection and timing of dose administration for the pembrolizumab arm is provided in Appendix 4.

The first on study radiographic imaging assessment was performed at 9 weeks (±7 days) from randomisation and then every 6 weeks (±7 days) thereafter or more frequently if clinically indicated.

Treatment on study continued until one of the following:

- Radiographic disease progression as determined by the investigator/site radiologist
- Unacceptable adverse experiences (AEs)
- Intercurrent illness that prevented further administration of treatment
- Investigator's decision to withdraw the subject
- The subject had a confirmed positive serum pregnancy test
- Non-compliance with trial treatment or procedure requirements
- The subject was lost to follow-up
- Completed 24 months of treatment with pembrolizumab (Note: 24 months of study medication was calculated from the date of first dose. Patients who stopped pembrolizumab after 24 months could be eligible for up to1 year of additional study treatment if they progressed after stopping study treatment provided they met the requirements as specified in the study protocol)
- Administrative reasons
- Withdrawal of consent for treatment

When a subject discontinued/withdrew from participation in the trial, all applicable activities scheduled for the final trial visit were performed at the time of discontinuation. A subject who discontinued from the trial was not replaced.

Discontinuation of treatment was to be considered for subjects in the pembrolizumab arm who had attained a confirmed CR that had been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who subsequently experienced radiographic disease progression could be eligible for up to 1 year of additional treatment with pembrolizumab at the discretion of the

Investigator if no cancer treatment had been administered since the last dose of pembrolizumab, the subject met the safety parameters listed in the Inclusion/Exclusion criteria, and the trial was open. This retreatment is termed the Second Course Phase of this study. Subjects resumed therapy at the same dose and schedule at the time of initial discontinuation, and treatment was to be administered for up to one additional year. Response or progression in the Second Course Phase did not count towards the ORR and PFS of the primary endpoint in this trial.

Each subject in KEYNOTE-045 was followed for 30 days after the end of treatment, for AE monitoring (serious adverse events (SAEs) were collected for 90 days after the end of treatment). Subjects who discontinued for reasons other than PD had post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented PD, each subject was followed by telephone for OS every 12 weeks until death, withdrawal of consent, or the end of the trial, whichever occurred first.

Eligibility criteria:

The key inclusion/exclusion criteria are provided below:

Key inclusion criteria:

A patient must have met all of the following criteria to be eligible to participate in this study:

- Be willing and able to provide written informed consent/assent for the trial.
- Be ≥18 years of age on day of signing informed consent.
- Have histologically or cytologically-confirmed diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies were allowed, but transitional cell carcinoma had to be the predominant histology. Subjects with non-urothelial cancer of the urinary tract were not allowed.
- Have had progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (cisplatin or carboplatin):
    - Received a first-line platinum-containing regimen in the metastatic setting or for inoperable locally advanced disease; or
    - Received adjuvant platinum-containing therapy following cystectomy for localised muscle-invasive urothelial cancer, with recurrence/progression ≤12 months following completion of therapy; or

- Received neoadjuvant platinum-containing therapy prior to cystectomy for localised muscle-invasive urothelial cancer, with recurrence ≤12 months following completion of therapy.

  Note: Primary chemoradiation given for subjects who were not considered surgical candidates was not considered a line of therapy for the purpose of this study.

  Note: Subjects with locally advanced unresectable disease who subsequently became eligible for surgery after platinum containing therapy were not eligible for this study, unless they subsequently had disease recurrence in the metastatic setting

- Have received no more than two prior lines of systemic chemotherapy for metastatic urothelial cancer.
  - Subjects for whom the most recent therapy had been a non-platinum-based regimen following progression/recurrence on platinum-based therapy (i.e. third-line subjects) were eligible if they had progressed/recurred on their most recent therapy.

    Note: primary chemoradiation for unresectable muscle-invasive bladder cancer with the aim of bladder preservation was not considered a prior line of systemic therapy for the purposes of determining study eligibility.
- Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated.
- Have measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist.
- Have a performance status of 0, 1 or 2 on the ECOG Performance Scale, as assessed within 10 days prior to treatment initiation.
- Demonstrated adequate organ function as defined in the study protocol.
- Female subjects of childbearing potential had to have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication.
- Female subjects of childbearing potential had to be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab or 180 days after the last dose of paclitaxel, docetaxel or vinflunine.
- Male subjects had to agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study pembrolizumab or 180 days after the last dose of paclitaxel, docetaxel or vinflunine.

Key exclusion criteria

Subjects were excluded from participating in the trial if they met any of the following criteria:

- Had disease that was suitable for local therapy administered with curative intent.
- Was currently participating in or had participated in a study of an investigational agent or was using an investigational device within 4 weeks prior to the first dose of trial treatment.
- Had a diagnosis of immunodeficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids could have been approved after consultation with the Sponsor.
- Had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who had not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
- Had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who had not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to a previously administered agent.
  Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia were an exception to this criterion and could qualify for the study.
  Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Had a known additional malignancy that was progressing or required active treatment. Exceptions included basal cell carcinoma of the skin, squamous cell carcinoma of the skin that had undergone potentially curative therapy or *in situ* cervical cancer. A history of prostate cancer that was identified incidentally following cystoprostatectomy for bladder cancer was acceptable, provided that the following criteria were met: Stage T2N0M0 or lower; Gleason score ≤6, prostate specific antigen undetectable
- Had known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
- Had an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that required systemic or immunosuppressive agents.
- Had active cardiac disease, defined as:
  - Myocardial infarction or unstable angina pectoris within 6 months of the first date of study therapy.

    - History of serious ventricular arrhythmia (i.e. ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.
    - New York Heart Association (NYHA) Class III or greater congestive heart failure, or left ventricular ejection fraction of < 40%.
- Had evidence of interstitial lung disease or active non-infectious pneumonitis.
- Had an active infection requiring systemic therapy.
- Had a history of severe hypersensitivity reaction to paclitaxel or to other drugs formulated with polyoxyethylated castor oil, to docetaxel or other drugs formulated with polysorbate 80, or to vinflunine or other vinca alkaloids.
- Required ongoing therapy with a medication that was a strong inhibitor of the CYP3A4 enzymes.
- Had a history or current evidence of any condition, therapy, or laboratory abnormality that could confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or was not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Had known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Was pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
- Had received prior therapy with an anti-PD-1 or anti-PD-L1 agent, or with an agent directed to another co-inhibitory T-cell receptor.
- Had received prior chemotherapy for urothelial cancer with all available study therapies in the control arm (i.e. both prior paclitaxel and docetaxel in regions where vinflunine is not an approved therapy, or prior paclitaxel, docetaxel and vinflunine in regions where vinflunine is an approved therapy).
- Had a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).
- Had known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- Had received a live virus vaccine within 30 days of planned start of trial treatment.

Settings and locations where the data were collected:

This was a global study conducted in 29 countries: Japan, United States, Israel, Italy, Spain, France, Hungary, Taiwan, Austria, Denmark, Germany, Turkey, Australia, the Netherlands, South Korea, Belgium, Canada, Chile, New Zealand, Norway, Portugal, Romania, United Kingdom, Ireland, Peru, Poland, Puerto Rico, Singapore, and Sweden .

Four patients from the UK participated in the study at two UK sites.

Trial drugs and concomitant medications:

Subjects were randomised in a 1:1 ratio to receive IV pembrolizumab 200mg Q3W or the control, which comprised the investigator's choice of SOC chemotherapy (paclitaxel, docetaxel or vinflunine). Details of the trails treatments are provided in Table 8 below:

Table 8: KEYNOTE-045 trial treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle	Experimental
Paclitaxel[a]	175 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator
Docetaxel[a]	75 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator
Vinflunine[b]	320 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator

[a] In case of mild hepatic impairment (total bilirubin ≥ 1.25 × ULN), paclitaxel was to be started at a dose of 135 mg/m^2. Docetaxel was a comparator option only for subjects with a total bilirubin ≤ 1 × ULN, and an AST and/or ALT ≤ 1.5 × ULN if alkaline phosphatase was also > 2.5 × ULN.

[b] In case of ECOG-PS of ≥ 1 or ECOG-PS of 0 and prior pelvic irradiation, vinflunine was to be started at a dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose was to be increased to 320 mg/m^2 Q3W for the subsequent cycles. See Section 5.2.1.2.1 of the protocol [16.1.1] for additional guidelines on dose modification for vinflunine, including starting doses in the setting of mild renal and hepatic impairment and in the elderly.

Note: Vinflunine was only a comparator option in countries where vinflunine was approved for the treatment of metastatic urothelial cancer.

IV = intravenous

For the control chemotherapy options, Investigators had to select one treatment among the control arm options before randomisation occurred to use in the event that the subject was randomised to the control arm.

Concomitant medications

All treatments that the Investigator considered necessary for a subject's welfare could be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medications were recorded on the electronic case report form

(eCRF) including all prescription, over the counter, herbal supplements, and intravenous (IV) medications and fluids. If changes occurred during the trial period, documentation of drug dosage, frequency, route, and date were to be included on the eCRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment were to be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment were to be recorded for SAEs and events of clinical interest (ECIs). Further details of acceptable and prohibited concomitant medications are provided in Appendix 5.

Primary, secondary and tertiary objectives

Primary objectives:

- To evaluate progression-free survival (PFS) per RECIST 1.1 by blinded independent radiologists' (BICR) review of **all subjects** with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

- To evaluate the overall survival (OS) of **all subjects** with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy (recurrent/progressive metastatic urothelial cancer), when treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

- To evaluate the PFS per RECIST 1.1 by BICR review of subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 positive** urothelial cancer treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine.

- To evaluate the OS of subjects with platinum-refractory metastatic or locally advanced/unresectable **PD-L1 positive** urothelial cancer, when treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine.

- To evaluate the PFS per RECIST 1.1 by BICR review of subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 strongly positive** urothelial cancer treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine.

- To evaluate the OS of subjects with platinum-refractory metastatic or locally advanced/unresectable **PD-L1 strongly positive** urothelial cancer, when treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine

The study was considered to have met its primary objective if the pembrolizumab arm was superior to paclitaxel, docetaxel or vinflunine at an interim or final analysis when considering any of the above primary endpoints.

PD-L1 expression of CPS (combined positive score) ≥1% was described in the protocol as **PD-L1 positive**. **Strongly positive PD-L1 expression** was defined as CPS ≥10% based on data from KEYNOTE-052 (external to KEYNOTE-045). The CPS consisted of the percentage of PD-L1–positive tumour cells (TCs) and infiltrating immune cells relative to the total number of TCs as measured using the PD-L1 IHC 22C3 pharmDx assay on samples collected by core needle or excisional biopsies or in resected tissue.

PFS was defined as the time from randomisation to the first documented progressive disease (PD) per RECIST 1.1 based on BICR review or death due to any cause, whichever occurred first.

OS was defined as the time from randomisation to death due to any cause. Patients without documented death at the time of the final analysis were to be censored at the date of the last follow-up.

Secondary objectives:

- To evaluate the safety and tolerability profile of pembrolizumab (MK-3475) in subjects with recurrent/progressive metastatic urothelial cancer.

- To evaluate the objective response rate (ORR) per RECIST 1.1. by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

- To evaluate PFS per modified RECIST 1.1 by BICR review of PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

- To evaluate the objective response rate (ORR) per modified RECIST 1.1 by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

- To evaluate response duration per RECIST 1.1 by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

- To evaluate PFS per RECIST 1.1 from randomisation to specific time points (6 months, 12 months) by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK -3475) compared to paclitaxel, docetaxel or vinflunine.

ORR was defined as the proportion of the subjects in the analysis population who had either a complete response (CR) or partial response (PR). Responses were based upon BICR review per RECIST 1.1. A supportive analysis of ORR was conducted using site radiology review as defined in the Imaging Review Charter.

PFS and ORR per modified RECIST (mRECIST) were defined as specified for the respective endpoints using RECIST 1.1, with the exception that a confirmation assessment of progressive disease (PD) (at least 4 weeks after the initial PD assessment) was required for subjects who

remained on treatment following a documented PD per RECIST 1.1. Subjects who discontinued treatment following a documented PD assessment per RECIST 1.1 were counted as having disease progression on the date of the documented PD assessment. Supportive analyses were conducted using site radiology review as defined in the Imaging Review Charter.

For subjects who demonstrated CR or PR, response duration was defined as the time from first documented evidence of CR or PR until disease progression or death. Response duration for subjects who had not progressed or died at the time of analysis were to be censored at the date of their last tumour assessment. Response duration was to be calculated for RECIST 1.1 based on BICR review and site review.

Of note, the terms Blinded independent central review (BICR), blinded central radiologists' review and independent radiologists' review all refer to the blinded central radiology assessment and were used interchangeably throughout the study protocol and CSR[16].

Exploratory objectives:

- To evaluate changes in health-related quality-of-life (HRQoL) assessments from baseline in subjects with recurrent/progressive metastatic urothelial cancer using the EORTC QLQ-C30.

- To characterise utilities in previously-treated subjects with recurrent/progressive metastatic urothelial cancer using the EuroQol EQ-5D.

- To investigate the relationship between PD-L1 expression and response to pembrolizumab (MK-3475) treatment utilising newly obtained or archival FFPE tumour tissue.

- To investigate the relationship between pembrolizumab (MK-3475) treatment and biomarkers predicting response (e.g. immunohistochemistry, proteomic signatures, genetic variation, and gene expression signatures) utilising newly obtained or archival FFPE tumour tissue and blood.

- To evaluate PFS as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

Clinical procedures/ assessments

Biomarker assessment

Either an archival formalin-fixed, paraffin-embedded (FFPE) tumour sample or a newly obtained core or excisional biopsy (fine needle aspirate not adequate) was required to be submitted to a central laboratory for characterisation of PD-L1 expression. PD-L1 expression was evaluated prospectively in this trial. The tumour tissue had to be received by the central vendor and deemed adequate for evaluation prior to subject randomisation. If new scientific data emerged that indicated that an existing biopsy or surgical specimen was sub-optimal for identification of subjects, only new biopsies would be acceptable for determination of PD-L1 status.

Tumour imaging and assessment of disease

Tumour imaging could be performed by computed tomography (CT) or magnetic resonance imaging (MRI), but the same imaging technique should have been used in a subject throughout the trial. CT scan was the preferred imaging modality for this study. Bone scans were also utilised to assess osseous metastases. Additionally, plain X-ray evaluation was obtained for symptomatic sites with negative bone scan evaluations.

Local site investigator/radiology assessment based on RECIST 1.1 was used to determine subject eligibility. All scheduled images for all study subjects from the sites were submitted to the central imaging vendor. Also, additional imaging (including other modalities) that were obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, were also to be submitted to the central imaging vendor.

Initial tumour imaging

Initial tumour imaging was to be performed within 28 days prior to the first dose of trial treatment. The investigator/site radiologist must have reviewed pre-trial images to confirm the subject had measurable disease per RECIST 1.1. The baseline imaging scan should also have been submitted to the central imaging vendor. Bone scans were to be performed at baseline for all subjects.

Scans performed as part of routine clinical management were acceptable for use as the screening scan if they were of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. The same imaging technique was to be used in a subject throughout the trial.

Tumour imaging during trial

The first imaging assessment was to be performed at 9 weeks (63 days ±7 days) from randomisation. Subsequent imaging was to be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After the first 12 months on trial therapy, the imaging interval should have decreased to every 12 weeks (±7 days). Imaging should not have been delayed for delays in cycle starts or extension of pembrolizumab cycle intervals.

If radiologic imaging by local/site assessment showed PD, tumour assessment could be repeated by the site ≥ 4 weeks in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression (Table 9). If repeat imaging showed stable disease (SD), partial response (PR), or complete response (CR), treatment could be continued as per treatment calendar. If repeat imaging still met the threshold for PD (≥20% increase in tumour burden compared to nadir) but showed a reduction in tumour burden compared to the previous time point, treatment could be continued as per treatment calendar after consultation with Applicant. If repeat imaging confirmed PD without reduction in tumour burden compared with the previous time point, subjects were discontinued from study treatment. In determining whether or not the tumour burden had increased or decreased, Investigators were to consider all target lesions as well as non-target lesions.

The decision to continue study treatment after the first evidence of disease progression was at the Investigator's discretion based on the clinical status of the subject. Confirmatory imaging could be performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point (every 42 days ± 7 days) could be used as confirmation. Subjects could receive study treatment while waiting for confirmation of PD if they were clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease

- Absence of progressive tumour at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention
- Subjects exhibiting toxicity from trial therapy could not continue to receive trial therapy.

Table 9: KEYNOTE-045 - Imaging and pembrolizumab treatment after first radiologic evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD (no reduction in tumour burden from prior scan)	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan confirms PD (reduction in tumour burden from prior scan)	Continue regularly scheduled imaging assessments	Continue study treatment after consultation with Applicant	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator and Applicant's discretion
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion
NOTE: If a subject with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumour dimensions at the confirmatory scan (as assessed by the investigator and site radiologist), an exception may be considered to continue treatment upon consultation with the Sponsor.				

Imaging should have continued to be performed until disease progression was assessed by the investigator, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurred first. Disease progression may have been confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Subjects who had unconfirmed disease progression may have continued on treatment until progression was confirmed.

Bone scans

Bone scans were performed at baseline for all subjects. Subjects with positive bone scans at baseline were to be followed with additional scans performed at 9 weeks (Day 63 ±7 days) from randomisation. Subsequent scans were to be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After the first 12 months on trial therapy, the scanning interval should have been decreased to every 12 weeks (±7 days). Subjects with new symptoms concerning osseous metastasis (e.g. new persistently elevated alkaline phosphatase) were to be evaluated with a bone scan. Additionally, plain X-ray evaluation was to be obtained for symptomatic sites with negative bone scan evaluations. New osseous uptake, upon confirmation with CT, was to be assessed for progression per RECIST 1.1. Lytic/mixed lesions with soft tissue component may have been included in the evaluation of disease burden if it met measurability criteria while blastic lesions were considered non-measurable, in accordance with RECIST 1.1.

Tumour tissue collection and correlative blood sampling

Either an archival FFPE tumour sample or a newly obtained core or excisional biopsy (fine needle aspirate not adequate) must have been submitted to a central laboratory for characterisation of PD-L1 expression. PD-L1 expression was to be evaluated prospectively in this trial. The tumour tissue must have been received by the central vendor and been deemed adequate for evaluation prior to subject randomisation. If new scientific data emerged that indicated that an existing biopsy or surgical specimen is suboptimal for identification of subjects, only new biopsies would then be acceptable for determination of PD-L1 status. If a tumour biopsy was to be obtained from an intended target lesion during eligibility assessment, the biopsy should have been performed prior to obtaining the baseline scan. Otherwise a new baseline scan should have been obtained.

Blood for correlative biomarker studies should have been collected prior to Cycle 1, Cycle 2, Cycle 3 and at treatment discontinuation.

Patient Reported Outcomes (PROs)

The EuroQol EQ-5D and EORTC QLQ-C30 questionnaires were administered by trained site personnel and completed electronically by subjects.

Assessment of disease

For the purposes of the primary study endpoints, RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumour response and date of

disease progression. The primary analysis of PFS was based on BICR using RECIST 1.1. Supportive analyses based on Investigators' assessments using RECIST 1.1 were also performed.

Populations used for analysis:

The study population used for analysis of each endpoint is defined in section 4.4.2.

4.3.2: Comparative summary of the methodology of the RCTs

Table 10: Comparative summary of trial methodology

Trial number (acronym)	**KEYNOTE-045**[16, 17]
Location	Global study conducted in 29 countries: Japan, United States, Israel, Italy, Spain, France, Hungary, Taiwan, Austria, Denmark, Germany, Turkey, Australia, the Netherlands, South Korea, Belgium, Canada, Chile, New Zealand, Norway, Portugal, Romania, United Kingdom, Ireland, Peru, Poland, Puerto Rico, Singapore, and Sweden.
Trial design	Randomised, active-controlled, multi-site, open-label phase III trial of intravenous (IV) pembrolizumab monotherapy versus investigator's choice of either paclitaxel, docetaxel or vinflunine, in patients with metastatic or locally advanced/unresectable urothelial cancer that had recurred or progressed following platinum-containing chemotherapy. Tumour response centrally reviewed by blinded independent radiologists.
Key eligibility criteria for participants	• Histologically or cytologically-confirmed diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies were allowed, but transitional cell carcinoma had to be the predominant histology. Subjects with non-urothelial cancer of the urinary tract were not allowed. • Have had progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (cisplatin or carboplatin) • Have received no more than two prior lines of systemic chemotherapy for metastatic urothelial cancer. • Have measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. • Have a performance status of 0, 1 or 2 on the ECOG Performance Scale
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as out-patients.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=) and comparator(s) (n=)** **Permitted and disallowed concomitant medication**	Patients were randomised in a 1:1 ratio to receive pembrolizumab 200 mg IV Q3W (n= 270) or control (n= 272), which comprised of the investigator's choice of one of the SOC chemotherapy regimens listed below: • Paclitaxel 175 mg/m^2 Q3W • Docetaxel 75 mg/m^2 Q3W • Vinflunine 320 mg/m^2 Q3W Disallowed concomitant medicines: • Antineoplastic systemic chemotherapy or biological therapy • Immunotherapy not specified in this protocol • Chemotherapy not specified in this protocol • Investigational agents other than pembrolizumab • Radiation therapy • Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. • Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic aetiology. • Strong inhibitors or inducers of the CYP3A4 enzymes.

	• QT/QTc-prolonging drugs for subjects receiving vinflunine. Exclusion criteria list provides further details of other medications prohibited in this trial.
Primary outcomes (including scoring methods and timings of assessments)	The primary objectives were as follows: • To evaluate PFS per RECIST 1.1 by BICR review of all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine • To evaluate the OS of all subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy (recurrent/progressive metastatic urothelial cancer), when treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine. • To evaluate the PFS per RECIST 1.1 by BICR review of subjects with platinum-refractory recurrent/progressive metastatic PD-L1 positive urothelial cancer treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine • To evaluate the OS of subjects with platinum-refractory metastatic or locally advanced/unresectable PD-L1 positive urothelial cancer, when treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine • To evaluate the PFS per RECIST 1.1 by BICR review of subjects with platinum-refractory recurrent/progressive metastatic PD-L1 strongly positive urothelial cancer treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine • To evaluate the OS of subjects with platinum-refractory metastatic or locally advanced/unresectable PD-L1 strongly positive urothelial cancer, when treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine PD-L1 expression of CPS ≥1% was described in the protocol as PD-L1 positive. Strongly positive PD-L1 expression was defined as CPS ≥10%. PFS was defined as the time from randomisation to the first documented progressive disease (PD) per RECIST 1.1 based on BICR review or death due to any cause, whichever occurred first. OS was defined as the time from randomisation to death due to any cause. Patients without documented death at the time of the final analysis were to be censored at the date of the last follow-up. ITT population served as the primary population for the analyses of PFS and OS. The first on-study imaging assessment was performed at 9 weeks (63 days ±7 days) from randomisation. Subsequent imaging was to be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After the first 12 months on trial therapy, the imaging interval should have decreased to every 12 weeks (±7 days) Subjects who discontinued pembrolizumab after attaining a CR (that had been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared), may have been eligible for re-treatment in the Second Course Phase after experiencing PD, at the discretion of the investigator. Response or progression

	in the Second Course Phase did not count towards the ORR and PFS of the primary endpoint in this trial. Retreatment was limited to 1 year of additional treatment in the second course phase.
Secondary/ tertiary outcomes (including scoring methods and timings of assessments)	The secondary objectives were as follows: • To evaluate the safety and tolerability profile of pembrolizumab (MK-3475) in subjects with recurrent/progressive metastatic urothelial cancer. • To evaluate the ORR per RECIST 1.1. by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine. • To evaluate PFS per modified RECIST 1.1 by BICR review of PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine. • To evaluate the ORR per modified RECIST 1.1 by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine. • To evaluate response duration per RECIST 1.1 by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine. • To evaluate PFS per RECIST 1.1 from randomisation to specific time points (6 months, 12 months) by BICR review in PD-L1 strongly positive, PD-L1 positive and all subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK -3475) compared to paclitaxel, docetaxel or vinflunine ORR was defined as the proportion of the subjects in the analysis population who had either a CR or PR. Responses were based upon BICR review per RECIST 1.1. A supportive analysis of ORR was conducted using site radiology review as defined in the Imaging Review Charter.
Pre-planned subgroups	Subgroup analyses based on clinically relevant baseline patient or tumour characteristics as per study protocol: • Age category (≤65 vs. >65 years) • PD-L1 subgroup (positive vs. negative) • High PD-L1 subgroup (to be defined based on emerging external data) • Sex (female vs. male) • Race (white vs. non-white) • ECOG status (0 / 1 vs. 2 and 0 vs 1 / 2) • Geographic region of enrolling site (East Asia vs. non-East Asia and EU vs. non-EU) • Prior platinum therapy (carboplatin vs. cisplatin)

	• Setting of most recent prior therapy (neoadjuvant vs. adjuvant vs. 1L metastatic vs. 2L metastatic) • Presence or absence of liver metastases at baseline • Baseline haemoglobin (≥ 10 g/dL vs. <10 g/dL) • Time from completion/discontinuation of most recent prior therapy to baseline (<3months vs. ≥3 months) • Histology (transitional cell vs. mixed transitional/non-transitional histology) • Smoking status (never vs. former vs. current) • Brain metastasis status (prior brain metastasis vs. no prior brain metastasis) • Investigators' choice of paclitaxel, docetaxel or vinflunine • Burden of disease in terms of baseline tumour volume
ITT = intention to treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RR = response rate; CR = complete response; PR = partial response	

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

4.4.1: Statistical analysis:

KEYNOTE-045[16, 17]

Primary hypotheses

The primary hypotheses of the KEYNOTE-045 study were as follows:

- **Hypotheses (H1):** Pembrolizumab (MK-3475) prolongs PFS per RECIST 1.1 by BICR review in **all subjects** with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel or vinflunine.
- **Hypothesis (H2):** Pembrolizumab (MK-3475) prolongs OS in **all subjects** with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel or vinflunine
- **Hypotheses (H3):** Pembrolizumab prolongs PFS per RECIST 1.1 by BICR review in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.
- **Hypothesis (H4):** Pembrolizumab prolongs OS in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.
- **Hypotheses (H5):** Pembrolizumab prolongs PFS per RECIST 1.1 by BICR review in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 strongly positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

- **Hypothesis (H6):** Pembrolizumab prolongs OS in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 strongly positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

Analysis and stopping guidelines

The primary efficacy endpoints were PFS (i.e. time from randomisation to documented PD or death due to any cause, whichever occurred first) and OS (i.e. time from randomisation to death due to any cause) in PD-L1 CPS ≥10%, PD-L1 CPS ≥1%, and all subjects. The primary analysis of PFS was based on BICR using RECIST 1.1. Supportive analyses based on Investigators' assessments using RECIST 1.1 were also performed. The secondary endpoints included PFS per mRECIST, ORR per RECIST 1.1, and modified RECIST based on BICR.

Since disease progression is assessed periodically, progressive disease (PD) could occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD was documented. For the primary analysis, for the subjects who have PD, the true date of disease progression was to be approximated by the date of the first assessment at which PD was objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Death was always considered as a confirmed PD event. Sensitivity analyses were planned to be performed for comparison of PFS based on investigator's assessment.

Two interim analyses were planned based on all subjects and PD-L1 strongly positive subjects (CPS ≥10%). For PD-L1 positive subjects (CPS ≥1%), the hypotheses of PFS and OS were only tested at the first interim analysis (IA1). The futility bounds of this trial were nonbinding and the bounds were considered guidance rather than strict bounds. Results of the interim analysis were to be reviewed by an external data monitoring committee (eDMC).

The timing, sample size, and decision guidance for the planned PFS and OS analyses for PD-L1 CPS ≥10% and all subjects under one hypothetical scenario with initially assigned type I rates only are summarised in Table 11. The futility boundaries of the OS hypotheses at the interim analysis are summarised in Table 12. The actual boundaries were to be determined from the actual number of PFS or OS events at the time of the specified interim analysis using the alpha and beta spending functions.

The study protocol specified that the final analysis would take place when approximately 370 deaths in all subjects and 110 deaths in PD-L1 CPS ≥10% subjects have occurred between the pembrolizumab arm and the standard treatment arm in all subjects, which is expected to occur ~30 months after trial start. If the timing of events occur faster than anticipated, the test boundary at the final analysis is to be adjusted to use the remaining Type I error not spent at earlier analyses. A 95% confidence interval (CI) is to be provided for the hazard ratio to characterise the OS effect in the case that superiority is not demonstrated.

Table 11: KEYNOTE-045 Summary of timing, sample size and decision guidance at the planned PFS and OS analyses

Analysis	Criteria for Conduct of Analysis (Projected timing)	Value	Approx. Number of Events	Efficacy Boundary†		
				Z Statistic	p-value (1-sided) at Boundary	Approx. Observed HR at Boundary
IA 1: PFS (H1, H3, H5) OS (H2, H4, H6)	Full enrollment ~ 185 OS events (50% information) for all subjects	H1 PFS All Subjects	273	3.500	0.0002	0.655
		H2 OS All Subjects	185	3.494	0.0002	0.598
		H3 PFS CPS ≥1%	151	3.500	0.0002	0.566
		H4 OS CPS ≥1%	99	2.913	0.0018	0.557
		H5 PFS PD-L1 CPS ≥10%	89	3.196	0.0007	0.508
		H6 OS PD-L1 CPS ≥10%	55	3.384	0.0004	0.402
IA 2: PFS (H1 and H5) OS (H2 and H6)	~277 OS events (75% information) for all subjects and ~ 82 OS events (75% information) for PD-L1 Strongly Positive Subjects	H1 PFS All Subjects	357	3.345	0.0004	0.702
		H2 OS All Subjects	277	2.683	0.0036	0.725
		H5 PFS PD-L1 CPS ≥10%	116	2.865	0.0021	0.588
		H6 OS PD-L1 CPS ≥10%	82	2.745	0.0030	0.546
Final Analysis: PFS (H1and H5)	~ 370 OS events for all subjects and ~110 OS events for PD-	H1 PFS All Subjects	420	3.182	0.0007	0.733
		H2 OS All Subjects	370	2.381	0.0086	0.781
		H5 PFS PD-L1	137	2.782	0.0027	0.622

OS (H2 and H6)	L1 Strongly Positive Subjects	CPS ≥10%				
		H6 OS PD-L1 CPS ≥10%	110	2.459	0.0070	0.625
† Based on initially assigned type I error rate before any alpha roll-over and projected number of events at trial mile stones. Actual efficacy boundaries will be based on actual numbers of events available at trial milestones.						

Table 12: Summary of Futility Boundary at the Planned Interim Analyses on OS

Analysis	Value	Approx. Number of Events	Non-binding Futility Boundary		
			Z Statistic	p-value (1-sided) at Boundary	Approx. Observed HR at Boundary
IA 1	H2 OS All Subjects	185	-1.767	0.961	1.297
	H4 OS PD-L1 Positive	99	-1.938	0.974	1.476
	H6 OS PD-L1 Strongly Positive	55	-1.715	0.957	1.587
IA 2	H2 OS All Subjects	277	0.100	0.460	0.988
	H6 OS PD-L1 Strongly Positive	82	0.148	0.441	0.968
For demonstration purpose, the beta in this table is based on initially assigned alpha only; actual futility bounds will be updated if overall beta is changed with respect to alpha roll-over.					

For PFS hypotheses (H1, H3 and H5), a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) was constructed to implement group sequential boundaries that control the type I error rates. The pembrolizumab arm was to be compared to the paclitaxel, docetaxel or vinflunine arm. At IA1, an approximate observed HR of ~0.655 or less would demonstrate PFS superiority for all subjects at α = 0.02% (onesided).

This hazard ratio corresponds to approximately 2.1 month improvement over the median PFS of 4 months in the paclitaxel, docetaxel or vinflunine arm. However, because immunotherapies have been shown to impact PFS curves at later time points (i.e. the tail of the curve), the observed difference in medians may be an underrepresentation of the treatment effect. If there were fewer than or more than the projected number of PFS events at the time of the IA1, the alpha functions were to be adjusted to accommodate the revised interim analysis timing using the fraction of the estimated total PFS events.

For all OS hypotheses (H2, H4 and H6), a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) and beta-spending function with gamma (-20) were constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis.

Sample size

The trial planned to randomise 470 subjects in a 1:1 ratio between pembrolizumab and the standard treatment arm. The trial was event driven and the sample size calculation was driven by survival events. Assuming the prevalence rates of PD-L1 CPS ≥1% subjects and PD-L1 CPS ≥10% subjects among the overall population would be 55% and 33%, respectively, a sample size of 470 all subjects would provide approximately 260 PD-L1 CPS ≥1% subjects and 156 PD-L1 CPS ≥10% subjects.

The sample size and power calculation of PFS was based on the following assumptions:

- PFS follows an exponential distribution with a median of 4 months in the standard treatment arm;
- The true hazard ratios between pembrolizumab and standard therapy are 0.45, 0.5, and 0.5 for PD-L1 CPS ≥10%, PD-L1 CPS ≥1%, and all subjects, respectively;
- An enrolment period of 12 months;
- A yearly drop-out rate of 5%.

The numbers of PFS events in PD-L1 CPS ≥10% and all subjects at the final PFS evaluation were estimated to be 137 and 420, respectively. The trial provides 97% power for the PFS hypothesis in PD-L1 CPS ≥10% subjects and >99% power for the PFS hypothesis in all subjects.

The final OS analysis is to be carried out after approximately 370 deaths in all subjects and 110 deaths in PD-L1 CPS ≥10% subjects have occurred between the pembrolizumab arm and the standard treatment arm for all subjects, barring early stopping for futility or efficacy. With the above numbers of events and before any alpha roll over, the trial provides 88% and 86% power to demonstrate superiority of OS of pembrolizumab relative to standard therapy at the pre-specified initial alpha (one sided) levels in PD-L1 CPS ≥10% and all subjects, respectively. The sample size and power calculation of OS were based on the following assumptions:

- OS follows an exponential distribution with a median of 8 months in the standard treatment arm;
- The hazard ratio for OS between pembrolizumab and standard treatment is 0.5, 0.6, and 0.7 for PD-L1 CPS ≥10%, PD-L1 CPS ≥1%, and all subjects, respectively (deemed to be clinically meaningful in this population);

- An enrolment period of 12 months and a minimum of 18 months follow up after enrolment completion;
- A yearly drop out rate of 2%.

Multiplicity

Full details on the strategy to address multiplicity issues with regard to multiple efficacy endpoints and multiple analyses is described in Appendix 6.

Based on emerging biomarker data external to this trial, the initial alpha allocation among the primary hypotheses was revised in a subsequent protocol amendment to reflect the change in biomarker strategy. The re-allocation of alpha was to occur after the conduct of IA1, and proper adjustment has been made to maintain the control of Family-wise type 1 error rate (FWER) with the implementation of this change. The type I error actually spent at IA1 was to be kept intact and the reallocation was to be applied only to the remaining unspent alpha. The family wise type I error rate for this trial was to be strongly controlled at 2.5% (one sided) across all primary hypotheses on PFS and OS and the secondary hypothesis on ORR (full details in Appendix 6). The alpha spent at IA1 was based on the assumption of the planned information fractions along with the original pre-specified alpha allocation prior to Amendment 13 by the pre-specified alpha spending function of Hwang Shih DeCani (HSD) with gamma parameter (-4).

Under the revised alpha allocation, the alpha spending at IA2 and final analysis were determined by first applying the same HSD gamma (-4) spending function to distribute unspent alpha to IA2 and final analysis, respectively, and then incorporating them with the alpha that has already been spent at IA1 to form an interpolated alpha spending among the 3 analyses.

Statistical methods used to compare groups for primary and secondary outcomes

The statistical methods and analysis strategy for the primary and secondary efficacy endpoints are summarised in the Table 13 below.

Table 13: KEYNOTE-045: Efficacy analysis methods for primary and secondary efficacy endpoints

Endpoint/Variable (Description, Time Point)	Primary (P) or Supportive (S) Approach	Statistical Method	Analysis Population†	Missing Data Approach
Primary Endpoints:				
PFS (RECIST 1.1) by independent radiologists' review	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 14
PFS (RECIST 1.1) by independent radiologists' review – Sensitivity analyses 1 and 2	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 14**Error! Reference source not found.**
OS	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based (censored at last contact date)
OS	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at time of initiation of new therapy or last assessment date
OS	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method using initiation of new therapy as time-dependent covariate	ITT	Censored at last contact date
Secondary Endpoints:				
ORR (RECIST 1.1) by independent radiologists' review	P	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
PFS (modified RECIST) by independent radiologists' review	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 14
ORR (modified RECIST) by independent radiologists' review	P	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
Response duration (RECIST 1.1) by independent radiologists' review	P	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded from analysis
†The analysis populations for H3 and H4 are ITT in PD-L1 CPS ≥1% subjects, and for H5 and H6 are ITT in PD-L1 CPS ≥10% subjects.				

The non-parametric Kaplan-Meier (KM) method was used to estimate the PFS curve in each treatment group and the survival curves. The treatment difference in PFS and the treatment difference in survival were each assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms for each analysis. All the stratified analyses were based on the stratification factors implemented for enrolment, including ECOG-PS (0/1 vs 2), presence or absence of liver metastases, haemoglobin (≥10 g/dL vs <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months).

Subjects in the standard treatment arm may have switched to another anti-PD-1 treatment following confirmation of progressive disease. Exploratory analyses to adjust for the effect of switching (to other PD-1 therapies) on OS were intended to be performed based on recognized methods, e.g. the Rank Preserving Structural Failure Time (RPSFT) model[59], 2-stage model, etc. The choice of the method was to be based on an examination of the appropriateness of the data to the assumptions required by the method.

Methods for additional analyses, such as subgroup analyses and adjusted analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint was planned to be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- PD-L1 subgroup (positive vs. negative)
- High PD-L1 subgroup (to be defined based on emerging external data)
- Sex (female vs. male)
- Race (white vs. non-white)
- ECOG status (0 / 1 vs. 2 and 0 vs 1 / 2)
- Geographic region of enrolling site (East Asia vs. non-East Asia and EU vs. non-EU)
- Prior platinum therapy (carboplatin vs. cisplatin)
- Setting of most recent prior therapy (neoadjuvant vs. adjuvant vs. 1L metastatic vs. 2L metastatic)
- Presence or absence of liver metastases at baseline
- Baseline haemoglobin (≥ 10 g/dL vs. <10 g/dL)
- Time from completion/discontinuation of most recent prior therapy to baseline (<3 months vs. ≥3 months)

- Histology (transitional cell vs. mixed transitional/non-transitional histology)
- Smoking status (never vs. former vs. current)
- Brain metastasis status (prior brain metastasis vs. no prior brain metastasis)
- Investigators' choice of paclitaxel, docetaxel or vinflunine
- Burden of disease in terms of baseline tumour volume
- The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

4.4.2: Trial population included in primary analysis of the primary outcome and methods to take account of missing data

KEYNOTE-045[16, 17]

Trial population

The analysis of primary efficacy endpoints were based on the intention-to-treat (ITT) population, i.e. subjects were included in the treatment group to which they are randomised.

The All Patients as Treated (APaT) population was used for the analysis of safety data in this study. The APaT population consists of all randomised subjects who received at least 1 dose of study treatment. Subjects were included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data. Subjects who took incorrect trial treatment for the entire treatment period were included in the treatment group corresponding to the trial treatment actually received. The baseline measurement and at least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment was required for inclusion in the analysis of each specific parameter.

Missing data approach and censoring methods

The approach for dealing with missing data in KEYNOTE-045 is described previously in Table 13.

In order to evaluate the robustness of the PFS endpoint, sensitivity analyses were performed with different sets of censoring rules. The censoring rules for primary and sensitivity analyses are summarised below in Table 14.

Table 14: KEYNOTE-045 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation				Analysis Approach		
Event Status	Study Therapy Discontinued	New Anti-Cancer Therapy Initiated	# Missed Disease Assessments Before Event	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and No Death	No	No	N/A	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No PD and No Death	Yes	No	N/A	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation
No PD and No Death	Yes or No	Yes	N/A	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and No Death	Yes or No	No	≥ 2 consecutive assessments	Censored at last disease assessment	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Censored at last disease assessment
PD or Death	Yes or No	No	≤ 1	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or Death	Yes or No	No	≥ 2 consecutive assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥2 missed disease assessments	Progressed at date of documented PD or death

4.4.3: Statistical tests used in primary analysis

Table 15: Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals

KEYNOTE-045[16, 17]	Primary hypotheses: 1. Pembrolizumab (MK-3475) prolongs PFS by RECIST 1.1 by BICR review in all subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel, or vinflunine 2. Pembrolizumab (MK-3475) prolongs OS in all subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel, or vinflunine. 3. Pembrolizumab prolongs PFS per RECIST 1.1 by BICR' review of subjects with platinum-refractory recurrent/progressive metastatic PD-L1 positive urothelial cancer compared to paclitaxel, docetaxel, or vinflunine. 4. Pembrolizumab prolongs OS in subjects with platinum-refractory recurrent/progressive metastatic PD-L1 positive urothelial cancer compared to paclitaxel, docetaxel, or vinflunine. 5. Pembrolizumab prolongs PFS per RECIST 1.1 by BICR review in subjects with platinum-refractory recurrent/progressive metastatic PD-L1 strongly positive urothelial cancer	The ITT population served as the primary population for the analyses of efficacy data in this trial The trial provides 97% power for the PFS hypothesis in PD-L1 CPS ≥10% subjects and >99% power for the PFS hypothesis in all subjects. The trial provides 88% and 86% power to demonstrate superiority of OS of pembrolizumab relative to standard therapy at the pre-specified initial alpha (one sided) levels in PD-L1 CPS ≥10% and all subjects, respectively.	Event-driven study which and planned to randomise approximately 470 subjects in a 1:1 ratio between pembrolizumab and the standard treatment arm. The sample size calculation for PFS was based on the following assumptions: • PFS follows an exponential distribution with a median 4 months in the standard treatment arm, • The true hazard ratios between pembrolizumab and standard therapy are 0.45, 0.5, and 0.5 for PD-L1 CPS ≥10%, PD-L1 CPS ≥1%, and all subjects, respectively • An enrolment period of 12 months • A dropout rate of 5%. The sample size calculation for OS was based on the following assumptions: • OS follows an exponential distribution with a median 8 months in the standard treatment arm, • The hazard ratios for OS between pembrolizumab and standard treatment are 0.5, 0.6, and 0.7 for PD-L1 CPS ≥10%, PD-L1 CPS ≥1%, and all subjects, respectively (deemed to be clinically meaningful in this population)	Each patient participated in the trial from the time h/she signed the informed consent form through the final protocol-specified contact. Treatment on study continued until one of the following: • Radiographic disease progression as determined by the investigator/site radiologist • Unacceptable AEs • Intercurrent illness that prevented further administration of treatment • Investigator's decision to withdraw the subject • The subject had a confirmed positive serum pregnancy test • Noncompliance with trial treatment or procedure requirements • The subject was lost to follow-up • Completed 24 months of treatment with pembrolizumab (Note: 24 months of study medication was calculated from the date of first dose. Patients who stopped pembrolizumab after 24 months could be eligible for up to1 year of additional study treatment if they progressed after

	compared to paclitaxel, docetaxel, or vinflunine 6. Pembrolizumab prolongs OS in subjects with platinum-refractory recurrent/progressive metastatic PD-L1 strongly positive urothelial cancer compared to paclitaxel, docetaxel, or vinflunine		• An enrolment period of 12 months and a minimum of 18 months follow up after enrolment completion • A yearly drop-out rate of 2%.	stopping study treatment provided they met the requirements as specified in the study protocol) • Administrative reasons • Withdrawal of consent for treatment If a patient discontinued/ withdrew prior to study completion, all applicable activities scheduled for the final study visit were performed at the time of discontinuation.

4.5 Participant flow in the relevant randomised controlled trials

4.5.1: Number of patients eligible to enter each trial

KEYNOTE-045[16, 17]

The first subject was enrolled in the trial on 23-Oct-2014 and the last subject was enrolled on 13-Nov-2015. The data cut-off date for the second interim-analysis (IA2) presented in this submission was 07-Sep-2016.

A total of 542 subjects were randomised into this trial and included in the ITT population (control: 272; pembrolizumab: 270) (Table 16). At the time of data cut-off, more subjects in the pembrolizumab arm were continuing on trial (40%) compared with the control arm (24.6%). In addition, more subjects in the pembrolizumab arm were continuing to receive the drug on trial (18.4%) compared with the control arm (1.2%).

Among the subjects who discontinued from the trial, more subjects in the control arm were discontinued due to death, compared to the pembrolizumab arm (58.1% vs 50.7%). More subjects in the control arm discontinued the trial due to withdrawal by subject (11.0% vs 2.6%) compared with the pembrolizumab arm. A similar proportion of subjects in both arms discontinued the trial due to adverse event, physician decision, or lost to follow-up; 1 subject in the pembrolizumab arm was discontinued due to a protocol violation; this last subject was included in the ITT.

Of the 542 subjects randomised into this trial, more subjects in the pembrolizumab arm started study treatment (266 of 270) compared with the control arm (255 of 272). Among subjects who started study treatment, the majority of subjects in the trial had discontinued study treatment by the time of IA2 (81.6% in pembrolizumab arm, 98.8% in control arm), with approximately half of subjects in both arms discontinuing study treatment due to PD. Fewer subjects in the pembrolizumab arm compared with the control arm discontinued study treatment due to an AE (10.9% vs 15.7 %,), withdrawal by subject (1.1% vs 11.4%), or physician decision (2.3% vs 10.6%). The same proportion of subjects across the 2 arms discontinued study treatment due to clinical progression of disease (9.4%). Seven subjects (2.4%) in the pembrolizumab arm discontinued study treatment due to achieving a complete response, compared with 1 subject (0.4%) in the control arm. A total of 205 subjects were not randomised in the study, all due to not meeting inclusion/exclusion.

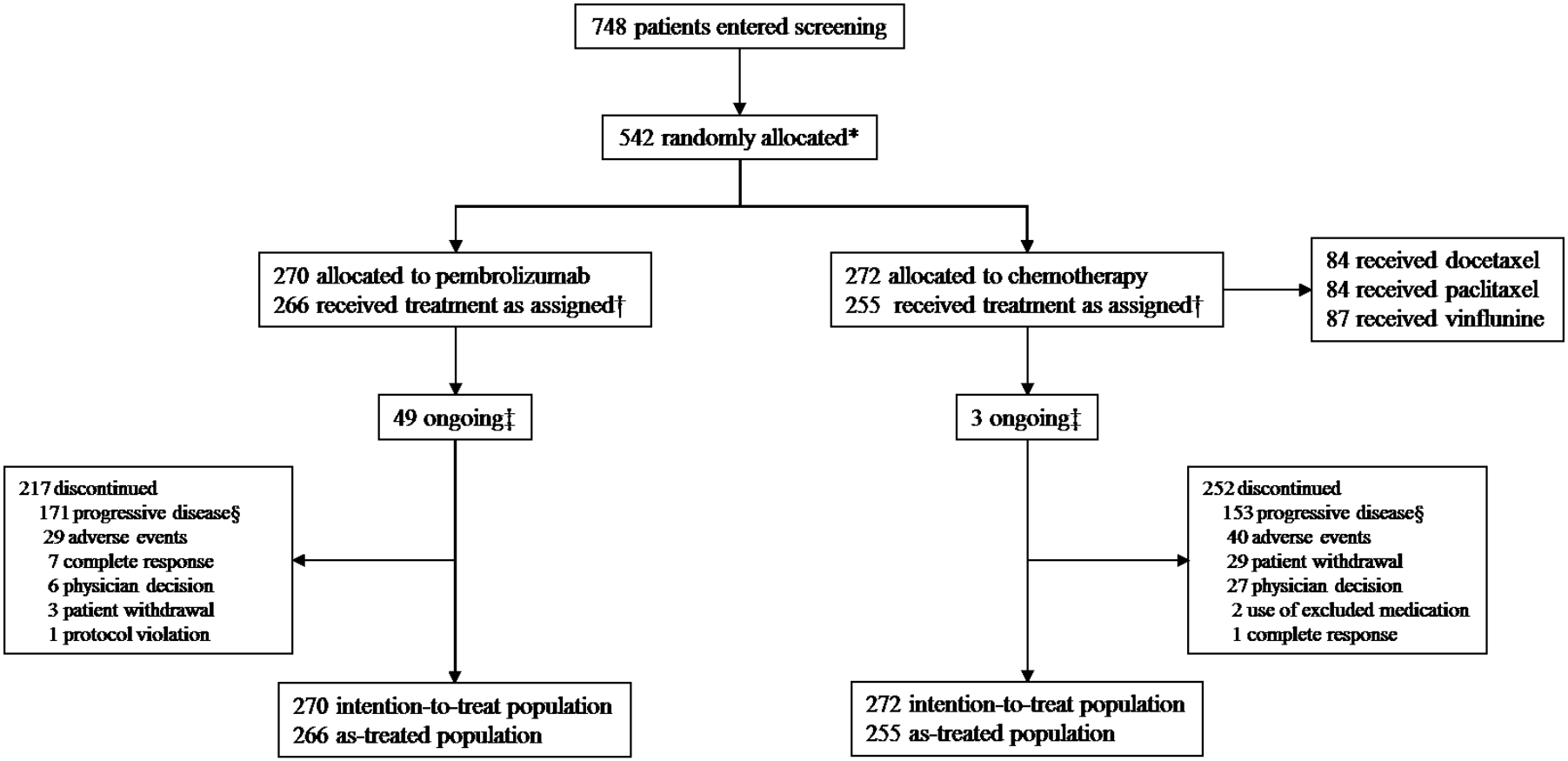
Table 16: KEYNOTE-045 - Subject Disposition - All Subjects (ITT Population)

	Control n (%)	Pembrolizumab n (%)
Subjects in population	272	270
Status for Trial		
Discontinued	205 (75.4)	162 (60.0)
Adverse Event	13 (4.8)	15 (5.6)
Death	158 (58.1)	137 (50.7)
Lost To Follow-Up	1 (0.4)	1 (0.4)
Physician Decision	3 (1.1)	1 (0.4)
Protocol Violation	0 (0.0)	1 (0.4)
Withdrawal By Subject	30 (11.0)	7 (2.6)
Ongoing in Trial	67 (24.6)	108 (40.0)
Status for Study Medication		
Started	255	266
Discontinued	252 (98.8)	217 (81.6)
Adverse Event	40 (15.7)	29 (10.9)
Clinical Progression	24 (9.4)	25 (9.4)
Complete Response	1 (0.4)	7 (2.6)
Excluded Medication	2 (0.8)	0 (0.0)
Physician Decision	27 (10.6)	6 (2.3)
Progressive Disease	129 (50.6)	146 (54.9)
Protocol Violation	0 (0.0)	1 (0.4)
Withdrawal By Subject	29 (11.4)	3 (1.1)
Treatment Ongoing	3 (1.2)	49 (18.4)

Each subject is counted once for Trial Status based on the latest Survival Follow-up record.
Each subject is counted once for Study Medication Status based on the latest corresponding disposition record.
Unknown: A disposition record did not exist at the time of reporting.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

The disposition of subjects in the ITT population from randomisation through to analysis is presented in Figure 7.

Figure 7: CONSORT diagram – KEYNOTE-045 (database cut-off date: 07-09-2016)



**Reasons for screen failure were inadequate performance status (n=56), inadequate organ function (n=42), lack of written, informed consent (n=27), lack of tissue for biomarker analysis (n=23), lack of measurable disease based on Response Evaluation Criteria in Solid Tumours, version 1.1 (n=19), lack of progression on or recurrence after platinum-containing chemotherapy (n=18), prohibited concomitant condition (n=20), central nervous system metastases (n=10), receipt of >2 prior lines of systemic chemotherapy (n=9), lack of histologically or cytological confirmed, transitional cell or transitional cell predominant disease (n=8), additional metastases requiring active treatment (n=8), active infection requiring systemic therapy (n=7), age <18 years (n=6), inadequate contraception (n=6), diagnosis of immunodeficiency or receiving systemic corticosteroid therapy or other immunosuppressive therapy (n=6), received most recent anticancer therapy within the prohibited window or did not recover from all adverse events caused by a previously administered therapy (n=6), active cardiac disease (n=6), evidence of interstitial lung disease or active noninfectious pneumonitis (n=5), active hepatitis B or C infection (n=5), or other (n=37). Subjects may have failed screening for >1 reason.*
†Reasons for not receiving study treatment were randomisation in error based on failure to meet all eligibility criteria (n=2) and fatal adverse events (n=2) in the pembrolizumab group and withdrawal of consent after randomisation (n=15), worsening physical condition (n=1), and a decrease in platelet count that precluded treatment (n=1) in the chemotherapy group.
‡Patients without a completed study medication discontinuation form.
§Includes patients with radiologic and clinical disease progression.

4.5.2: Characteristics of participants at baseline for each trial

KEYNOTE-045[16, 17]

Baseline characteristics of the ITT population were as expected for patients with advanced urothelial cancer (Table 17). The majority of subjects in both arms were male, ≥65 year of age, White, non-Hispanic, and former or current smokers. With regards to risk factors, the majority of subjects in both arms had an ECOG-PS of 1, had visceral metastasis (including 34.3% with liver metastases), baseline haemoglobin ≥10 g/dL, and had completed prior therapy ≥3 months before being randomised to this trial.

The treatment arms were generally well balanced by all baseline characteristics. Slightly more subjects in the pembrolizumab arm were in the ≥65 years of age (61.1% vs 54.0%), ECOG-PS = 0 (44.1% vs 39%) and in the never smokers (38.5% vs 30%) subgroups compared with the control arm. Slightly fewer subjects in the pembrolizumab arm were in the PD-L1 CPS≥10% group (27.4% vs 33.1%) compared with the control arm, as PD-L1 status was not a stratification factor.

Table 17: Subject Characteristics All Subjects (ITT Population)

	Control		Pembrolizumab		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	272		270		542	
Gender						
Male	202	(74.3)	200	(74.1)	402	(74.2)
Female	70	(25.7)	70	(25.9)	140	(25.8)
Age (Years)						
< 65	125	(46.0)	105	(38.9)	230	(42.4)
>= 65	147	(54.0)	165	(61.1)	312	(57.6)
Mean	65.1		66.0		65.5	
SD	9.2		10.2		9.7	
Median	65.0		67.0		66.0	
Range	26 to 84		29 to 88		26 to 88	
Race						
Asian	58	(21.3)	64	(23.7)	122	(22.5)
Black Or African American	4	(1.5)	5	(1.9)	9	(1.7)
Multiple	1	(0.4)	1	(0.4)	2	(0.4)
White	201	(73.9)	188	(69.6)	389	(71.8)
Missing	8	(2.9)	12	(4.4)	20	(3.7)
Ethnicity						
Hispanic Or Latino	15	(5.5)	17	(6.3)	32	(5.9)
Not Hispanic Or Latino	235	(86.4)	221	(81.9)	456	(84.1)

Not Reported	16	(5.9)	28	(10.4)	44	(8.1)
Unknown	6	(2.2)	4	(1.5)	10	(1.8)
ECOG†						
[0] Normal Activity	106	(39.0)	119	(44.1)	225	(41.5)
[1] Symptoms, but ambulatory	158	(58.1)	143	(53.0)	301	(55.5)
[2] Ambulatory but unable to work	4	(1.5)	2	(0.7)	6	(1.1)
Missing	4	(1.5)	6	(2.2)	10	(1.8)
Metastatic Staging						
MX	0	(0.0)	2	(0.7)	2	(0.4)
M0	10	(3.7)	10	(3.7)	20	(3.7)
M1	261	(96.0)	258	(95.6)	519	(95.8)
Missing	1	(0.4)	0	(0.0)	1	(0.2)
Cancer Staging						
II	0	(0.0)	1	(0.4)	1	(0.2)
IV	271	(99.6)	269	(99.6)	540	(99.6)
Missing	1	(0.4)	0	(0.0)	1	(0.2)
Prior Platinum Therapy						
Cisplatin	213	(78.3)	198	(73.3)	411	(75.8)
Carboplatin	56	(20.6)	70	(25.9)	126	(23.2)
Other (oxaliplatin,nedaplatin)	2	(0.7)	1	(0.4)	3	(0.6)
Missing	1	(0.4)	1	(0.4)	2	(0.4)
Setting of Most Recent Prior Therapy						
Neo Adjuvant	22	(8.1)	19	(7.0)	41	(7.6)
Adjuvant	31	(11.4)	12	(4.4)	43	(7.9)
First Line	157	(57.7)	183	(67.8)	340	(62.7)
Second Line	60	(22.1)	55	(20.4)	115	(21.2)
Third Line	1	(0.4)	0	(0.0)	1	(0.2)
Missing	1	(0.4)	1	(0.4)	2	(0.4)
Liver Metastases						
Absent	176	(64.7)	179	(66.3)	355	(65.5)
Present	95	(34.9)	91	(33.7)	186	(34.3)
Missing	1	(0.4)	0	(0.0)	1	(0.2)
Baseline haemoglobin‡						
>=10 g/dL	223	(82.0)	219	(81.1)	442	(81.5)
<10 g/dL	44	(16.2)	43	(15.9)	87	(16.1)
Missing	5	(1.8)	8	(3.0)	13	(2.4)
Time from Completion/Discontinuation of Most recent Prior Therapy to Baseline						
>=3 Months	167	(61.4)	166	(61.5)	333	(61.4)
<3 Months	104	(38.2)	103	(38.1)	207	(38.2)
Missing	1	(0.4)	1	(0.4)	2	(0.4)
Prior Brain Metastasis Status						
Absent	267	(98.2)	268	(99.3)	535	(98.7)
Present	5	(1.8)	2	(0.7)	7	(1.3)
Geographic Region EU						
EU	117	(43.0)	106	(39.3)	223	(41.1)
Non-EU	155	(57.0)	164	(60.7)	319	(58.9)

Geographic Region US						
US	59	(21.7)	47	(17.4)	106	(19.6)
Non-US	213	(78.3)	223	(82.6)	436	(80.4)
Geographic Region Asian						
East-Asian	48	(17.6)	58	(21.5)	106	(19.6)
Non-East Asian	224	(82.4)	212	(78.5)	436	(80.4)
Study Medication Breakdown§						
Paclitaxel	84	(30.9)	0	(0.0)	84	(15.5)
Docetaxel	84	(30.9)	0	(0.0)	84	(15.5)
Vinflunine	87	(32.0)	0	(0.0)	87	(16.1)
Pembrolizumab	0	(0.0)	266	(98.5)	266	(49.1)
Missing	17	(6.3)	4	(1.5)	21	(3.9)
Smoking Status						
Never Smoker	83	(30.5)	104	(38.5)	187	(34.5)
Ex Smoker	148	(54.4)	136	(50.4)	284	(52.4)
Current Smoker	38	(14.0)	29	(10.7)	67	(12.4)
Missing	3	(1.1)	1	(0.4)	4	(0.7)
Histology						
Pure Transitional Cell	197	(72.4)	186	(68.9)	383	(70.7)
Predominantly Transitional Cell	73	(26.8)	82	(30.4)	155	(28.6)
Other	0	(0.0)	2	(0.7)	2	(0.4)
Missing	2	(0.7)	0	(0.0)	2	(0.4)
PD-L1 CPS 1% Cut-off						
PD-L1 CPS < 1%	147	(54.0)	151	(55.9)	298	(55.0)
PD-L1 CPS >= 1%	120	(44.1)	110	(40.7)	230	(42.4)
Missing	5	(1.8)	9	(3.3)	14	(2.6)
PD-L1 CPS 10% Cut-off						
PD-L1 CPS < 10%	176	(64.7)	186	(68.9)	362	(66.8)
PD-L1 CPS >= 10%	90	(33.1)	74	(27.4)	164	(30.3)
Missing	6	(2.2)	10	(3.7)	16	(3.0)
Sum of Target Lesion at Baseline§§						
<Median	117	(43.0)	132	(48.9)	249	(45.9)
>=Median	135	(49.6)	115	(42.6)	250	(46.1)
Missing	20	(7.4)	23	(8.5)	43	(7.9)
Risk Scores						
0	44	(16.2)	54	(20.0)	98	(18.1)
1	97	(35.7)	96	(35.6)	193	(35.6)
2	80	(29.4)	66	(24.4)	146	(26.9)
3-4	45	(16.5)	45	(16.7)	90	(16.6)
Missing	6	(2.2)	9	(3.3)	15	(2.8)
Prior Cystectomy/Nephrectom						
No	221	(81.3)	209	(77.4)	430	(79.3)
Yes	51	(18.8)	61	(22.6)	112	(20.7)
Site of Primary Tumour						
Upper Tract	37	(13.6)	38	(14.1)	75	(13.8)
Lower Tract	234	(86.0)	232	(85.9)	466	(86.0)
Missing	1	(0.4)	0	(0.0)	1	(0.2)
Prior BCG Therapy						

No	250	(91.9)	238	(88.1)	488	(90.0)
Yes	22	(8.1)	32	(11.9)	54	(10.0)
Visceral Disease at Baseline						
Lymph Node Only	38	(14.0)	29	(10.7)	67	(12.4)
Visceral Disease	233	(85.7)	240	(88.9)	473	(87.3)
Missing	1	(0.4)	1	(0.4)	2	(0.4)

† Nine out of the 10 subjects (5 in pembrolizumab; 4 in control) with missing values in this category had ECOG documented after the randomisation date and prior to or on Cycle 1 Day 1.

‡ Ten out of the 13 subjects (6 in pembrolizumab; 4 in control) with missing values in this category had non-missing measurements after the randomisation date and prior to or on Cycle 1 Day 1.

§ Actual study medication received by patients. Missing values in this category are randomised subjects who did not take study medication.

§§ RECIST 1.1 measurable disease as assessed by blinded independent central reviewer.

Baseline values shown in this table were collected on or before randomisation date

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

4.6 Quality assessment of the relevant randomised controlled trials

A complete quality assessment for each trial is included in Appendix 7.

A tabulated summary of the quality assessment results is presented in Table 18 below.

Table 18: Quality assessment results for parallel group RCTs

Trial	KEYNOTE-045
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
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

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

4.7 Clinical effectiveness results of the relevant randomised controlled trials

KEYNOTE-045 Results – Interim Analysis 2 (IA2): data cut-off 07 September 2016[16, 17]

Emerging evidence suggests that PD-L1 expression level and clinical outcomes may be correlated in patients with epithelial malignancies (urothelial carcinoma included) treated with PD-1/PD-L1 agents. Therefore, efficacy was evaluated according to PD-L1 positivity and strong positivity in addition to analysis of the trial population as a whole.

PD-L1 expression of CPS ≥1% was described in the protocol as PD-L1 positive. Strongly positive PD-L1 expression was defined as CPS ≥10% based on data from KEYNOTE-052 (external to KEYNOTE-045). Data from KEYNOTE-052 demonstrated a clinically meaningful response rate and durable responses in all subjects, including those who were considered to be PD-L1 negative (PD-L1 CPS <1%). Response rates were also meaningfully increased when a cutpoint of PD-L1 CPS ≥10% was applied. In contrast, the magnitude of enrichment using a cutpoint of PD-L1 CPS ≥1% in this population was not clinically meaningful. Based on these observations from KEYNOTE-052, a single cutpoint of PD-L1 CPS ≥10% was identified for urothelial carcinoma. Therefore, in the second interim analysis (IA2) and final analysis, only primary hypotheses of PD-L1 strongly positive subjects and all subjects were included in the multiplicity controlled statistical testing.

Results are presented from the second interim analysis (IA2) of data (data cut-off date 07 September 2016) for the primary endpoints (OS and PFS) and secondary endpoints (ORR, duration of response [DOR], and PFS/ORR per modified RECIST) in the ITT population for all subjects, subjects with PD-L1 CPS ≥10%, and subjects with PD-L1 CPS ≥1%. Exploratory analyses of electronically-collected patient-reported outcome (ePRO) data are also summarised for all subjects. A first interim analysis of the data had been previously performed on 16-Mar-2016 (data cut-off date 01-Feb-2016), with a recommendation to continue the trial as planned. Based on the results of the pre-specified interim analysis (IA2), an independent Data Monitoring Committee (DMC) recommended that the trial be stopped early.

The median (range) follow-up duration for all subjects in the intent-to-treat (ITT) population was 10.3 (0.2 to 20.8) months in the pembrolizumab arm and 7.9 (0.3 to 20.3) months in the control arm (Table 19).

Table 19: Summary of Follow-up Duration - All Subjects (ITT Population)

	Control (N=272)	Pembrolizumab (N=270)	Total (N=542)
Follow-up duration (months)†			
Median (Range)	7.9(0.3-20.3)	10.3(0.2-20.8)	9(0.2-20.8)
Mean (SD)	8.4(5.1)	9.1(5.6)	8.7(5.4)

† Follow-up duration is defined as the time from randomisation to the date of death or the database cut-off date if the patient was still alive.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016.

A summary of the clinical efficacy outcome results in the overall population based on IA2 of KEYNOTE-045 for pembrolizumab 200 mg IV Q3W vs SOC is presented in

Table 20 below:

Table 20: KENOTE-045 - Summary of efficacy endpoints

	Pembrolizumab N= 270	Control N= 272
Primary endpoints		
OS - I TT population		
Median (95% CI), [months]	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
	HR 0.73 (95% CI 0.59, 0.91) *p = 0.00224*	
OS rate at 6 months	63.9%	56.7 %
OS rate at 12 months	43.9%	30.7%
PFS - (BICR per RECIST 1.1) – ITT population		
Median (95% CI), [months]	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
	HR 0.98 (95% CI 0.81, 1.19); *p=0.41648*	
PFS rate at 6 months	28.8%	26.8%
PFS rate at12 months	16.8%	6.2%
Secondary endpoints		
ORR (BIRC per RECIST 1.1) - ITT Population		
Confirmed ORR %	21.1 %	11.4 %
Time to Response		
Number of responders (n) Median [months] Range [months]	57 2.1 (1.4 – 6.3)	31 2.1 (1.7-4.9)
Response Duration (BIRC assessment) - ITT Population		
Median [months] Range [months]	not reached (1.6+ - 15.6+)	4.3 (1.4+ - 15.4+)
% of subjects who achieved an objective response (CR + PR)	21.1%	11.4%

% of subjects who achieved a CR	7.0%	3.3%

Efficacy results are presented in more detail below:

Primary Endpoints:

Overall Survival (OS)

- OS among all subjects

At the time of data cut-off for IA2 (07 September 2016), a total of 334 (61.6%) deaths were observed among all subjects in the ITT population (Table 21). Treatment with pembrolizumab was associated with a statistically significant and clinically meaningful improvement in OS compared with treatment with the control (comprised of Investigator's choice of SOC chemotherapy: paclitaxel, docetaxel, or vinflunine); the HR for OS was 0.73 (95% CI: 0.59, 0.91), with a one-sided p-value of 0.002 over the control (Table 22). The median OS was 10.3 months (95% CI: 8.0, 11.8) in the pembrolizumab arm versus 7.4 months (95% CI: 6.1, 8.3) in the control arm.

Although the initial part of the OS curves appears to favour the control, the difference is small and transient. Kaplan-Meier (KM) estimates of OS show a clear separation beginning at approximately month 3 favouring pembrolizumab over control, with most censoring occurring after the 10-month time point (Figure 8). The shape of the KM OS curve for pembrolizumab began to plateau at around 12 months, whereas the control arm curve maintained its slope. The tail of the survival curve represents subjects treated with pembrolizumab who have the potential for long lasting survival benefit, as has been observed in other immunotherapy studies and with pembrolizumab.

The OS rate at 6 months was 63.9% for pembrolizumab and 56.7% for control, and at 12 months was 43.9% for pembrolizumab and 30.7% for control (Table 21).

Table 21: Analysis of OS - All subjects (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 6 in % † (95% CI)	OS Rate at Months 12 in % † (95% CI)	Pembrolizumab vs. Control	
								Hazard Ratio‡ (95% CI)‡	p-Value§
Control	272	179 (65.8)	1935.1	9.3	7.4 (6.1, 8.3)	56.7 (50.3, 62.6)	30.7 (25.0, 36.7)		
Pembrolizumab	270	155 (57.4)	2364.7	6.6	10.3 (8.0, 11.8)	63.9 (57.9, 69.4)	43.9 (37.8, 49.9)	0.73 (0.59, 0.91)	0.00224

† *From product-limit (Kaplan-Meier) method for censored data.*

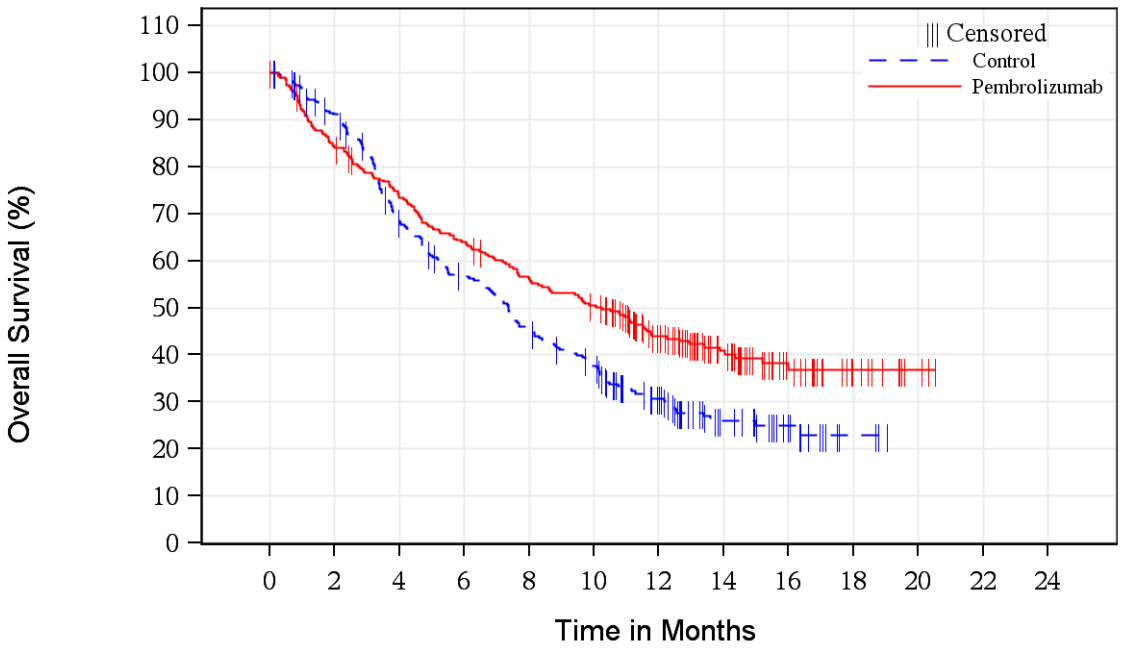
‡ *Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)*

§ *One-sided p-value based on stratified log-rank test.*

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 8: KM estimates of OS - All subjects (ITT population)



Number of subject at risk

Control	272	232	171	138	109	89	55	27	14	3	0	0	0
Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

- OS among subjects with PD-L1 CPS ≥10%

A total of 104 deaths were observed among subjects with PD-L1 CPS ≥10% as of the data cut-off date of 07-Sep-2016 (Table 22). Consistent with the overall ITT population, treatment with pembrolizumab was associated with a statistically significant and clinically meaningful improvement in OS compared with treatment with control, with median OS = 8.0 months (95% CI: 5.0, 12.3) versus 5.2 months (95% CI: 4.0, 7.4), respectively (observed HR [95% CI] = 0.57 [0.37, 0.88]; p=0.005). The median OS in this sub-population was lower than in the overall population in both pembrolizumab and control arms, suggesting that PD-L1 CPS ≥10% may be a negative prognostic factor.

The KM curve in the PD-L1 CPS ≥10% was consistent with the curve of the overall population in that there were initially small differences between the curves with an initial crossover, followed by an increasingly pronounced separation favouring pembrolizumab, and a developing plateau along the tail of the pembrolizumab curve (Figure 9). Once again, the tail of the survival curve represents subjects who have the potential for long lasting survival benefit.

Table 22: Analysis of OS - Subjects with PD-L1 CPS >= 10% (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 6 in % † (95% CI)	OS Rate at Months 12 in % † (95% CI)	Pembrolizumab vs. Control	
								Hazard Ratio‡ (95% CI)‡	p-Value§
Control	90	60 (66.7)	570.3	10.5	5.2 (4.0, 7.4)	47.2 (36.0, 57.6)	26.9 (17.5, 37.2)		
Pembrolizumab	74	44 (59.5)	589.1	7.5	8.0 (5.0, 12.3)	58.5 (46.3, 68.9)	39.8 (28.0, 51.3)	0.57 (0.37, 0.88)	0.00483

† From product-limit (Kaplan-Meier) method for censored data.

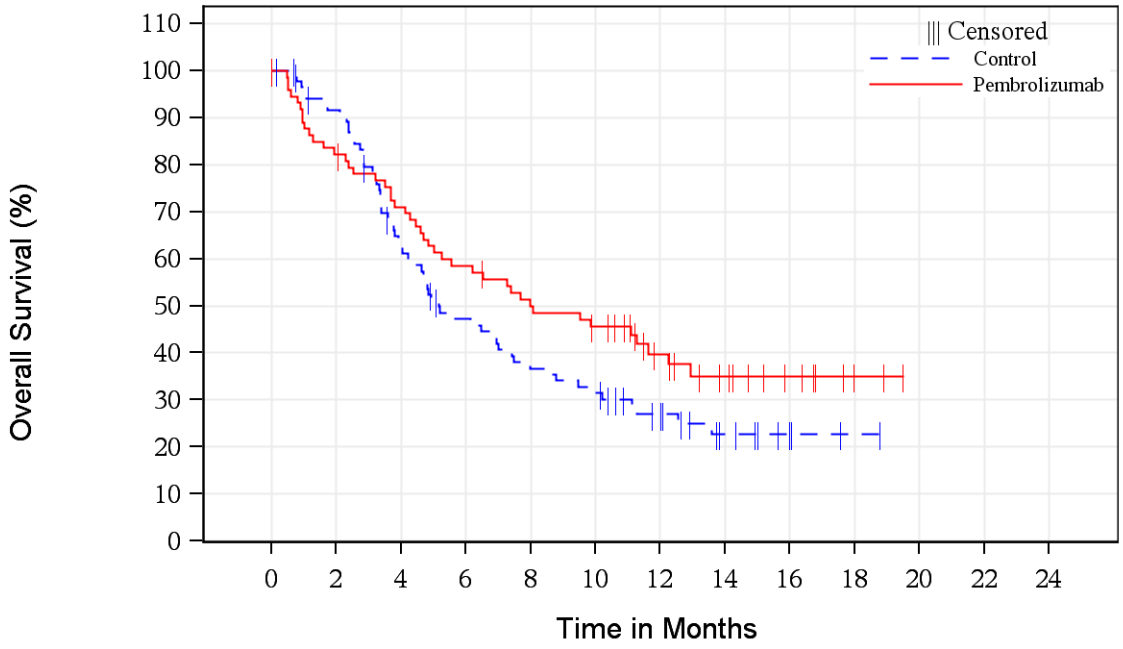
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 9: KM estimates of OS - Subjects with PD-L1 CPS >= 10% (ITT population)



Number of subject at risk

Control	90	76	51	36	28	24	16	8	4	1	0	0	0
Pembrolizumab	74	60	51	42	35	31	18	12	7	3	0	0	0

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

- OS among subjects with PD-L1 CPS ≥1%

A total of 142 deaths were observed among subjects with PD-L1 CPS ≥1% as of the data cut-off date of 07 September 2016. Consistent with the overall ITT population, treatment with pembrolizumab was associated with an improvement in OS compared with treatment with control (median OS = 11.3 months [95% CI: 7.7, 16.0] versus 6.9 months [95% CI: 4.7, 8.8], respectively) (HR [95% CI] = 0.61 [0.43, 0.86]; p=0.002) (Table 23; Figure 10); this p value is not multiplicity adjusted (see Appendix 6).

Table 23: Analysis of OS - Subjects with PD-L1 CPS >= 1% (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 6 in % † (95% CI)	OS Rate at Months 12 in % † (95% CI)	Pembrolizumab vs. Control	
								Hazard Ratio‡ (95% CI)‡	p-Value§
Control	120	81 (67.5)	823.0	9.8	6.9 (4.7, 8.8)	51.6 (41.9, 60.4)	28.8 (20.4, 37.7)		
Pembrolizumab	110	61 (55.5)	971.1	6.3	11.3 (7.7, 16.0)	65.9 (56.1, 73.9)	46.5 (36.4, 55.8)	0.61 (0.43, 0.86)	0.00239

† From product-limit (Kaplan-Meier) method for censored data.

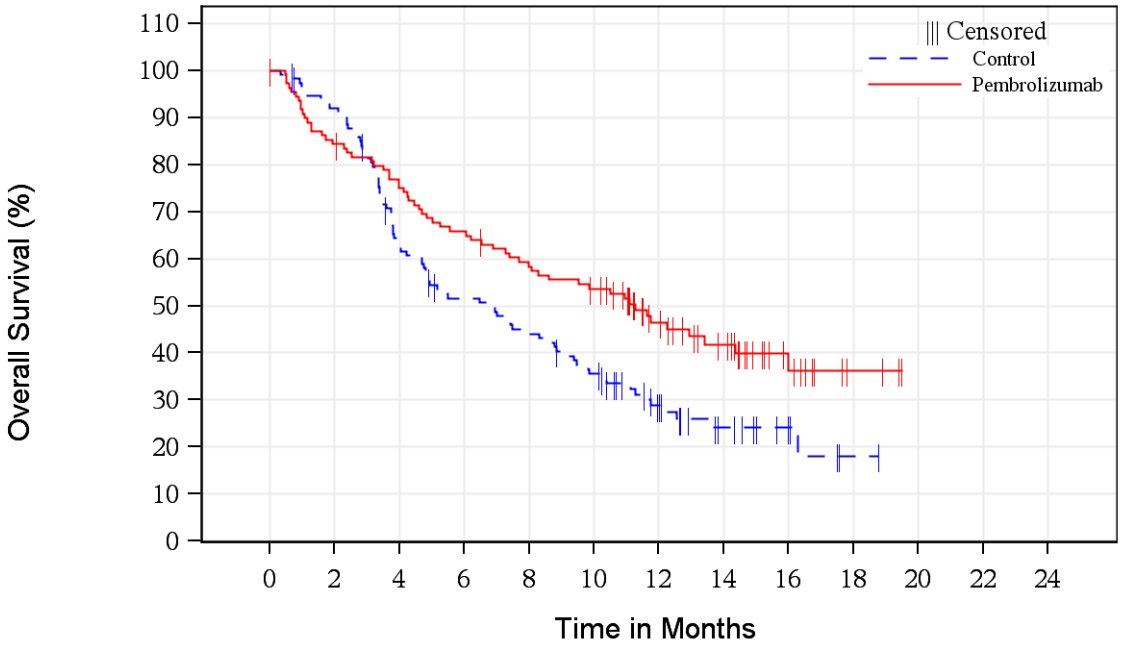
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 10: KM Estimates of OS - Subjects with PD-L1 CPS >= 1% (ITT population)



Number of subject at risk

Control	120	104	70	55	47	37	22	11	6	1	0	0	0
Pembrolizumab	110	92	81	71	62	56	34	24	11	3	0	0	0

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

Progression-Free Survival (PFS) per RECIST 1.1 by Central Radiology Assessment

Primary PFS analyses were performed by BICR. Of note, blinded independent central review, blinded central radiologists' review and independent radiologists' review all refer to the blinded central radiology assessment and are used interchangeably throughout the CSR for KEYNOTE-045[16].

- PFS among all subjects

A total of 437 PFS events were reported at the time of the data cut-off. The primary analysis of PFS among all subjects in the ITT population showed no statistically significant improvement in PFS for pembrolizumab compared with control (Table 24): as per the primary analysis method, median PFS was 2.1 months (95% CI: 2.0, 2.2) in the pembrolizumab arm versus 3.3 months (95% CI: 2.3, 3.5) in the control arm (HR [95% CI] = 0.98 [0.81, 1.19]; *p*=0.416). However, KM estimates show separation in favour of pembrolizumab after 6 months with a plateau in the tail of the curve, suggesting a meaningful benefit for some subjects from 6 months and onwards (Figure 11); the PFS rates at 6 months and 12 months were greater in the pembrolizumab arm (Table 24). Similar to OS, most censoring in the pembrolizumab arm occurred after the 10-month time point, due to the data cut-off.

The results of the PFS analyses per RECIST 1.1 by Site Radiology Assessment (Primary Censoring Rule) which were conducted as supportive analyses, are provided in Appendix 8. The median PFS, HRs, and *p*-values by Site Radiology Assessment are similar compared with the results by Central Radiology Assessment.

The results of the PFS analyses per RECIST 1.1 by Central Radiology Assessment (Sensitivity Censoring Rules) are provided in Appendix 8. The median PFS, HRs, and *p*-values are similar in sensitivity analyses compared with the primary analysis method. The results of the PFS analyses for confirmed response per mRECIST by Central Radiology Assessment for all subjects in the ITT population are also provided in Appendix 8.

Table 24: Analysis of PFS Based on RECIST 1.1 per central radiology assessment (primary censoring rule) - All subjects (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 6 in % † (95% CI)	PFS Rate at Months 12 in % † (95% CI)	Pembrolizumab vs. Control	
								Hazard Ratio‡ (95% CI)‡	p-Value§
Control	272	219 (80.5)	1014.1	21.6	3.3 (2.3, 3.5)	26.8 (21.2, 32.6)	6.2 (3.3, 10.2)		
Pembrolizumab	270	218 (80.7)	1206.7	18.1	2.1 (2.0, 2.2)	28.8 (23.5, 34.3)	16.8 (12.3, 22.0)	0.98 (0.81, 1.19)	0.41648

Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

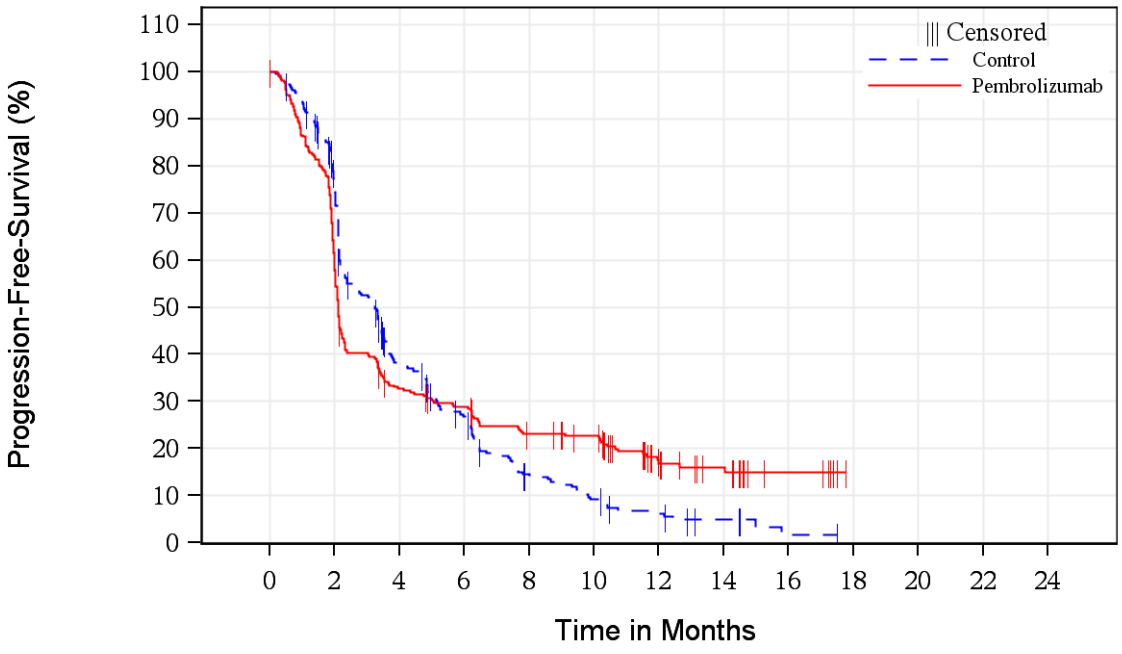
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 11: KM estimates of PFS Based on RECIST 1.1 per central radiology assessment (primary censoring rule) - All subjects (ITT population)



Number of subject at risk

Control	272	188	85	56	27	17	10	5	1	0	0	0	0
Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0	0	0

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

- PFS among subjects with PD-L1 CPS ≥10%

A total of 131 PFS events were reported at the time of the data cut-off. Similar to the overall population, the primary analysis of PFS among subjects with PD-L1 CPS ≥10% showed no statistically significant improvement in PFS for pembrolizumab compared with control (Table 25): The median PFS was 2.1 months (95% CI: 1.9, 2.1) in the pembrolizumab arm versus 3.1 months (95% CI: 2.2, 3.4) in the control arm (HR [95% CI] = 0.89 [0.61, 1.28]; p=0.240). However, KM estimates show a separation of effect favouring pembrolizumab after 6 months with a plateau in the tail of the curve, suggesting a meaningful benefit for some subjects from 6 months and onward (Figure 12). Among subjects with PD-L1 CPS ≥10%, the PFS rates at 6 months and 12 months were greater in the pembrolizumab arm (Table 25).

The results of the PFS analyses per RECIST 1.1 by Site Radiology Assessment (Primary Censoring Rule) which were conducted as supportive analyses among subjects with PD-L1 CPS ≥10% are provided in Appendix 8. The median PFS, HRs, and p values by Site Radiology Assessment are similar compared with the results by Central Radiology Assessment.

The results of the PFS analyses per RECIST 1.1 by Central Radiology Assessment (Sensitivity Censoring Rules) among subjects with PD-L1 CPS ≥10% are provided in Appendix 8. The results are similar in sensitivity analyses compared with the primary analysis method. The results of the PFS analyses for confirmed response per mRECIST by Central Radiology Assessment among subjects with PD-L1 CPS ≥10% are also provided in Appendix 8.

Table 25: Analysis of PFS Based on RECIST 1.1 per central radiology assessment (primary censoring rule) - Subjects with PD-L1 CPS >= 10% (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 6 in % † (95% CI)	PFS Rate at Months 12 in % † (95% CI)	Pembrolizumab vs. Control	
								Hazard Ratio‡ (95% CI)‡	p-Value§
Control	90	72 (80.0)	283.8	25.4	3.1 (2.2, 3.4)	18.5 (10.6, 28.1)	3.7 (0.7, 10.9)		
Pembrolizumab	74	59 (79.7)	316.4	18.6	2.1 (1.9, 2.1)	24.7 (15.5, 34.9)	17.7 (9.5, 27.9)	0.89 (0.61, 1.28)	0.23958

Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

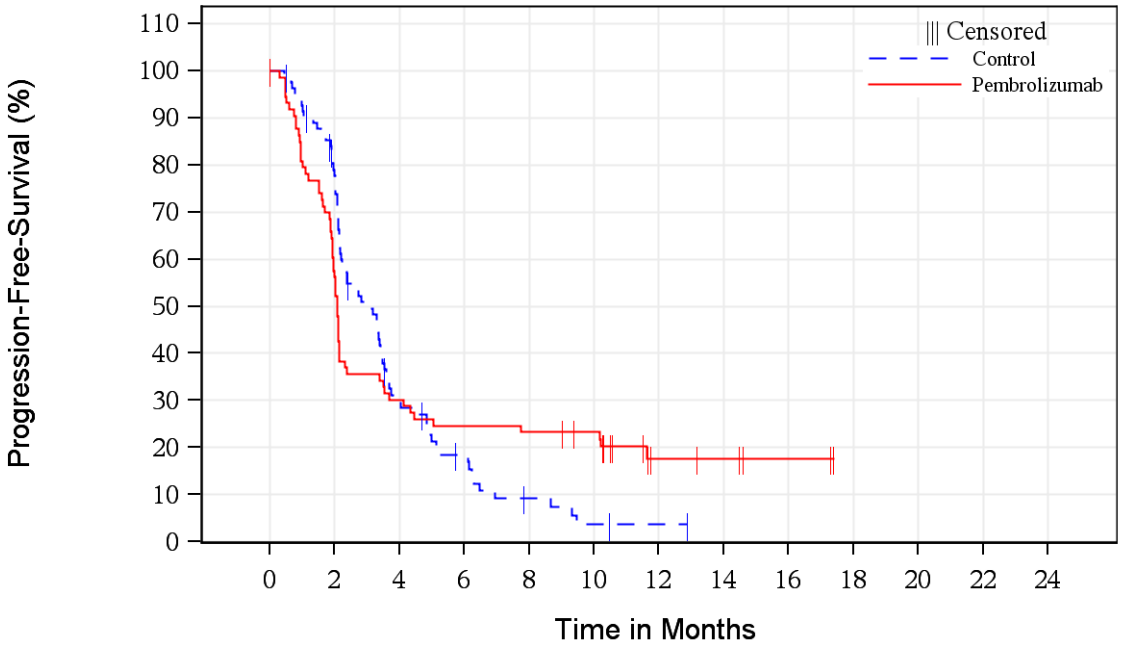
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 12: *KM estimates of PFS based on RECIST 1.1 per central radiology assessment (primary censoring rule) - Subjects with PD-L1 CPS >= 10% (ITT population)*



Number of subject at risk

Control	90	62	22	12	5	2	1	0	0	0	0	0	0
Pembrolizumab	74	42	22	18	17	15	5	4	2	0	0	0	0

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

- PFS among subjects with PD-L1 CPS ≥1%

Similar to the overall population, the analysis of PFS among subjects with PD-L1 CPS ≥1% showed no improvement for pembrolizumab compared with control (Table 26), although KM estimates show a separation of effect favouring pembrolizumab after 6 months (Figure 13). Median PFS was 2.1 months (95% CI: 2.0, 2.4) in the pembrolizumab arm versus 3.2 months (95% CI: 2.2, 3.4) in the control arm (HR [95% CI] = 0.91 [0.618, 1.24]; p=0.264) (Table 26). This p value is not multiplicity adjusted (see Appendix 6).

Table 26: Analysis of PFS based on RECIST 1.1 per central radiology assessment (primary censoring rule) - Subjects with PD-L1 CPS >= 1% (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 6 in % † (95% CI)	PFS Rate at Months 12 in % † (95% CI)	Pembrolizumab vs. Control	
								Hazard Ratio‡ (95% CI)‡	p-Value§
Control	120	98 (81.7)	421.3	23.3	3.2 (2.2, 3.4)	20.5 (13.3, 28.8)	4.4 (1.4, 10.4)		
Pembrolizumab	110	85 (77.3)	509.8	16.7	2.1 (2.0, 2.4)	28.4 (20.3, 37.1)	20.9 (13.6, 29.3)	0.91 (0.68, 1.24)	0.26443

Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

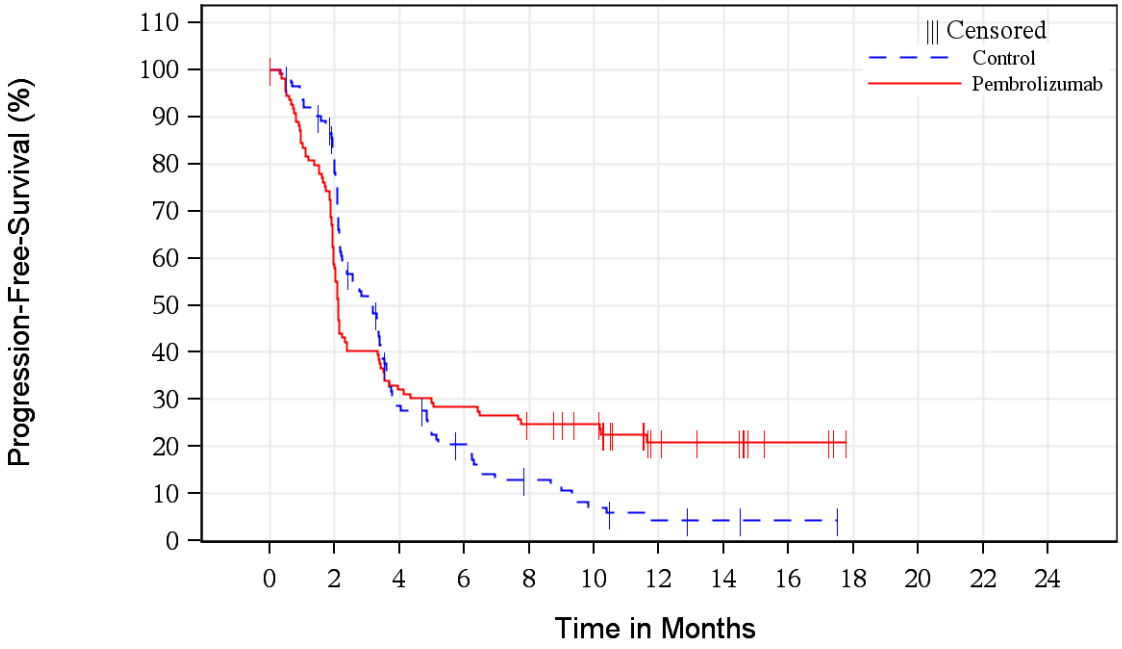
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 13: KM estimates of PFS based on RECIST 1.1 per central radiology assessment (primary censoring rule) - Subjects with PD-L1 CPS >= 1% (ITT population)



Number of subject at risk

Control	120	87	29	19	11	6	3	2	1	0	0	0	0
Pembrolizumab	110	64	35	31	26	23	10	8	3	0	0	0	0

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

The results of the PFS analyses per RECIST 1.1 by Site Radiology Assessment (Primary Censoring Rule), which were conducted as supportive analyses among subjects with PD-L1 CPS ≥1% are provided in Appendix 8. The median PFS, HRs, and p-values by Site Radiology Assessment are similar compared with the results by Central Radiology Assessment.

The results of the PFS analyses per RECIST 1.1 by Central Radiology Assessment (Sensitivity Censoring Rules) among subjects with PD-L1 CPS ≥1% are Appendix 8. The median PFS, HRs, and p values are similar in sensitivity analyses compared with the primary analysis method.

The results of the PFS analyses for confirmed response per mRECIST by Central Radiology Assessment among subjects with PD-L1 CPS ≥1% are also provided in Appendix 8.

Secondary Endpoints:

Objective Response Rate (ORR) per Confirmed RECIST 1.1 by Central Radiology Assessment)

Response analyses were performed by BICR. Of note, blinded independent central review blinded central radiologists' review and independent radiologists' review all refer to the blinded central radiology assessment and are used interchangeably throughout the CSR for KEYNOTE-045[16].

- ORR among all subjects in the ITT population

Treatment with pembrolizumab was associated with a statistically significant and clinically meaningful improvement in confirmed ORR for all subjects in the ITT population compared with control based on RECIST 1.1 as determined by Central Radiology Assessment. The ORR was 21.1% (95% CI: 16.4, 26.5) in the pembrolizumab arm compared with 11.4% (95% CI: 7.9, 15.8) in the control arm; the estimate of the difference was 9.6 (95% CI: 3.5, 15.9); *p*=0.001 (Table 27).

Table 27: Analysis of confirmed ORR based on RECIST 1.1 per central radiology assessment - All subjects (ITT population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate (95% CI)†	p-Value††
Control	272	31	11.4 (7.9,15.8)		
Pembrolizumab	270	57	21.1 (16.4,26.5)	9.6 (3.5,15.9)	0.00106

† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

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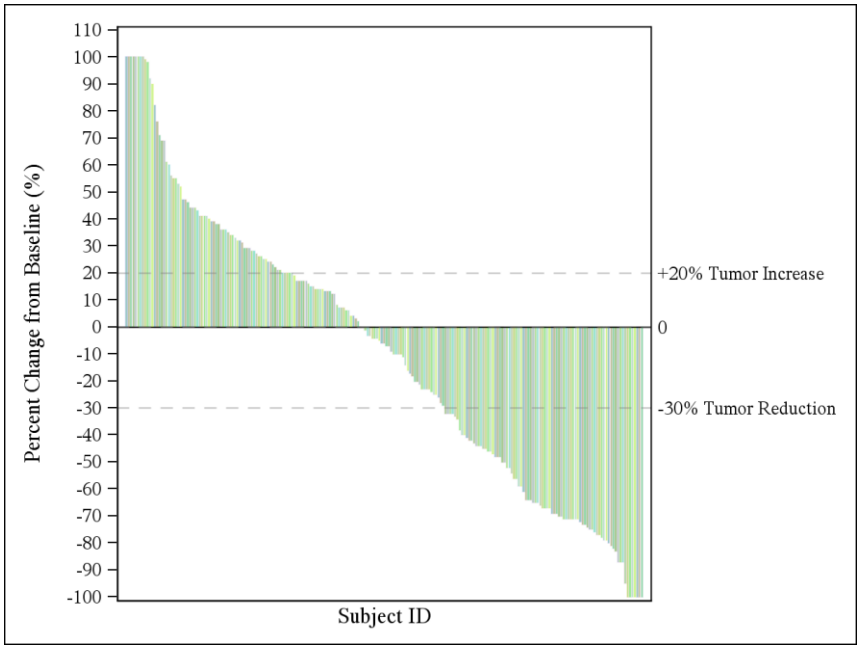
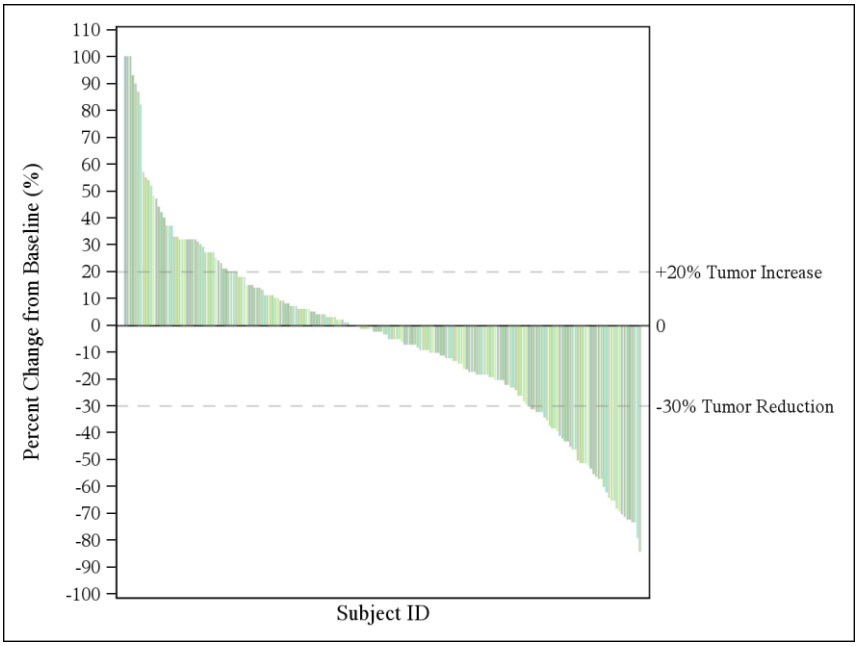
In the pembrolizumab arm, 118 of 219 subjects (53.9%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 14. In the control arm, 109 of 200 subjects (54.5%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 15.

Figure 14: Waterfall plot of best tumour change from baseline in pembrolizumab arm based on RECIST 1.1 per central radiology assessment - All subjects with measureable disease at baseline (ITT population)



Percentage changes >100% were truncated at 100%.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Figure 15: Waterfall plot of best tumour change from baseline in control arm based on RECIST1.1 per central radiology assessment - All subjects with measureable disease at baseline (ITT population)



Percentage changes >100% were truncated at 100%.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

The results of the ORR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment and per mRECIST by Central Radiology Assessment for all subjects in the ITT population are consistent with the Central Radiology Assessment and are provided in Table 28 and Table 29 respectively.

Table 28: Analysis of confirmed ORR based on RECIST 1.1 per site radiology assessment - All subjects (ITT population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate (95% CI)†	p-Value††
Control	272	31	11.4 (7.9,15.8)		
Pembrolizumab	270	63	23.3 (18.4,28.8)	11.9 (5.7,18.2)	0.00010

† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Table 29: Analysis of confirmed ORR based on modified RECIST 1.1 per central radiology assessment - All subjects (ITT population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate (95% CI)†	p-Value††
Control	272	32	11.8 (8.2,16.2)		
Pembrolizumab	270	68	25.2 (20.1,30.8)	13.4 (7.0,19.9)	0.00002

† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

More subjects in the overall ITT population receiving pembrolizumab than control had a best overall response (BOR) of complete response (CR) (19 [7.0%] vs 9 [3.3%], respectively) per RECIST 1.1 by Central Radiology Assessment. Likewise, more subjects in the pembrolizumab arm had a BOR of partial response (PR) (38 [14.1%] vs 22 [8.1%], respectively) (Table 30).

Table 30: Summary of BOR based on RECIST 1.1 per central radiology assessment - All subjects (ITT population)

Response Evaluation	Control (N=272)			Pembrolizumab (N=270)		
	n	%	95% CI†	n	%	95% CI†
Complete Response (CR)	9	3.3	(1.5, 6.2)	19	7.0	(4.3, 10.8)
Partial Response (PR)	22	8.1	(5.1, 12.0)	38	14.1	(10.2, 18.8)
Objective Response (CR+PR)	**31**	**11.4**	**(7.9, 15.8)**	**57**	**21.1**	**(16.4, 26.5)**
Stable Disease (SD)	91	33.5	(27.9, 39.4)	47	17.4	(13.1, 22.5)
Disease Control (CR+PR+SD)	**122**	**44.9**	**(38.8, 51.0)**	**104**	**38.5**	**(32.7, 44.6)**
Progressive Disease (PD)	90	33.1	(27.5, 39.0)	131	48.5	(42.4, 54.7)
Non-evaluable (NE)	9	3.3	(1.5, 6.2)	4	1.5	(0.4, 3.7)
No Assessment	51	18.8	(14.3, 23.9)	31	11.5	(7.9, 15.9)

Confirmed responses are included.
† Based on binomial exact confidence interval method.
Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.
No Assessment: subject had no post-baseline imaging.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Duration of follow-up (defined as the time from randomisation to the date of death or the database cut-off date if the patient was still alive) in responders with confirmed CR or PR was similar between arms and is presented in Appendix 8.

The results of the BOR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment, conducted as supportive analyses, for all subjects in the ITT population are consistent with the Central Radiology Assessment and are provided in Appendix 8. The results of the BOR analyses for confirmed response per mRECIST by Central Radiology Assessment for all subjects in the ITT population are consistent with the results per RECIST 1.1 and are also provided in Appendix 8.

- *ORR per confirmed RECIST 1.1 by central radiology assessment among subjects with PD-L1 CPS ≥10%*

Treatment with pembrolizumab was associated with an improvement in confirmed ORR among subjects with PD-L1 CPS ≥10% compared with control based on RECIST 1.1 as determined by Central Radiology Assessment. The ORR was 21.6% (95% CI: 12.9, 32.7) in the pembrolizumab arm compared with 6.7% (95% CI: 2.5, 13.9) in the control arm; the estimate of the difference was 19.3 (95% CI: 8.6, 31.7); p=0.0002 (Table 31). This p-value is not multiplicity-adjusted.

In the pembrolizumab arm, 30 of 55 subjects (54.5%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 16. In the control arm,

38 of 65 subjects (58.5%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 17.

Table 31: Analysis of confirmed ORR based on RECIST 1.1 per central radiology assessment - Subjects with PD-L1 CPS >= 10% (ITT population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate(95% CI)†	p-Value††
Control	90	6	6.7 (2.5,13.9)		
Pembrolizumab	74	16	21.6 (12.9,32.7)	19.3 (8.6,31.7)	0.00020

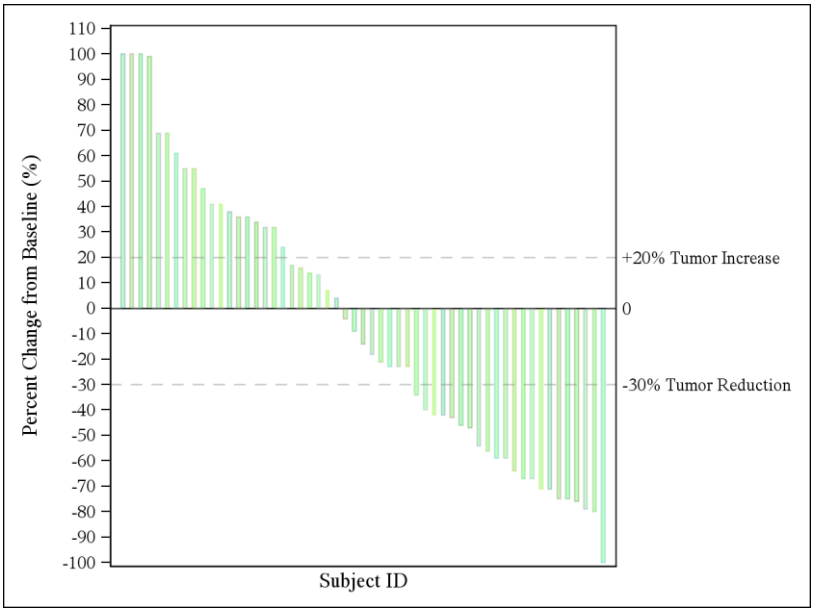
† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

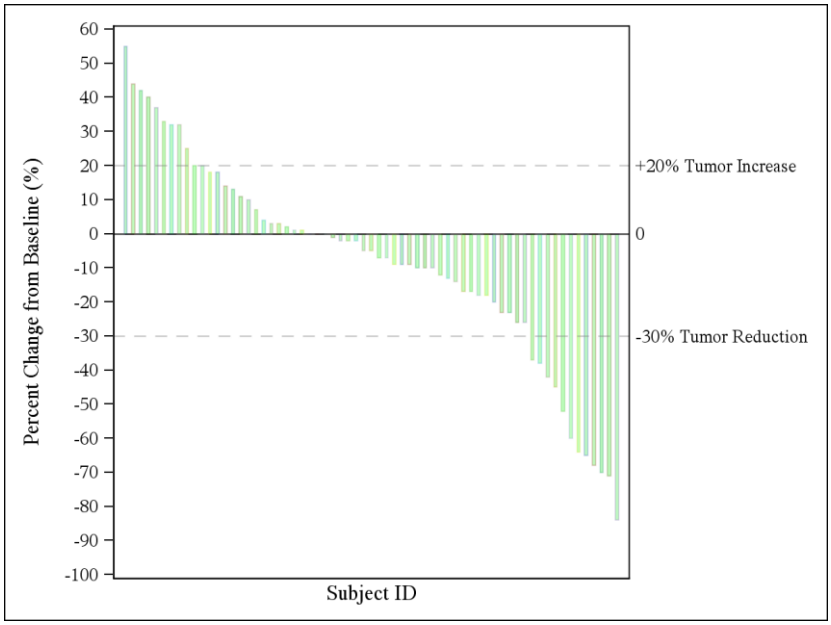
Database Cut-off Date: 07SEP2016

Figure 16: Waterfall plot of best tumour change from baseline in pembrolizumab arm based on RECIST 1.1 per central radiology assessment - Subjects with PD-L1 CPS >= 10% with measureable disease at baseline (ITT population)



Percentage changes >100% were truncated at 100%.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Figure 17: Waterfall plot of best tumour change from baseline in control arm based on RECIST 1.1 per central radiology assessment - subjects with PD-L1 CPS >= 10% with measureable disease at baseline (ITT population)



Percentage changes >100% were truncated at 100%.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

The results of the ORR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment and per mRECIST by Central Radiology Assessment for subjects with PD-L1 CPS ≥10% are consistent with the Central Radiology Assessment and are provided in Table 32 and Table 33, respectively.

Table 32: Analysis of confirmed ORR based on RECIST 1.1 per site radiology assessment - Subjects with PD-L1 CPS >= 10% (ITT population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate (95% CI)†	p-Value††
Control	90	7	7.8 (3.2,15.4)		
Pembrolizumab	74	19	25.7 (16.2,37.2)	21.8 (10.7,34.5)	0.00008

† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Table 33: Analysis of confirmed ORR based on modified RECIST 1.1 per central radiology assessment - Subjects with PD-L1 CPS >= 10% (ITT Population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate (95% CI)†	p-Value††
Control	90	7	7.8 (3.2,15.4)		
Pembrolizumab	74	19	25.7 (16.2,37.2)	22.5 (11.0,35.3)	0.00006

† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Consistent with the overall ITT population, more subjects in the PD-L1 CPS ≥10% population receiving pembrolizumab versus control had a BOR of CR (5 [6.8%] vs 2 [2.2%], respectively) per RECIST 1.1 by Central Radiology. Likewise, more subjects in the pembrolizumab arm had a BOR of PR (11 [14.9%] vs 4 [4.4%], respectively) (Table 34).

Table 34: Summary of BOR based on RECIST 1.1 per central radiology assessment - Subjects with PD-L1 CPS >= 10% (ITT population)

Response Evaluation	Control (N=90)			Pembrolizumab (N=74)		
	n	%	95% CI†	n	%	95% CI†
Complete Response (CR)	2	2.2	(0.3, 7.8)	5	6.8	(2.2, 15.1)
Partial Response (PR)	4	4.4	(1.2, 11.0)	11	14.9	(7.7, 25.0)
Objective Response (CR+PR)	**6**	**6.7**	**(2.5, 13.9)**	**16**	**21.6**	**(12.9, 32.7)**
Stable Disease (SD)	32	35.6	(25.7, 46.3)	9	12.2	(5.7, 21.8)
Disease Control (CR+PR+SD)	**38**	**42.2**	**(31.9, 53.1)**	**25**	**33.8**	**(23.2, 45.7)**
Progressive Disease (PD)	28	31.1	(21.8, 41.7)	37	50.0	(38.1, 61.9)
Non-evaluable (NE)	4	4.4	(1.2, 11.0)	0	0.0	(0.0, 4.9)
No Assessment	20	22.2	(14.1, 32.2)	12	16.2	(8.7, 26.6)

Confirmed responses are included.

† Based on binomial exact confidence interval method.

Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.

No Assessment: subject had no post-baseline imaging.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Duration of follow-up in responders with confirmed CR or PR was similar between arms and is presented in Appendix 8.

The results of the BOR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment and for confirmed response per mRECIST by Central Radiology Assessment, conducted as supportive analyses, for subjects with PD-L1 CPS ≥10% are consistent with the Central Radiology Assessment and are provided in Appendix 8. Summaries of the BOR analyses including confirmed and unconfirmed responses for subjects with PD-L1 CPS ≥10% per central and per site radiology assessment are also provided in Appendix 8.

- *ORR per confirmed RECIST 1.1 by central radiology assessment among subjects with PD-L1 CPS ≥1%*

Results of confirmed ORR by Central Radiology Assessment among subjects with PD-L1 CPS ≥1% can be found in Table 35. Waterfall plots for pembrolizumab and control arms are shown in Figure 18 and Figure 19 respectively.

Table 35: Analysis of Confirmed Objective Response Based on RECIST 1.1 per Central Radiology Assessment - Subjects with PD-L1 CPS >= 1% (ITT Population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate (95% CI)†	p-Value††
Control	120	10	8.3 (4.1,14.8)		
Pembrolizumab	110	26	23.6 (16.1,32.7)	16.9 (7.7,27.0)	0.00022

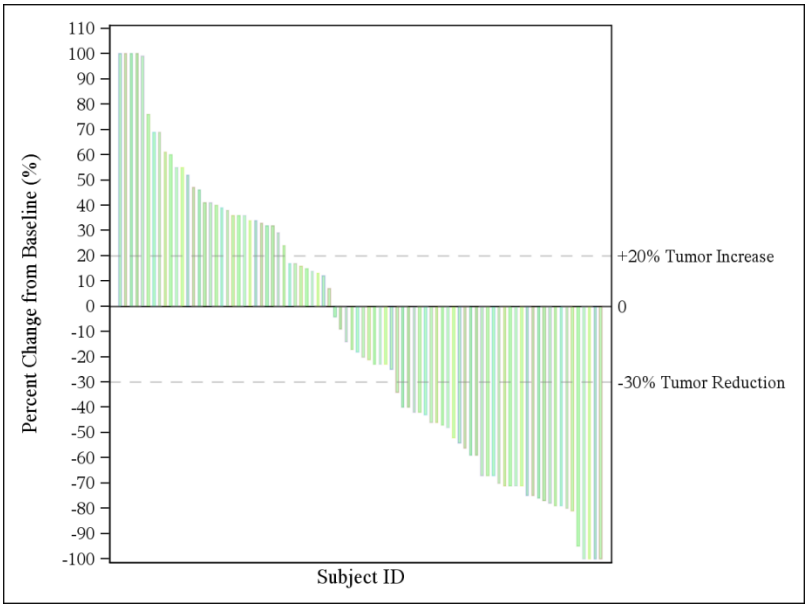
† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

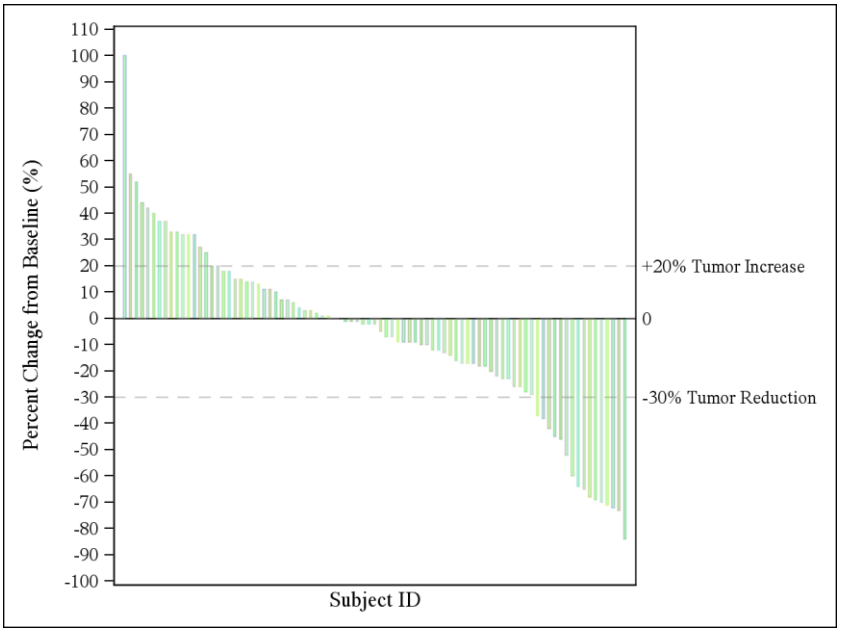
Database Cut-off Date: 07SEP2016

Figure 18: Waterfall plot of best tumour change from baseline in pembrolizumab arm based on RECIST 1.1 per central radiology assessment - Subjects with PD-L1 CPS >= 1% with measureable disease at baseline (ITT population)



Percentage changes >100% were truncated at 100%.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Figure 19: Waterfall plot of best tumour change from baseline in control arm based on RECIST 1.1 per central radiology assessment - Subjects with PD-L1 CPS >= 1% with measureable disease at baseline (ITT population)



Percentage changes >100% were truncated at 100%.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

The results of the ORR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment and per mRECIST by Central Radiology Assessment for subjects with PD-L1 CPS ≥1% are provided Appendix 8. Results for BOR by Central Radiology Assessment, for confirmed response per mRECIST by Central Radiology Assessment, and for confirmed response per RECIST 1.1 by Site Radiology Assessment for subjects with PD-L1 CPS ≥1% can be found in Appendix 8.

Summaries of the BOR analyses including confirmed and unconfirmed responses for subjects with PD-L1 CPS ≥1% per central and per site radiology assessment are also provided in Appendix 8.

Time to Response (TTR) and Response Duration

- *TTR and response duration by central radiology assessment among all subjects*

TTR was defined as the time from randomisation to the first assessment of a complete response (CR) or partial response (PR). Response duration was defined as the time from the first CR/PR to documented PD. Only confirmed CR/PRs were included in the analysis for TTR and response duration. Subjects who did not have PD were censored at the time of the last disease response assessment.

The median TTR for responders per Central Radiology Assessment was similar in the pembrolizumab (2.1 months, range: 1.4 to 6.3) and control (2.1 months, range: 1.7 to 4.9) arms (Table 36; Figure 20).

Median duration of response (DOR) for the 57 subjects receiving pembrolizumab with confirmed CR/PR had not yet been reached at the time of data cut-off (range: 1.6+ to 15.6+ months), whereas median DOR for the 31 subjects receiving control with confirmed CR/PR was established at 4.3 months (range: 1.4+ to 15.4+ months) (Table 36). The results indicate very durable responses with pembrolizumab, particularly considering the maturity of the dataset, with a clear difference with regard to durability versus control (Figure 20). As assessed by the KM method, there were more subjects in the pembrolizumab arm than in the control arm with responses ≥6 months (78% vs 40%) and ≥12 months (68% vs 35%).

The results of the DOR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment for all subjects in the ITT population are consistent with the Central Radiology Assessment and are provided in Appendix 8.

Table 36: Summary of TTR and response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response - All subjects (ITT population)

	Control (N=272)	Pembrolizumab (N=270)
Number of Subjects with Response†	31	57
Time to Response† (months)		
Mean (SD)	2.4 (0.8)	2.7 (1.2)
Median (Range)	2.1 (1.7-4.9)	2.1 (1.4-6.3)
Response Duration‡ (months)		
Median (Range)§	4.3 (1.4+ - 15.4+)	Not reached (1.6+ - 15.6+)
Number of Subjects with Response ≥ 6 Months (%)‡	7 (40)	41 (78)
Number of Subjects with Response ≥ 12 Months (%)‡	3 (35)	14 (68)

† *Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.*

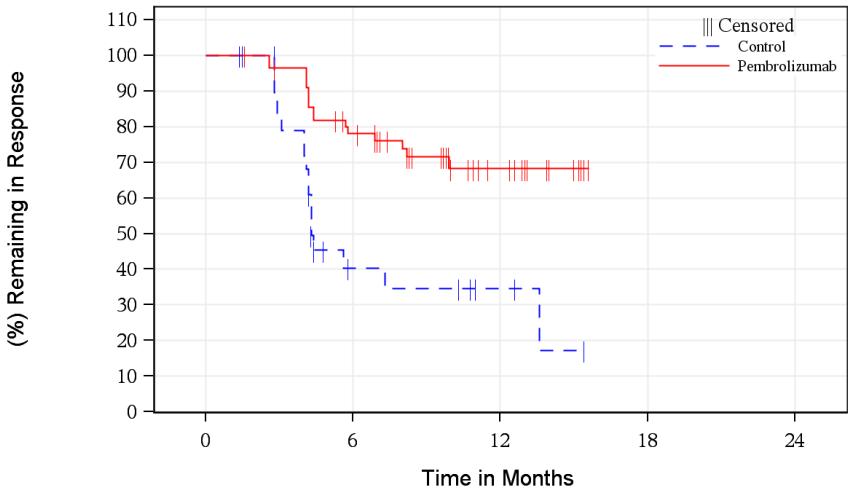
‡ *Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.*

§ *"+" indicates the response duration is censored.*

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 20: KM estimates of objective response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response - All subjects (ITT population)



Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

- *TTR and response duration by central radiology assessment – PD-L1 CPS ≥10% population*

The median TTR for responders in the PD-L1 CPS ≥10% population per Central Radiology Assessment was similar in both arms (pembrolizumab = 2.1 months, range: 1.4 to 5.3; control = 2.1 months, range: 1.9 to 2.2). Consistent with the overall ITT population, median DOR for 16 subjects with PD-L1 CPS ≥10% receiving pembrolizumab with a confirmed CR/PR had not yet been reached at the time of data cut-off (range: 1.6+ to 15.4+ months), whereas median DOR for the 6 subjects with PD-L1 CPS ≥10% receiving control was established at 4.4 months (range: 1.5+ to 10.8+ months) (Table 37 and Figure 21).

There were 14 subjects with PD-L1 CPS ≥10% in the pembrolizumab arm and 1 subject in the control arm with responses ≥6 months. There were 3 subjects in the pembrolizumab arm and no subjects in the control arm with response ≥12 months (Table 37).

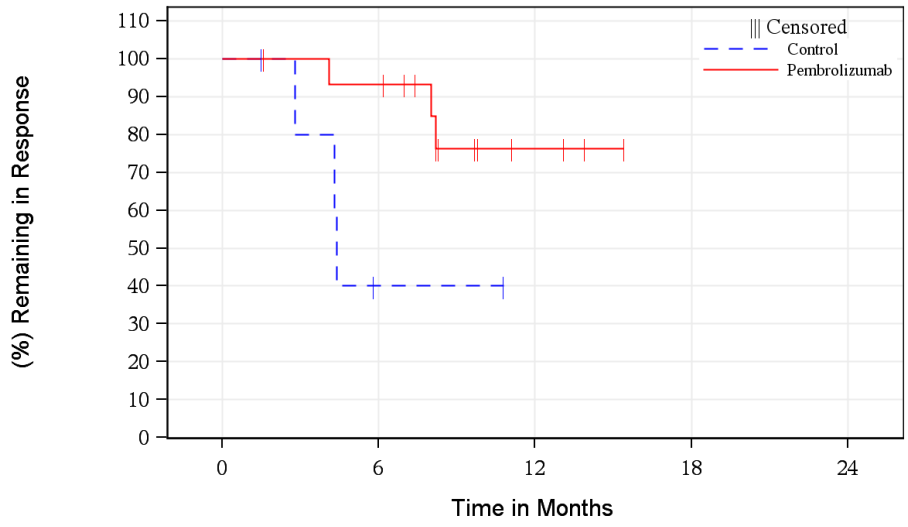
The results of the DOR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment for subjects with PD-L1 CPS ≥10% are consistent with the Central Radiology Assessment and are provided in Appendix 8.

Table 37: Summary of TTR and response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response - Subjects with PD-L1 CPS >= 10% (ITT population)

	Control (N=90)	Pembrolizumab (N=74)
Number of Subjects with Response†	6	16
Time to Response† (months)		
Mean (SD)	2.0 (0.1)	2.5 (1.0)
Median (Range)	2.1 (1.9-2.2)	2.1 (1.4-5.3)
Response Duration‡ (months)		
Median (Range)§	4.4 (1.5+ - 10.8+)	Not reached (1.6+ - 15.4+)
Number of Subjects with Response ≥ 6 Months (%)‡	1 (40)	14 (93)
Number of Subjects with Response ≥ 12 Months (%)‡	0	3 (76)

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates the response duration is censored.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Figure 21: KM estimates of objective response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response - Subjects with PD-L1 CPS >= 10% (ITT population)



Number of subject at risk

Control	6	1	0	0	0
Pembrolizumab	16	14	3	0	0

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cut-off date: 07SEP2016)

The results of response duration and the TTR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment are provided for PD-L1 CPS ≥10% subjects in Appendix 8.

- *TTR and response duration by central radiology assessment among subjects with PD-L1 CPS ≥1%*

The median TTR for responders was similar for both treatment arms (Table 38). Median DOR for the subjects with PD-L1 CPS ≥1% receiving pembrolizumab or control with confirmed CR/PR had not yet been reached at the time of data cut-off.

There were more subjects in the pembrolizumab arm than in the control arm with responses ≥6 months and ≥12 months.

Table 38: Summary of TTR and response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response - Subjects with PD-L1 CPS >= 1% (ITT population)

	Control (N=120)	Pembrolizumab (N=110)
Number of Subjects with Response†	10	26
Time to Response† (months)		
Mean (SD)	2.0 (0.1)	2.6 (1.0)
Median (Range)	2.1 (1.9-2.2)	2.2 (1.4-5.3)
Response Duration‡ (months)		
Median (Range)§	Not reached (1.5+ - 15.4+)	Not reached (1.6+ - 15.6+)
Number of Subjects with Response ≥ 6 Months (%)‡	3 (56)	21 (88)
Number of Subjects with Response ≥ 12 Months (%)‡	2 (56)	7 (78)

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates the response duration is censored.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

A summary of the reasons subjects with PD-L1 CPS ≥1% with a confirmed response based on RECIST 1.1 per Central Radiology Assessment were censored from the DOR analysis is provided in Appendix 8.

The results of the DOR analyses for confirmed response per RECIST 1.1 by Site Radiology Assessment for subjects with PD-L1 CPS ≥1% are consistent with the Central Radiology Assessment Appendix 8.

PFS per RECIST 1.1 by central radiology assessment at 6 and 12 months

- *PFS per RECIST 1.1 by central radiology assessment at 6 and 12 months among all subjects*

As a secondary endpoint, analyses of PFS based on RECIST 1.1 by Central Radiology Assessment were performed for all subjects in the ITT population at 6 months and 12 months of treatment. At 6 months, the PFS rate for the pembrolizumab arm was 28.8% compared with 26.8% in the control arm, and at 12 months, the PFS rate for the pembrolizumab arm was 16.8% compared with 6.2% in the control arm (Table 24).

Results of the analyses of PFS per mRECIST by Central Radiology Assessment at 6 and 12 months among all subjects in the ITT population are consistent with results per RECIST 1.1 and may be found in Appendix 8.

- *PFS per RECIST 1.1 by central radiology assessment at 6 and 12 months among subjects with PD-L1 CPS ≥10%*

As a secondary endpoint, analyses of PFS based on RECIST 1.1 by Central Radiology Assessment were performed for subjects with PD-L1 CPS ≥10% at 6 months and 12 months of treatment. Results showed that at 6 months, the PFS rate for the pembrolizumab arm was 24.7% compared with 18.5% in the control arm, and at 12 months, the PFS rate for the pembrolizumab arm was 17.7% compared with 3.7% in the control arm (Table 25).

Results of the analysis of PFS per mRECIST by Central Radiology Assessment at 6 and 12 months among subjects with PD-L1 CPS ≥10% are consistent with results per RECIST 1.1 and may be found in Appendix 8.

- *PFS per RECIST 1.1 by central radiology assessment at 6 and 12 months among subjects with PD-L1 CPS ≥1%*

As a secondary endpoint, analyses of PFS based on RECIST 1.1 by Central Radiology Assessment showed that the 6-month and 12-month PFS rates were higher for the pembrolizumab arm than in the control arm (Table 26).

Results of the analysis of PFS per mRECIST by Central Radiology Assessment at 6 and 12 months among subjects with PD-L1 CPS ≥1% are consistent with results per RECIST 1.1 and may be found in Appendix 8.

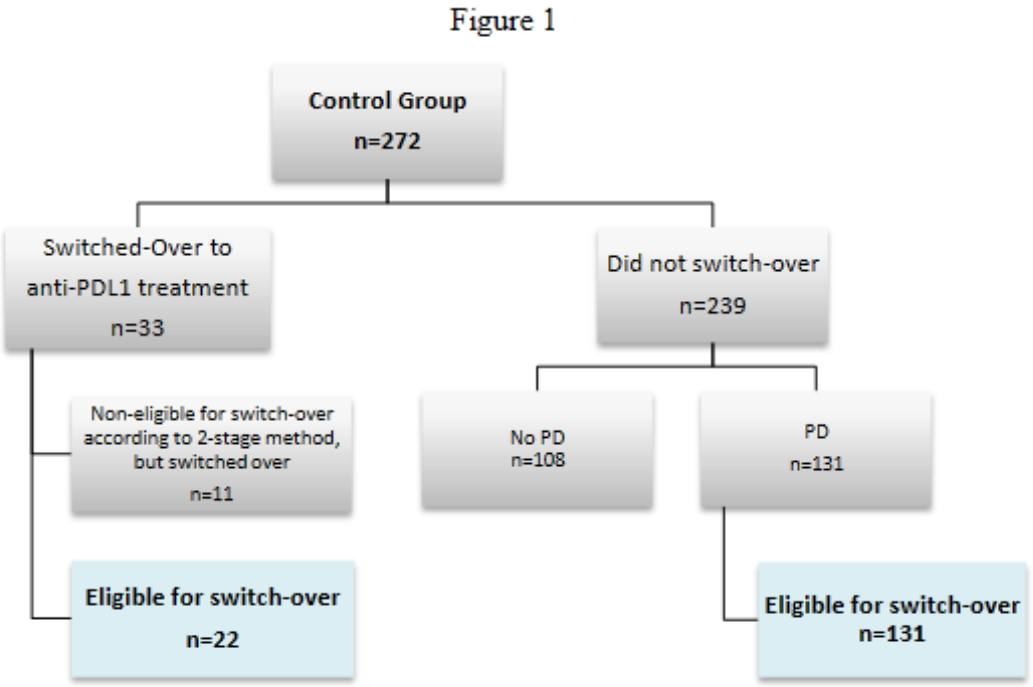
Modelling approaches on OS analysis after adjusting for switching

Overall survival (OS) data were analysed using the ITT approach, as planned in the CSR analyses. ITT results of the OS analysis result in a hazard ratio of 0.73, p=0.004 (2-sided), (95% CI: 0.59; 0.91) corresponding to a substantial reduction of 27% in hazard (see Table 21).

In KEYNOTE-045, 272 patients were randomised to the control arm. A total of 33/272 (12.1%) patients switched over to anti-PD-1/anti-PD-L1 treatment including 22 patients who had experienced documented progressive disease and therefore met the eligibility criteria for switch-over. In 239 non-switched over patients, 131 patients met the eligibility criteria for switch-over. A total of 153 eligible patients (22 switchers vs. 131 non-switchers) were included in the first stage model to estimate the acceleration factor.

The breakdown of the disposition of the control group is depicted in Figure **22**.

Figure 22: Disposition of patients in the KEYNOTE-045 control group according to switch



As the survival benefit associated with pembrolizumab is diluted due to switching, conventional survival analysis will underestimate the survival benefit associated with pembrolizumab. Therefore, for the estimation of the OS in the control arm, OS was adjusted, using alternative treatment switching adjustment methods, to reflect the actual benefit of patients receiving the regimens in the control arm in the absence of treatment switching to alternative therapies, as it is reflective of clinical practice. Three statistical methods were applied to adjust for treatment switching: the rank preserving structural failure time method (RPSFT),[59] the simplified 2-stage method[60] and the inverse probability of censoring weighting method (IPCW).[61]

The RPSFT method had been pre-specified in the study protocol to adjust for the anticipated treatment switching effect in advance of the availability of trial based information needed to determine the clinical validity of the approach, which should be assessed a posteriori. Following the NICE DSU recommendations for the adjustment of treatment switching in clinical trials,[60] additional adjustments (two-stage and the IPCW) were implemented to better understand the control-related OS in the absence of treatment switching.

RPSFT adjustment

The RPSFT method is based on the assumption of common treatment effect, a strong assumption that cannot be formally tested based on the data. It assumes that the multiplicative treatment effect of pembrolizumab is constant, irrespective of the time of initiation of the treatment (at randomisation or switch). Under this assumption, the adjusted estimated hazard ratio was 0.68 (95% CI: 0.58; 0.88).

Two-stage adjustment

The two-stage simplified model is most appropriate when patients are allowed to switch to the new treatment shortly after progression of disease and there is a clear definition of a new secondary baseline. These conditions were met in KEYNOTE-045. In stage 1, the switch effect was estimated after adjustment for other covariates. The estimated post-progression treatment estimate was 3.02 (95% CI: 1.90; 5.65). This point estimate suggests that switching to pembrolizumab increases survival time by a factor of 3.02. Adjustment of survival time based on this factor had a strong impact on survival. In addition, re-censoring using this factor would reduce the information and provide less reliable results. Therefore, the two-stage methodology was finally used without re-censoring. The estimated hazard ratio of 0.69 (95% CI: 0.55; 0.86) from the two-stage simplified method is consistent with the survival adjustment resulting from the stage 1 estimate.

IPCW adjustment

The inverse-probability-of-censoring weighting (IPCW) method adjusts ITT overall survival analysis by weighting the contribution from each subject in the control arm during a particular time interval prior to switching. Subjects who switched were censored at the time of switching. There were, 13/179 observed deaths (7.3%), in the control arm lost due to the informative censoring in both scenarios, which were consequently adjusted for using the IPC weights. In the primary analysis scenario, the IPCW-adjusted hazard ratio of mortality in the pembrolizumab arm compared to control is 0.70 (95% CI 0.56, 0.88) – a 30% statistically significant reduction in hazard of mortality.

The results from the ITT approach and results from the methods adjusting for switching are summarized in

Table 39 below. The three adjustment methods provided estimated hazard ratios smaller than the HR derived from the ITT analysis (larger treatment effect), within a narrow range of 0.68 to 0.70.

Table 39: Summary Results of OS Analyses (switching adjustment)

Treatment switch correction method	Pembrolizumab vs. Control		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT	0.73	(0.59; 0.91)	0.004
Simplified two-stage (no re-censoring)	0.69	(0.55; 0.86)	0.0045*
RPSFT	0.68	(0.58; 0.88)	0.0045*
IPCW	0.70	(0.56; 0.87)	0.002
** P-value retained from the ITT analysis based on distribution of the test statistic under the null hypothesis of no treatment effect*			

A summary of the median OS in the pembrolizumab study arm and SOC study arm, with and without various treatment switching correction methods applied, is summarised below in Table 40.

Table 40: Analysis of median OS using Two-stage, RPSFT and IPCW methods

Treatment switch correction method	Median OS (months) (95% CI)
Control (no correction for treatment switching)	7.4 (6.1, 8.3)
Control - Simplified two-stage correction (no re-censoring)	7.0 (5.5, 7.7)
Control – RPSFT correction	7.1 (6.0, 7.7)
Control – IPCW correction	6.9 (5.5, 7.7)

Figure 23: Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis - No recensoring (ITT Population)

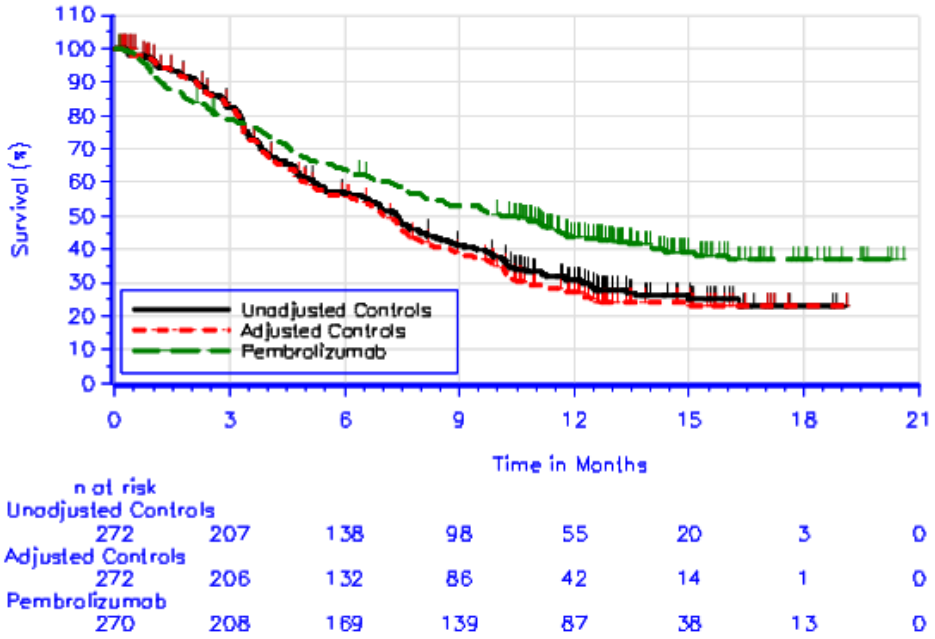


Figure 24: Analysis of Overall Survival with RPSFT Correction (ITT population)

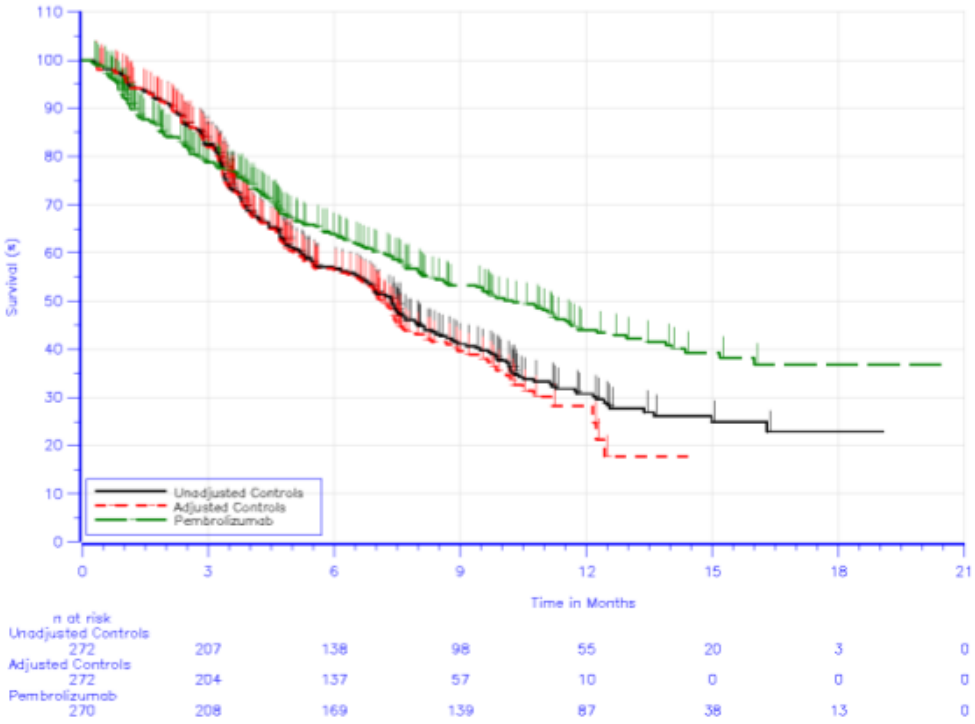
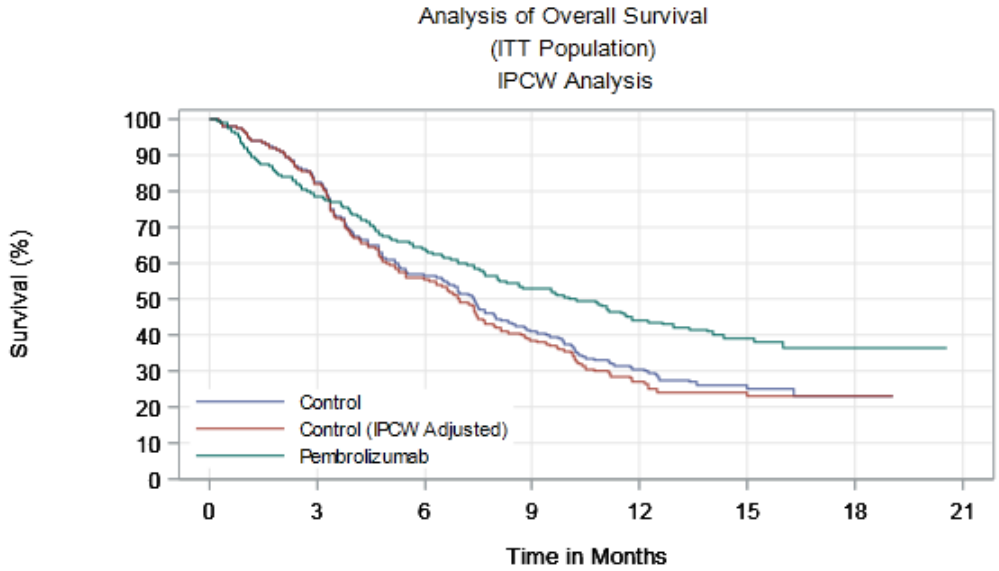


Figure 25: Analysis of Overall Survival with IPCW correction (ITT population)



Number of Subjects at Risk

Control	272	207	138	98	55	20	3	0
Control (IPCW Adjusted)	272	202	123	81	37	10	1	0
Pembrolizumab	270	208	169	139	87	38	13	0

Inverse-Probability-of-Censoring Weights (IPCW) applied from study entry to all subjects in the SOC arm
(Database Cutoff Date: 07SEP2016)

Exploratory endpoints: Patient-reported outcome (PRO) analyses

The primary analysis approach for the pre-specified PRO endpoints was based on a quality-of-life-related full analysis set (FAS) population, which consists of all randomised subjects who received at least 1 dose of study treatment, and had completed at least 1 PRO assessment.

EORTC QLQ-30 and EQ-5D compliance rate and completion rate

In the PRO FAS population, there were 266 subjects in the pembrolizumab arm and 254 subjects in the control arm. Compliance rates for EORTC QLQ-C30 at baseline were similar and above 95% in both the pembrolizumab and control arms (97.7% vs 95.7%) and remained high at Week 15 (87.7% vs 88.1%). Compliance rates for EQ-5D at baseline were 100% in both the pembrolizumab and control arms and remained high at Week 15 (88.1% vs 87.7%). Completion rates continued to decrease at each time point as more and more subjects discontinued the trial due to disease progression, physician decision, AEs, or death.

EORTC QLQ-C30 analyses

- *EORTC QLQ-C30 score change from baseline to Week 9 and Week 15*

Baseline global health status/QoL scores were similar between treatment arms. At Week 9, the global health status/QoL score was stable from baseline (least squares [LS] mean = -1.37 points; 95% CI: -4.10, 1.35) in the pembrolizumab arm, and a greater worsening of -5.75 points (95% CI: -8.62, -2.87) was observed in the control arm. The difference in LS means between pembrolizumab and the control arm at Week 9 was 4.38 points (95% CI: 0.59, 8.16; two-sided p=0.02, not controlled for multiplicity) (Table 41). At Week 15, there was an even greater difference in LS means between pembrolizumab arm and control (9.05 points; 95% CI: 4.61, 13.48; two-sided p<0.001, not controlled for multiplicity) (Table 42). A mean difference of 10 points or more has been widely viewed as being clinically significant when interpreting the results of randomised trials employing EORTC QLQ-C30;[62, 63] however, minimally important differences as low as 4 points have been reported for EORTC QLQ-C30 in other cancer trials.[64]

Table 41: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at Week 9 - (FAS population)

Treatment	Baseline		Week 9		Change from Baseline at Week 9	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Control	243	59.12 (22.144)	176	58.48 (21.849)	254	-5.75 (-8.62, -2.87)
Pembrolizumab	260	61.51 (23.107)	200	63.04 (22.964)	266	-1.37 (-4.10, 1.35)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Control	4.38 (0.59, 8.16)	0.024

† *1. Based on cLDA model with the PRO scores as the response variable, treatment by study visit interaction, and stratification factors: Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months), as covariates.*

For baseline and Week 9, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off: 07SEP2016

Table 42: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at Week 15 - (FAS population)

Treatment	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Control	243	59.12 (22.144)	118	57.91 (19.516)	254	-8.30 (-11.76, -4.83)
Pembrolizumab	260	61.51 (23.107)	157	67.57 (22.558)	266	0.75 (-2.34, 3.83)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Control	9.05 (4.61, 13.48)	<.001

† *1. Based on cLDA model with the PRO scores as the response variable, treatment by study visit interaction, and stratification factors: Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months), as covariates.*

For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off: 07SEP2016

- *EORTC QLQ-C30 global health status score at each visit to Week 27*

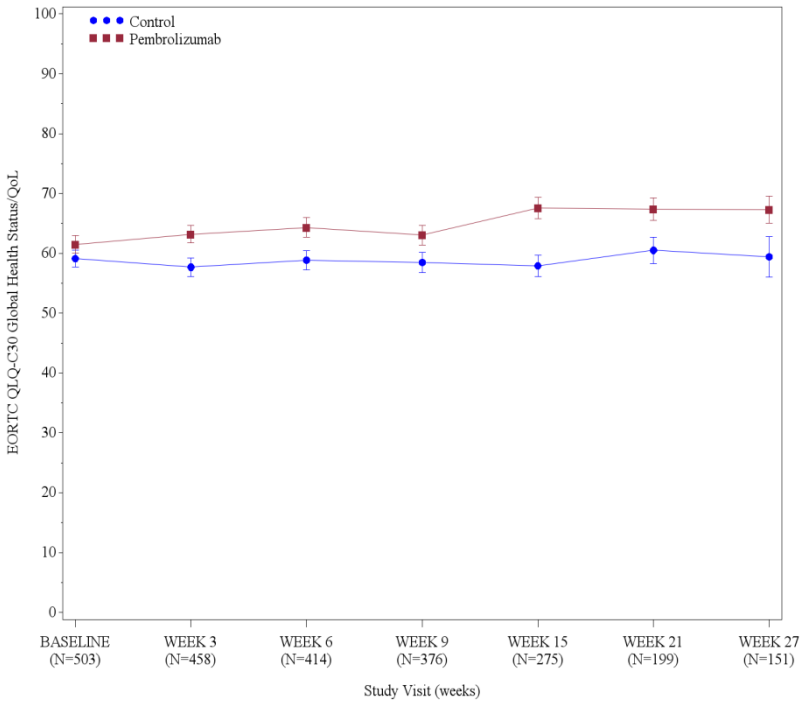
The EORTC QLQ-C30 global health status/QoL scores at baseline were similar between the 2 treatment arms. Beginning at Week 3, subjects in the pembrolizumab arm had higher global health status/QoL scores compared with controls (i.e. 95% CI did not overlap) (Table 43 and Figure 26).

Table 43: Summary of QLQ-C30 global health status/QoL at study visit - (FAS population)

Study Visit	Treatment			
	Control (N†=254)		Pembrolizumab (N†=266)	
	n	Mean (SE)	n	Mean (SE)
BASELINE	243	59.1 (1.4)	260	61.5 (1.4)
WEEK 3	220	57.7 (1.5)	238	63.2 (1.4)
WEEK 6	199	58.9 (1.6)	215	64.3 (1.6)
WEEK 9	176	58.5 (1.6)	200	63.0 (1.6)
WEEK 15	118	57.9 (1.8)	157	67.6 (1.8)
WEEK 21	73	60.5 (2.2)	126	67.4 (1.8)
WEEK 27	46	59.4 (3.4)	105	67.3 (2.3)

†: Number of subjects in Full Analysis Set population.
Database Cut-off: 07SEP2016

Figure 26: Summary of EORTC QLQ-C30 Global health status/QoL at Study Visit - Mean +/- SE - (FAS Population)



Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off: 07SEP2016

- *Time to deterioration analysis of EORTC QLQ-C30 global health status/QoL score*

Pembrolizumab prolonged the time to traditional deterioration (i.e. defined as the time to the first onset of a 10-point or greater score decrease from baseline in the EORTC QLQ-C30 global health status/QoL score) when compared with the control arm (HR = 0.70; 95% CI: 0.55, 0.90; two-sided *p*=0.002, not controlled for multiplicity) (Table 44 and Figure 31).

Table 44: Time to traditional deterioration for EORTC QLQ-C30 global health status/QoL - (FAS population with baseline)

Treatment	N	Deterioration Events (%)	Pembrolizumab vs. Control	
			Hazard Ratio‡ (95% CI)‡	p-Value§
Control	243	133 (54.7)		
Pembrolizumab	260	137 (52.7)	0.70 (0.55, 0.90)	0.00182

Traditional deterioration is defined as time to first onset of 10 or more decrease from baseline without confirmation under right-censoring rule (the last observation).

† From product-limit (Kaplan-Meier) method for censored data.

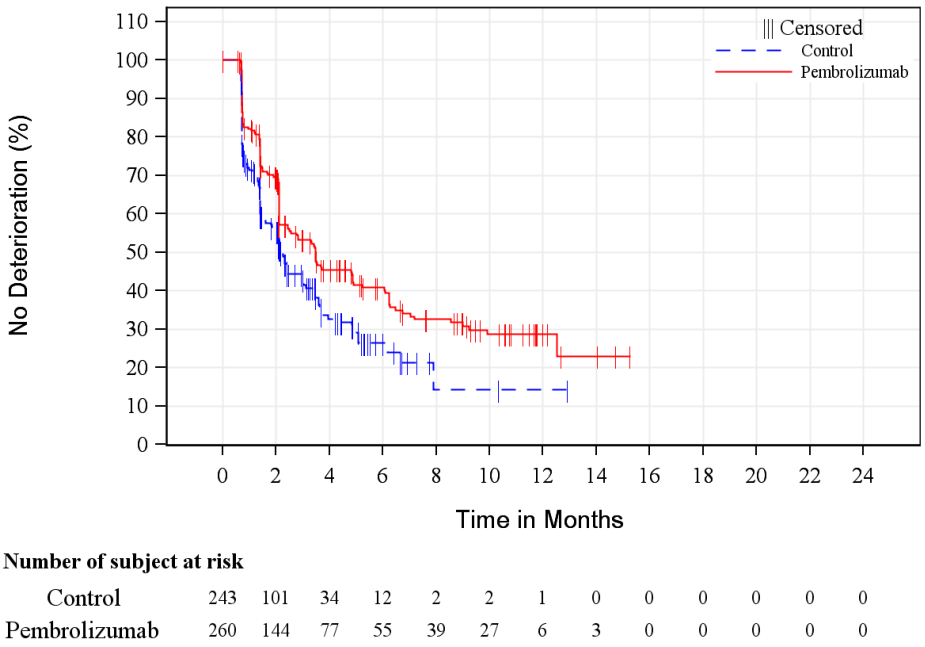
‡ Based on Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Figure 27: Kaplan-Meier of Time to Traditional Deterioration for EORTC QLQ-C30 Global health status/QoL - (FAS Population with Baseline)



Database Cut-off Date: 07SEP2016

- *Summary of EQ-5D Analyses*

Results from EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses. Both the EQ-5D visual analog score (Table 45) and the EQ-5D Utility scores (Table 46) were stable over time for subjects in the pembrolizumab arm, whereas a worsening of EQ-5D VAS and Utility scores was observed in the control group.

Table 45: Summary of change from baseline in EuroQol EQ-5D VAS by time point - (FAS population)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change From Baseline at Time Point				
				Mean (SD)	Q1	Median	Q3	95% CI
WEEK 3								
Control	209	67.3 (20.03)	66.1 (20.10)	-1.2 (17.84)	-9.0	0.0	9.0	(-3.7, 1.2)
Pembrolizumab	232	68.0 (20.10)	69.1 (19.32)	1.1 (16.50)	-8.0	0.0	9.0	(-1.1, 3.2)
WEEK 6								
Control	191	69.8 (17.81)	65.6 (20.78)	-4.1 (18.35)	-12.0	-3.0	6.0	(-6.7, -1.5)
Pembrolizumab	210	68.8 (19.48)	69.3 (19.25)	0.5 (16.90)	-10.0	0.0	10.0	(-1.8, 2.8)
WEEK 9								
Control	169	70.5 (18.54)	66.5 (19.80)	-4.0 (17.37)	-12.0	-2.0	6.0	(-6.7, -1.4)
Pembrolizumab	195	69.2 (19.63)	70.0 (20.22)	0.8 (18.34)	-7.0	0.0	10.0	(-1.8, 3.4)
WEEK 15								
Control	112	70.8 (17.69)	67.7 (18.44)	-3.1 (17.53)	-12.0	-1.0	9.0	(-6.4, 0.2)
Pembrolizumab	153	71.8 (19.07)	73.4 (18.38)	1.6 (17.35)	-10.0	1.0	11.0	(-1.1, 4.4)
WEEK 21								
Control	67	71.1 (18.20)	67.2 (18.75)	-3.9 (18.75)	-15.0	-4.0	7.0	(-8.5, 0.7)
Pembrolizumab	123	71.8 (18.75)	73.2 (18.65)	1.4 (22.06)	-9.0	1.0	11.0	(-2.5, 5.3)
WEEK 27								
Control	43	72.5 (16.99)	66.3 (19.48)	-6.2 (22.95)	-22.0	-3.0	7.0	(-13.3, 0.8)
Pembrolizumab	104	71.7 (18.49)	75.1 (19.00)	3.4 (19.19)	-5.0	2.5	13.0	(-0.3, 7.1)

Q1=25th percentile; Q3=75th percentile; CI=Confidence Interval
N= the number of treated subjects with valid value at baseline and at the time point for EuroQol EQ-5D VAS.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Table 46: Summary of change from baseline in EuroQol EQ-5D utility score (using European algorithm) by time point - (FAS population)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change From Baseline at Time Point				
				Mean (SD)	Q1	Median	Q3	95% CI
WEEK 3								
Control	209	0.70 (0.22)	0.68 (0.23)	-0.02 (0.19)	-0.12	0.00	0.07	(-0.05, 0.00)
Pembrolizumab	232	0.72 (0.22)	0.70 (0.24)	-0.02 (0.19)	-0.10	0.00	0.06	(-0.05, 0.00)
WEEK 6								
Control	191	0.73 (0.19)	0.66 (0.24)	-0.07 (0.22)	-0.21	0.00	0.02	(-0.10, -0.04)
Pembrolizumab	210	0.73 (0.22)	0.70 (0.25)	-0.03 (0.22)	-0.12	0.00	0.09	(-0.06, 0.00)
WEEK 9								
Control	169	0.73 (0.20)	0.65 (0.26)	-0.08 (0.23)	-0.22	0.00	0.00	(-0.12, -0.05)
Pembrolizumab	195	0.73 (0.22)	0.70 (0.27)	-0.03 (0.23)	-0.12	0.00	0.09	(-0.07, -0.00)
WEEK 15								
Control	112	0.76 (0.19)	0.67 (0.23)	-0.09 (0.21)	-0.22	-0.00	0.01	(-0.12, -0.05)
Pembrolizumab	153	0.76 (0.22)	0.74 (0.24)	-0.01 (0.20)	-0.10	0.00	0.09	(-0.05, 0.02)
WEEK 21								
Control	67	0.77 (0.19)	0.68 (0.22)	-0.09 (0.20)	-0.22	-0.07	0.00	(-0.14, -0.04)
Pembrolizumab	123	0.77 (0.20)	0.77 (0.21)	-0.00 (0.20)	-0.09	0.00	0.09	(-0.04, 0.03)
WEEK 27								
Control	43	0.78 (0.19)	0.69 (0.25)	-0.09 (0.22)	-0.22	-0.03	0.02	(-0.16, -0.03)
Pembrolizumab	104	0.77 (0.21)	0.76 (0.25)	-0.01 (0.23)	-0.13	0.00	0.17	(-0.06, 0.03)

Q1=25th percentile; Q3=75th percentile; CI=Confidence Interval
N= the number of treated subjects with valid value at baseline and at the time point for EuroQol EQ-5D utility score.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

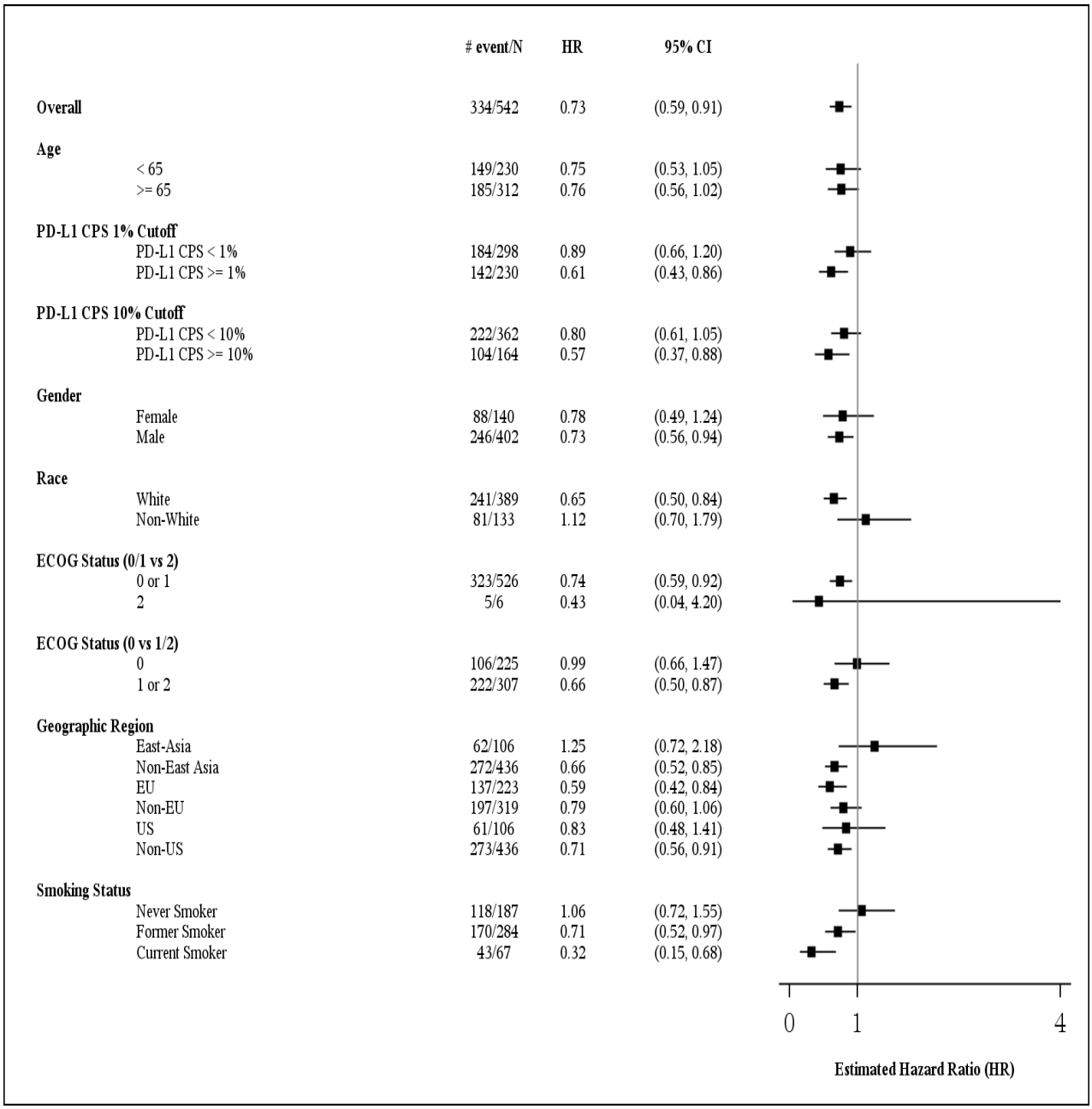
4.8 Subgroup analysis

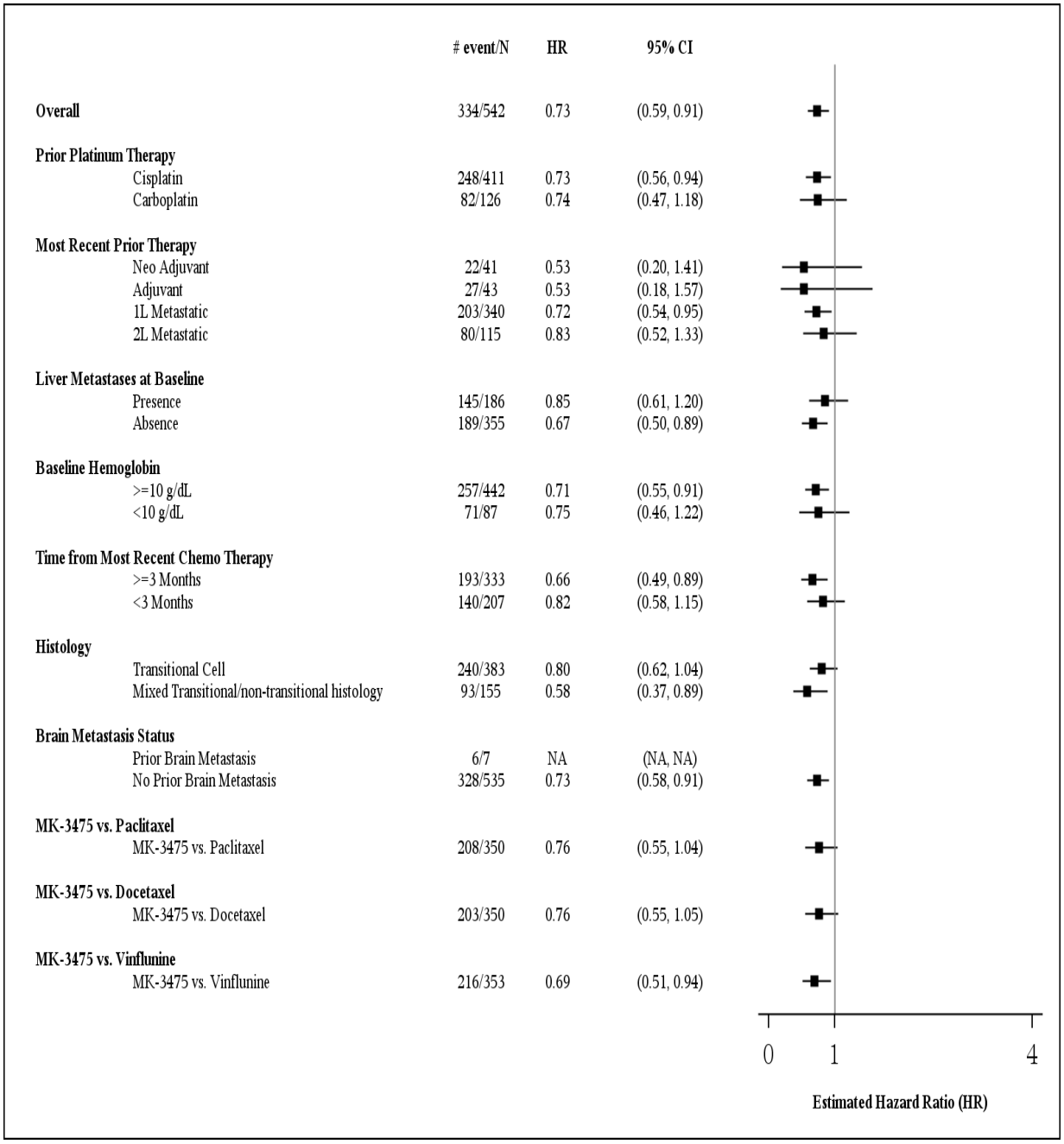
KEYNOTE-045[16]

Subgroup analyses: OS – ITT population

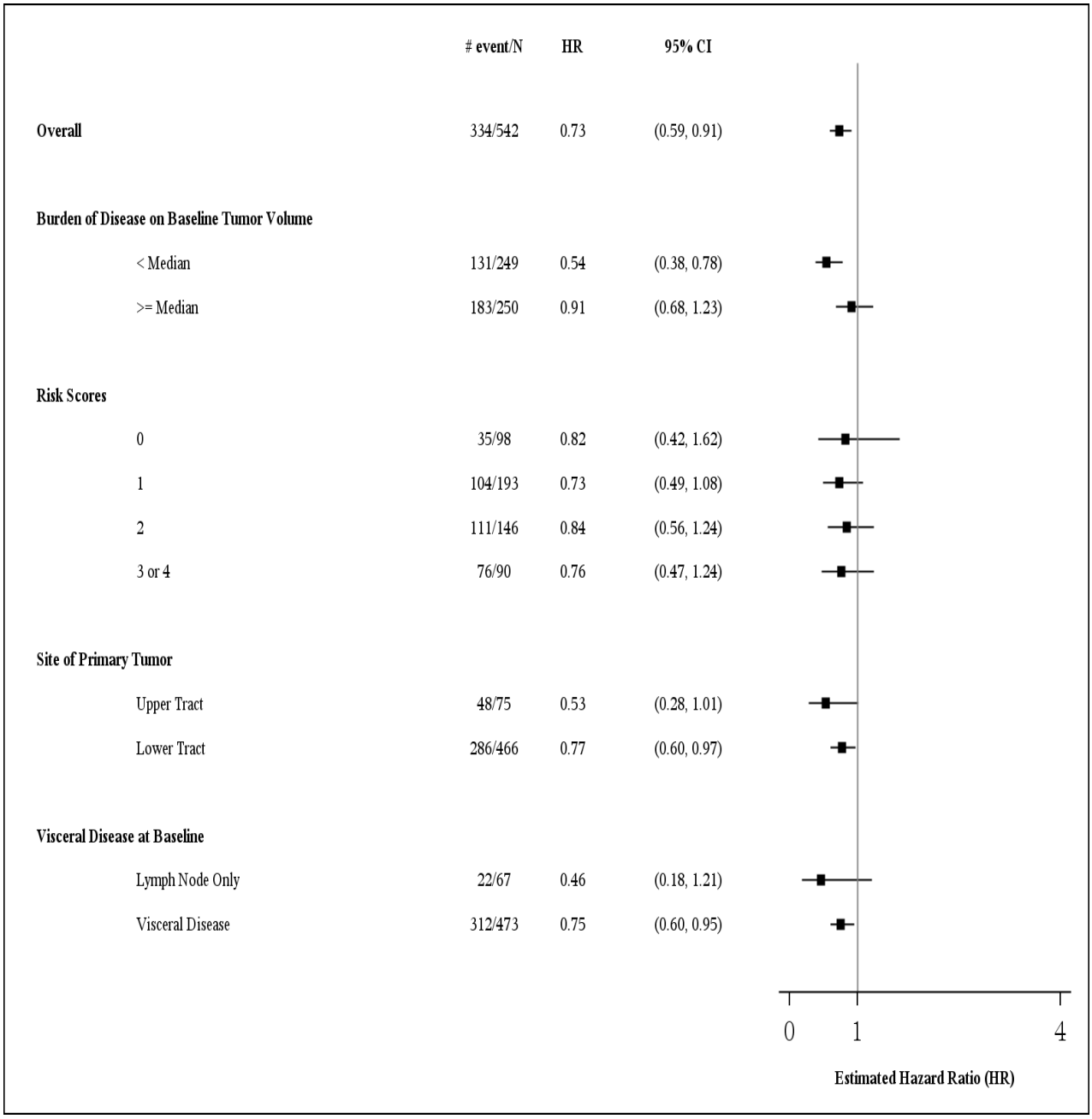
Analyses of OS (total population) by subgroup (Forest plot: Figure 28) showed consistency of survival benefit favouring pembrolizumab across subgroups, with consistent point estimates for the HR in subgroups such as ECOG-PS, liver metastasis, haemoglobin, time from prior chemotherapy, prior platinum (cisplatin versus carboplatin), Investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine), and Bellmunt risk scores. Few exceptions were noted (eg, 'non-White,' 'East Asia,' and 'never smoker'). The small numbers of events in some subgroups result in wide CIs and preclude an accurate interpretation of treatment effect (Figure 28).

Figure 28: OS by subgroup factors - Point estimate and nominal 95% confidence interval - All subjects (ITT population)





event/N
HR
95% CI
Overall
334/542
0.73
(0.59, 0.91)
Prior Platinum Therapy
Cisplatin
248/411
0.73
(0.56, 0.94)
Carboplatin
82/126
0.74
(0.47, 1.18)
Most Recent Prior Therapy
Neo Adjuvant
22/41
0.53
(0.20, 1.41)
Adjuvant
27/43
0.53
(0.18, 1.57)
1L Metastatic
203/340
0.72
(0.54, 0.95)
2L Metastatic
80/115
0.83
(0.52, 1.33)
Liver Metastases at Baseline
Presence
145/186
0.85
(0.61, 1.20)
Absence
189/355
0.67
(0.50, 0.89)
Baseline Hemoglobin
>=10 g/dL
257/442
0.71
(0.55, 0.91)
<10 g/dL
71/87
0.75
(0.46, 1.22)
Time from Most Recent Chemo Therapy
>=3 Months
193/333
0.66
(0.49, 0.89)
<3 Months
140/207
0.82
(0.58, 1.15)
Histology
Transitional Cell
240/383
0.80
(0.62, 1.04)
Mixed Transitional/non-transitional histology
93/155
0.58
(0.37, 0.89)
Brain Metastasis Status
Prior Brain Metastasis
6/7
NA
(NA, NA)
No Prior Brain Metastasis
328/535
0.73
(0.58, 0.91)
MK-3475 vs. Paclitaxel
MK-3475 vs. Paclitaxel
208/350
0.76
(0.55, 1.04)
MK-3475 vs. Docetaxel
MK-3475 vs. Docetaxel
203/350
0.76
(0.55, 1.05)
MK-3475 vs. Vinflunine
MK-3475 vs. Vinflunine
216/353
0.69
(0.51, 0.94)
0
1
4
Estimated Hazard Ratio (HR)

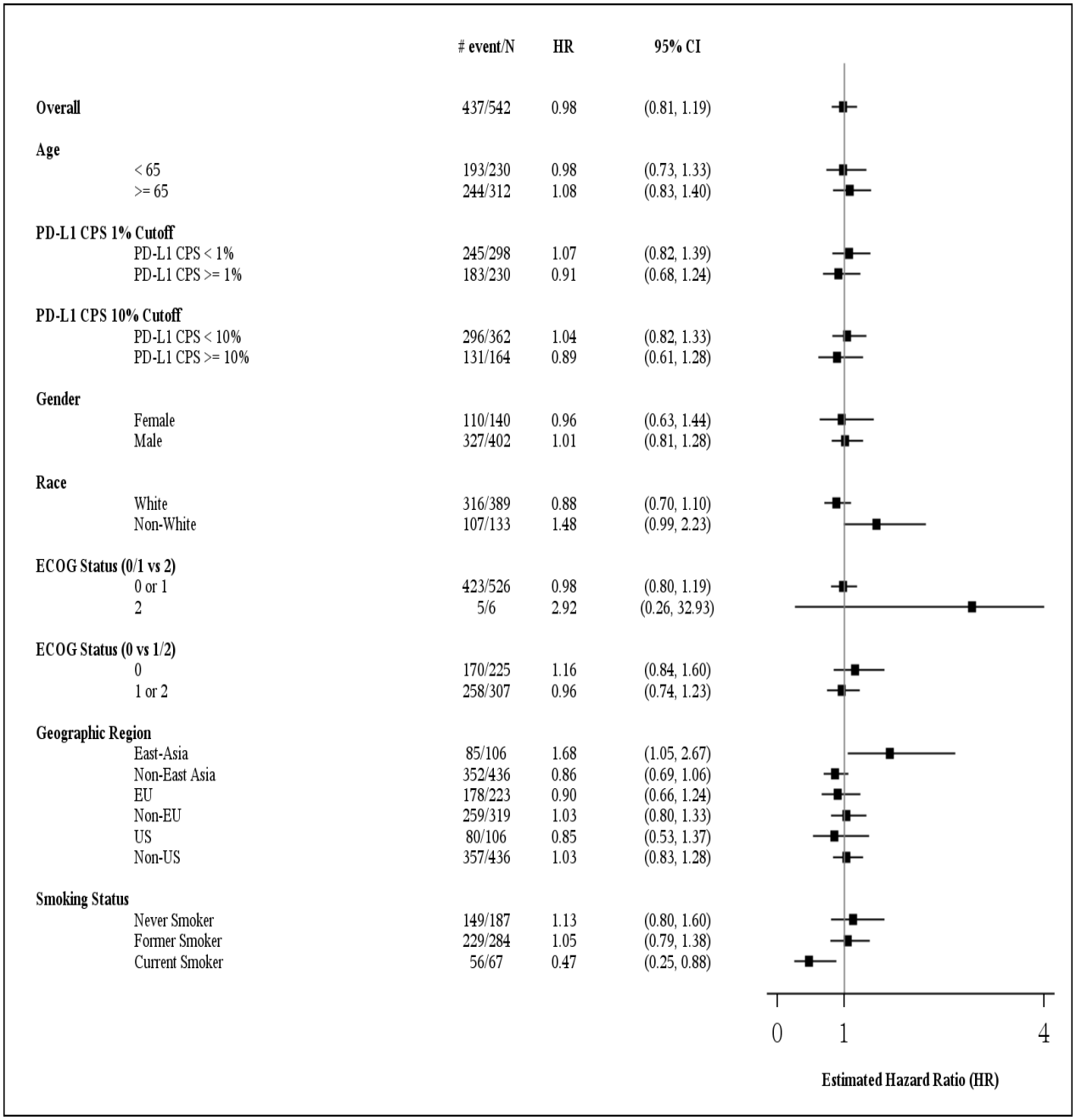


Based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (>=10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months)
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

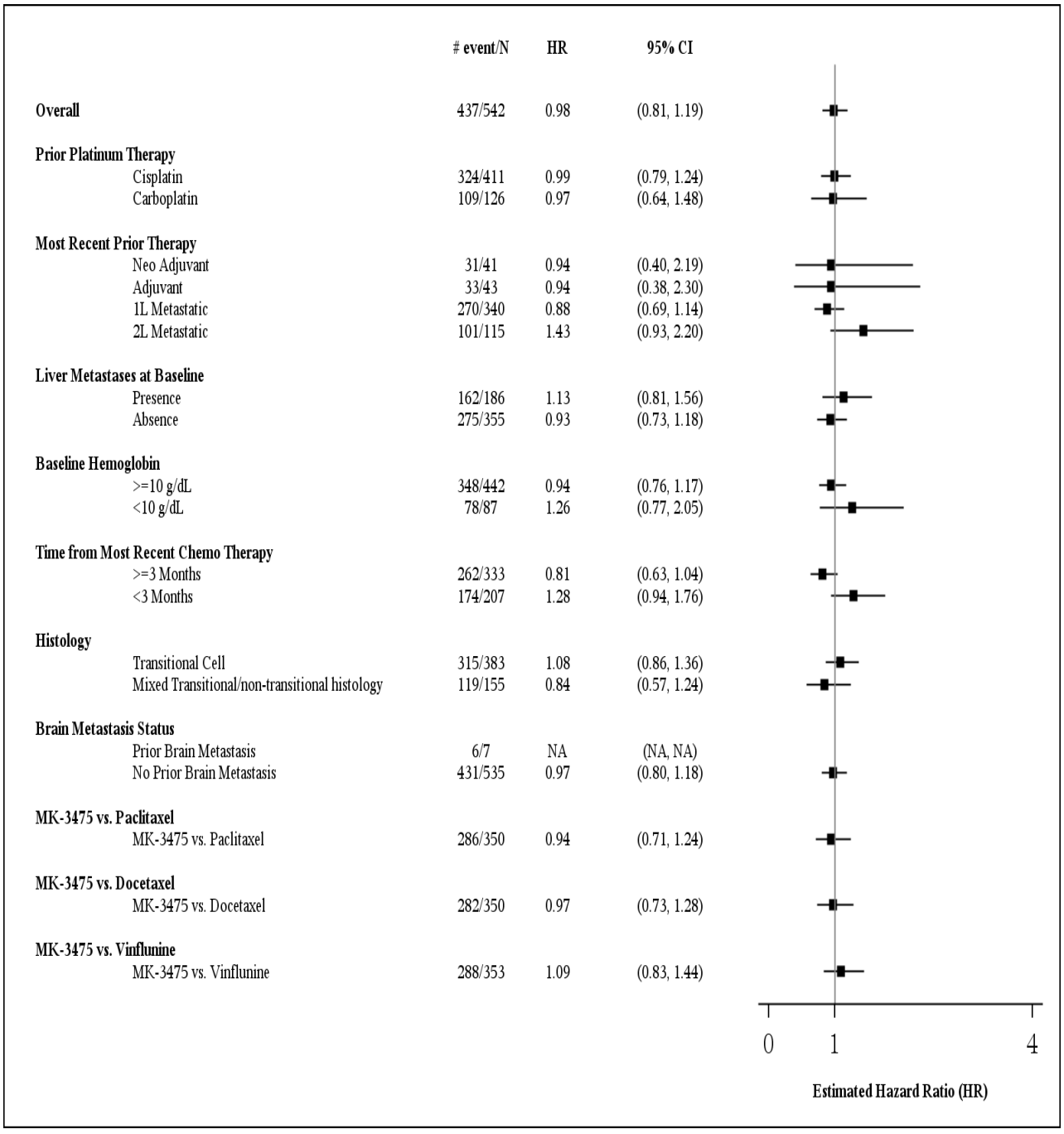
Subgroup analyses: PFS – ITT population

Results for analyses of PFS (total population) by subgroup (Forest plot) are consistent with the overall analysis and across subgroups (Figure 29).

Figure 29: Analysis of PFS based on RECIST 1.1 per central radiology assessment (primary censoring rule) by subgroup factors - Point estimate and nominal 95% confidence interval - All subjects (ITT population)



		# event/N	HR	95% CI
Overall		437/542	0.98	(0.81, 1.19)
Age				
	< 65	193/230	0.98	(0.73, 1.33)
	>= 65	244/312	1.08	(0.83, 1.40)
PD-L1 CPS 1% Cutoff				
	PD-L1 CPS < 1%	245/298	1.07	(0.82, 1.39)
	PD-L1 CPS >= 1%	183/230	0.91	(0.68, 1.24)
PD-L1 CPS 10% Cutoff				
	PD-L1 CPS < 10%	296/362	1.04	(0.82, 1.33)
	PD-L1 CPS >= 10%	131/164	0.89	(0.61, 1.28)
Gender				
	Female	110/140	0.96	(0.63, 1.44)
	Male	327/402	1.01	(0.81, 1.28)
Race				
	White	316/389	0.88	(0.70, 1.10)
	Non-White	107/133	1.48	(0.99, 2.23)
ECOG Status (0/1 vs 2)				
	0 or 1	423/526	0.98	(0.80, 1.19)
	2	5/6	2.92	(0.26, 32.93)
ECOG Status (0 vs 1/2)				
	0	170/225	1.16	(0.84, 1.60)
	1 or 2	258/307	0.96	(0.74, 1.23)
Geographic Region				
	East-Asia	85/106	1.68	(1.05, 2.67)
	Non-East Asia	352/436	0.86	(0.69, 1.06)
	EU	178/223	0.90	(0.66, 1.24)
	Non-EU	259/319	1.03	(0.80, 1.33)
	US	80/106	0.85	(0.53, 1.37)
	Non-US	357/436	1.03	(0.83, 1.28)
Smoking Status				
	Never Smoker	149/187	1.13	(0.80, 1.60)
	Former Smoker	229/284	1.05	(0.79, 1.38)
	Current Smoker	56/67	0.47	(0.25, 0.88)



event/N
HR
95% CI
Overall
437/542
0.98
(0.81, 1.19)
Prior Platinum Therapy
Cisplatin
324/411
0.99
(0.79, 1.24)
Carboplatin
109/126
0.97
(0.64, 1.48)
Most Recent Prior Therapy
Neo Adjuvant
31/41
0.94
(0.40, 2.19)
Adjuvant
33/43
0.94
(0.38, 2.30)
1L Metastatic
270/340
0.88
(0.69, 1.14)
2L Metastatic
101/115
1.43
(0.93, 2.20)
Liver Metastases at Baseline
Presence
162/186
1.13
(0.81, 1.56)
Absence
275/355
0.93
(0.73, 1.18)
Baseline Hemoglobin
>=10 g/dL
348/442
0.94
(0.76, 1.17)
<10 g/dL
78/87
1.26
(0.77, 2.05)
Time from Most Recent Chemo Therapy
>=3 Months
262/333
0.81
(0.63, 1.04)
<3 Months
174/207
1.28
(0.94, 1.76)
Histology
Transitional Cell
315/383
1.08
(0.86, 1.36)
Mixed Transitional/non-transitional histology
119/155
0.84
(0.57, 1.24)
Brain Metastasis Status
Prior Brain Metastasis
6/7
NA
(NA, NA)
No Prior Brain Metastasis
431/535
0.97
(0.80, 1.18)
MK-3475 vs. Paclitaxel
MK-3475 vs. Paclitaxel
286/350
0.94
(0.71, 1.24)
MK-3475 vs. Docetaxel
MK-3475 vs. Docetaxel
282/350
0.97
(0.73, 1.28)
MK-3475 vs. Vinflunine
MK-3475 vs. Vinflunine
288/353
1.09
(0.83, 1.44)
0
1
4
Estimated Hazard Ratio (HR)

The baseline characteristics of the following patient subgroups are provided in Appendix 9. All randomised subjects were included in the analyses according to the treatment group to which they were randomised (ITT population).

- Patients with PD-L1 CPS ≥ 1% (PD-L1 Positive) (ITT population)
- Patients with PD-L1 CPS ≥ 10% (PD-L1 Strongly Positive) (ITT population)

The results of the OS and PFS analyses by subgroup among patients with PD-L1 CPS ≥ 1% and PD-L1 CPS ≥ 10% are also provided in Appendix 9. In both sub-populations, the subgroup analyses results showed overall consistency with the primary analysis for both OS and PFS endpoints.

Appendix 9 also provides baseline characteristics for the following sub-groups, which were analysed post-hoc:

- PDL1 Not Strongly Positive (CPS <10%)
- PDL1 Negative (CPS <1%)
- Pure Transitional Cell Histology
- Predominantly Transitional Cell Histology
- Pembrolizumab vs. Paclitaxel
    - Paclitaxel-assigned by investigator, pre-randomisation
- Pembrolizumab vs. Docetaxel
    - Docetaxel-assigned by investigator, pre-randomisation
- Pembrolizumab vs. Paclitaxel or Docetaxel
    - Paclitaxel- or docetaxel-assigned by investigator, pre-randomisation
- Received at least one dose of study treatment
- Discontinued before receiving study treatment

Analysis of Overall Survival Adjusting for Treatment Switch – Subgroup Analysis

Additional subgroup analyses were conducted post-hoc on the below-mentioned subgroups, which were defined as follows:

- by SOC treatment as assigned by investigator pre-randomisation (pembrolizumab vs. docetaxel, pembrolizumab vs. paclitaxel, pembrolizumab vs. (docetaxel or paclitaxel))

In KEYNOTE-045, it was not written into that protocol that patients randomised to the SOC arm were expressly allowed to receive anti-PD-1/anti-PD-L1 treatment after documented disease progression but neither was it prohibited within the protocol. Therefore for each of the above mentioned sub-populations, the aims of the post-hoc subgroup analyses were:

- To estimate the treatment difference (hazard ratio) between pembrolizumab 200 mg Q3W and SOC in overall survival, adjusted for treatment switch-over of control arm subjects to anti-PD-1/anti-PD-L1 treatment using Rank-Preserving Structure Failure Time (RPSFT) model, a simplified two-stage survival analysis model and Inverse Probability of Censoring Weighting (IPCW) model.

- To estimate the OS curve for the SOC treatment group, adjusted for the by-protocol allowed treatment switch-over of control arm subjects to anti-PD-1/anti-PD-L1 treatment using RPSFT model, simplified two-stage survival analysis model and Inverse Probability of Censoring Weighting (IPCW) model.

Full details of the analyses undertaken (methods and results) are presented in Appendix 10.

Table 47 summarises the main findings in the subgroups of patients defined by pre-randomisation SOC treatment assignment.The KM curves relating to these subgroup analyses results are presented in section 5.3.1.

Subgroup analyses are exploratory and therefore have to be interpreted with caution given the small sample sizes. For some subgroups (see Table 47), it was not possible to carry out the adjustment for switching-over using the simplified 2- stage model or IPCW model. The p-values should be interpreted as purely exploratory and within the context of the results in the overall population. Specifically, a small sample size reduces the power of the test and may generate type II errors (false negatives) while testing within several subgroups may generate type I errors (false positives). The focus is on estimation with uncertainty quantified by the 95% confidence interval. Nominal p-values within subgroups are provided for completeness.

Table 47: Analysis of OS adjusting for treatment switch: subgroups of patients defined by pre-randomisation SOC treatment assignment

Subgroup	Analysis	Treatment arm	N	Number of events (%)	Number of person-months	HR‡ (95%CI) *	P-value
Pembrolizumab vs. Paclitaxel	ITT	SOC	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	2-stage§			[redacted]			
	IPCW			[redacted]			
Pembrolizumab vs. Docetaxel	ITT	SOC	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	2-stage§			[redacted]			
	ICPW	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
Pembrolizumab vs. Paclitaxel or Docetaxel	ITT	SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	2-stage§	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	IPCW	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	

¶ *Re-censoring applied to all control patients*

§ *No Re-censoring applied*

* *P-value retained from ITT analysis by design*

†: *Bootstrap p-value*

Subgroup analyses based on PD-L1 status for paclitaxel- or docetaxel- pre-assigned subjects

Further post-hoc subgroup analyses were conducted specifically focussing on the the sub-population of subjects pre-assigned by investigator to docetaxel or paclitaxel pre-randomisation. Subjects pre-assigned to received vinflunine were excluded, given this comparator is not of relevance to the UK.

Within the sub-population of subjects pre-assigned by investigator to docetaxel or paclitaxel pre-randomisation, data concerning the subgroups of subjects defined by PD-L1 strongly positive status (strongly positive: CPS >=10%) and PD-L1 positive status (positive: CPS >=1%) were assessed with the following objectives:

- To estimate the treatment difference (hazard ratio) between pembrolizumab 200 mg Q3W and SOC in OS, adjusted for treatment switch-over of control arm subjects to anti-PD-1/anti-PD-L1 treatment using Rank-Preserving Structure Failure Time (RPSFT) model, a simplified two-stage survival analysis model and Inverse Probability of Censoring Weighting (IPCW) model.
- To estimate the OS curve for the SOC treatment group, adjusted for the by-protocol allowed treatment switch-over of control arm subjects to anti-PD-1/anti-PD-L1 treatment using RPSFT model, simplified two-stage survival analysis model and Inverse Probability of Censoring Weighting (IPCW) model.

Full details of the analyses undertaken (methods and results) are presented in Appendix 11.

The main findings of the subgroup analyses in patients defined by PD-L1 status (PD-L1 strongly positive (CPS >=10%) and PD-L1 positive (CPS>=1%), in the sub-population of subjects who were pre-assigned by investigator to paclitaxel or docetaxel, prior to randomisation, are summarised in Table 48.

Table 48: Analysis of OS adjusting for treatment switch: subgroups of patients defined by PD-L1 status within the sub-population from KEYNOTE-045 who were pre-assigned by investigator to paclitaxel or docetaxel, prior to randomisation

Subgroup	Analysis	Treatment arm	N	Number of events (%)	Number of person-months	HR‡ (95%CI) *
PD-L1 Strongly Positive (CPS>=10%)	ITT	SOC	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	
	2-stage§			[redacted]		
	ICPW			[redacted]		
PD-L1 Positive (CPS>=1%)	ITT	SOC	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	
	2-stage§			[redacted]		
	IPCW	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	

¶ *Re-censoring applied to all control patients*
§ *No Re-censoring applied*

Subgroup analyses are exploratory and therefore have to be interpreted with caution given the small sample size especially in the subgroup of subjects who were PD-L1 strongly positive and pre-assigned to paclitaxel or docetaxel at baseline, pre-randomisation. In this subgroup, it was not possible to carry out the adjustment for switching-over using the simplified 2-stage model or IPCW model. The focus is on estimation with uncertainty quantified by the 95% confidence interval.

4.9 Meta-analysis

There is only one randomised controlled trial for the intervention versus a relevant comparator (KEYNOTE-045). Therefore a meta-analysis of data was not possible.

4.10 Indirect and mixed treatment comparisons

In order to supplement the direct evidence for pembrolizumab from KEYNOTE-045, and in the absence of head to head RCTs of pembrolizumab versus all relevant comparators of interest, a systematic search of the evidence was conducted in order to assess the feasibility of conducting an indirect treatment comparison (ITC) by means of a network meta-analysis (NMA) of RCTs, to enable a comparison to be made for the purposes of this submission.[65-67]

4.10.1: Search strategy

A systematic literature review was conducted according to a previously prepared protocol, to identify relevant studies to inform both direct and indirect comparisons between the interventions of interest. The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design. Details of the search strategy are presented in section 4.1. Full description of the search strategy by database is presented in Appendix 2.

4.10.2: Details of treatments

The decision problem addressed in this submission is presented in section 1.1. The following treatments and comparators of interest were identified:

- Platinum-based chemotherapy
  - Paclitaxel/Gemcitabine
  - Carboplatin/Paclitaxel
  - Cisplatin+gemcitabine
  - MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
- Docetaxel
- Paclitaxel

4.10.3: Criteria used in trial selection

The inclusion and exclusion criteria and the study selection process are described in section 4.1 (see Table 6 PICOS eligibility criteria and Figure 5 PRISMA flow diagram).

For selection of studies potentially eligible for indirect and mixed treatment comparisons, we included RCTs with comparisons between any of the interventions of interest.

4.10.4: Summary of trials

A summary of included trials is provided in Table 49 below.

Table 49: Summary of the trials

Study	Treatment arms	Trial phase	N (ITT)	Blinding	Region	Crossover allowed	Comment
Bellmunt et al 2016 [17]; Company Clinical Study Report (KEYNOTE-045)[16]	Pembrolizumab	3	542	Open-label	Multinational	No	Provided by MSD
	Paclitaxel or docetaxel or vinflunine (Investigator's choice)						
NCT00315237[68-70]	BSC	3	370	Open-label	Multinational	No	Principal publication Bellmunt et al 2009; subsequent publications Bellmunt et al 2013 and Harshman et al 2013
	BSC + Vinflunine						
NCT00880334[71, 72]	Docetaxel + vantedanib	2	149	Double-blind	Spain	Yes*	Principal publication Choueiri et al 2012; subsequent publication Sonpavde et al 2015
	Docetaxel						
NCT01282463[73]	Docetaxel	2	148	Open-label	Multinational	No	Petrylak et al 2016 is principal publication
	Docetaxel + ramucirumab						
	Docetaxel + icrucumab						

* – crossover allowed at disease progression; ITT – intention-to-treat; BSC – best supportive care

4.10.5 Trials identified in search strategy

Table 49 presents a full list of included trials. An overview of the study characteristic and treatment regimens in each trial is included in Appendix 12.

The KEYNOTE-045 trial is represented by one conference proceeding[17] and one clinical study report.[16] This phase III, multinational trial compared pembrolizumab to investigator's choice (either paclitaxel, docetaxel, or vinflunine). This study was open-label and did not allow for crossover within the study plan, although patients in the control arm were permitted to switch to alternative therapies upon disease progression. Although a median treatment duration is not reported, the median follow-up was 14.1 months (range between 9.9 and 22.1 months).

The NCT00315237 trial is represented by a principal publication[68] and two subsequent publications.[69, 70] This phase III, multinational trial compared best supportive care (BSC) and the combination treatment of BSC and vinflunine. The study was open-label and did not allow for crossover. The principal publication presents data up to a median follow-up of 22.1 months while the one of the secondary publications[69] presents data up to a median follow-up of 45.4 months. Similarly, the other secondary publication[70] presented longer-term follow-up data, however focused on the influence of type of platinum therapy (cisplatin or non-cisplatin). Treatment details were not provided regarding BSC. Vinflunine was given intravenously every three weeks. The median treatment durations for best supportive care and the combination treatment of BSC and vinflunine are 9.4 and 9.4 weeks, respectively.

The NCT00880334 trial is represented by a principal publication[71] and a subsequent publication.[72] This phase II, Spanish trial compared docetaxel and the combination treatment of docetaxel and vantedanib. The study was double-blinded, but allowed for crossover upon disease progression. The subsequent publication[72] presents an analysis to assess the effect of previous paclitaxel exposure on outcomes of interest. Both docetaxel and vantedanib were given Q3W; docetaxel intravenously and vantedanib orally. The median treatment duration was only reported for the treatment arm assessing the combination treatment of docetaxel and vantedanib as 2 cycles (6 weeks).

The NCT01282463 trial is represented by a principal publication.[73] This phase II, multinational trial compared docetaxel, the combination treatment of docetaxel and ramucirumab, and the combination treatment of docetaxel and icrucumab. The study was open-label and did not allow for crossover. All treatments were given intravenously Q3W with the exception of icrucumab,

which was also given on day 8 of every three-week cycle. The median treatment duration was highest in the combination treatment arm of docetaxel and ramucirumab at 9.1 weeks (95% confidence interval [CI] 6 to 23.7 weeks) followed by docetaxel monotherapy (9.1 weeks [95% CI 6 to 16 weeks]) and the combination treatment of docetaxel and icrucumab (7 weeks [95% CI 6 to 18 weeks]).

4.10.6 Rationale for choice of outcome measure chosen

The outcomes of interest for the NMA were:

- OS (time-varying HR and constant HR)
- PFS (time-varying HR and constant HR)

Both OS and PFS are clinically relevant outcomes that were referenced in the final scope for this appraisal and the decision problem. OS is the gold standard endpoint to demonstrate superiority of antineoplastic therapy. PFS is an acceptable scientific endpoint for a randomised phase III trial to demonstrate superiority of a new antineoplastic therapy, especially if it is believed that the median time to OS with the new therapy may be significantly longer than that seen with standard of care. No network meta-analysis was proposed for adverse events or HRQoL, as these are inconsistently reported across trials, both in terms of grouping of adverse events and in terms of criteria for reporting (i.e. percent prevalence as a cut-off point for inclusion in publication).

4.10.7 Populations in the included trials

The population of interest includes patients with advanced/unresectable or metastatic urothelial carcinoma recurring or progressing following platinum-based chemotherapy (2L).

4.10.8 Apparent or potential differences in patient populations between the trials

Baseline patient characteristics are summarised in Appendix 13.

Between trials, patients were similar with regards to age (proportion of patients aged 65 or younger ranged between 30% and 55% while the median age in KEYNOTE-045[16, 17] was between 65 and 67, indicating approximately half of the patient population was under the age of 65) and distribution of females (proportion ranged between 19% and 32%). KEYNOTE-045,[16, 17] NCT00880334,[71, 72] and NCT01282463[73] had Caucasian patients making up more than 65% of the patient population. This was in contrast to NCT00315237,[68-70] which included only Asian

patients. Further, NCT00315237[68-70] reported the highest proportion of patients with an ECOG score of 1 (71.5% in the docetaxel vinflunine combination therapy group) compared with NCT00880334[71, 72] and NCT01282463,[73] which had study arms reporting proportion of patients with an ECOG score of 1 ranging between 42.9% and 63.3%. Further, NCT00315237[68-70] reported the highest proportion of patients with previous radiotherapy in the monotherapy arm (47.9%) compared with NCT00880334[71, 72] and NCT01282463,[73] which had study arms reporting proportion of patients with radiotherapy ranging between 11.1% and 26.5%. Finally, patients with EGFR mutations were only included in NCT00880334[71, 72] (100% of patients with EGFR mutation) while NCT00315237[68-70] reported 0 patients in both treatment arms (NCT01282463[73] did not report on EGFR status at baseline).

4.10.9; 4.10.10; 4.10.11 Methods, outcomes, baseline characteristics, risk of bias of each trial

As mentioned above, trial characteristics of included studies are presented in Appendix 12 and baseline patient characteristics are summarised in Appendix 13.

The reported outcomes from included trials are also summarised in Appendix 13.

Of the four included trials, both KEYNOTE-045[16, 17] and NCT00315237[68-70] were phase III trials while NCT00880334[71, 72] and NCT01282463[73] were both phase II trials. All trials were open-label with the exception of NCT00880334,[71, 72] which was double-blinded. Of note, NCT00880334[71, 72] was the only study to explicitly allow for crossover at disease progression.

Treatments schedules for all trial arms were based on three-week cycles where all treatments were administered once per cycle with the exception of icrucumab, which was given at days 1 and 8 of each cycle. Vantedanib was the only non-intravenously administered treatment (administered orally), however, this treatment arm also reported the shortest median treatment duration; 2 cycles (6 weeks). All other study arms reported treatment durations above 7 weeks the longest being the combination treatment of docetaxel and ramucirumab (median treatment duration of 14.3 weeks [95% CI 6 to 23.7]). Note that KEYNOTE-045[16, 17] only reported median follow-up and not median treatment duration

Overall, the combination treatment of docetaxel and ramucirumab[73] reported the longest OS followed by pembrolizumab. A similar trend was observed for PFS with the combination treatment of docetaxel and ramucirumab reporting the longest PFS followed by investigator's choice and

the combination treatment of BSC and vinflunine and docetaxel. All other treatments were similar with regard to efficacy measures with the exception of BSC, which reported least improved for all reported outcomes.

The two safety outcomes of interest were treatment-related adverse events (TRAEs) and discontinuations due to adverse-events (DAEs). Investigator's choice and the combination treatment of docetaxel and ramucirumab consistenly reported a relatively high proportion of patients experiencing these events: investigator's choice reported the highest proportion of patients with TRAEs (90.2%) while the combination treatment of docetaxel and ramucirumab reported the highest proportion of patients with DAEs (32.6%).

For all studies, we assessed the validity of individual trials using the Risk of Bias instrument, endorsed by the Cochrane Collaboration.[74] This instrument was used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The risk of bias instrument can be used to assign summary assessments of within-study bias; low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high-risk of bias (high-risk of bias for one or more key domains). Any disagreements between reviewers were resolved by discussion with a third reviewer.

Overall, NCT00315237[68-70] presented the highest risk of bias. Although KEYNOTE-045,[16, 17] NCT00315237,[68-70] and NCT01282463[73] presented a higher risk of performance bias due to the open label study design and unclear risk of bias due to industry funding, NCT00315237[68-70] presented an unclear risk of selection bias as methods for allocating patients and allocation concealment were not adequately described. NCT00880334[71, 72] was deemed to present the lowest risk of bias due to its double-blinded study design. Full results of the risk of bias assessment are presented in Appendix 14.

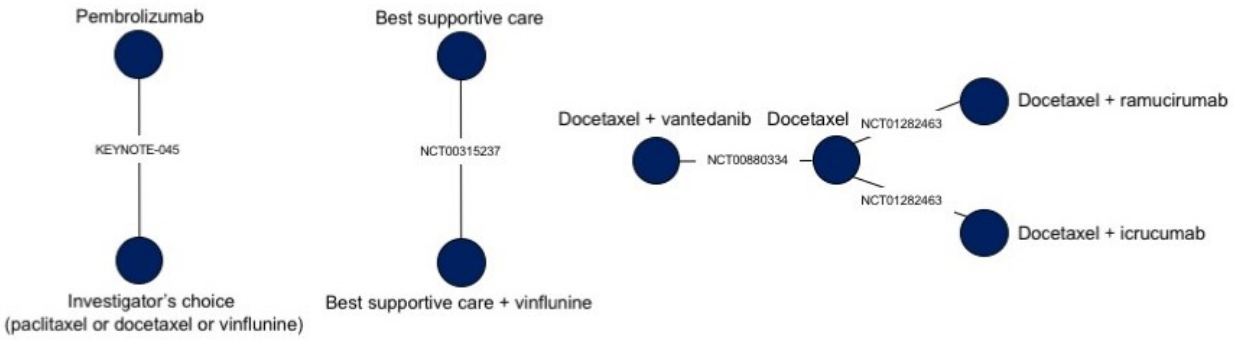
4.10.12 Methods of analysis and presentation of results

In the first stage of the feasibility assessment, network connectivity was determined. Of the four included studies, two trials (NCT00880334[71, 72] and NCT01282463[73]) assessed a common treatment (docetaxel). This allows for the indirect comparison between the combination

treatments of docetaxel and vantedanib, docetaxel and ramucirumab, and docetaxel and icrucumab (

Figure 30). The disconnected trials, KEYNOTE-045[16, 17] and NCT00315237,[68-70] assessed pembrolizumab (the primary treatment of interest), investigator's choice, best supportive care, and the combination treatment of best supportive care and vinflunine. Of the included treatments, only pembrolizumab, docetaxel, were deemed of interest a priori for the UK (see Table 6).

Figure 30: Network diagram of evidence base



Although NCT00880334[71, 72] and NCT01282463[73] have a common comparator (docetaxel), the only comparisons eligible for inclusion in the NMA would not include any treatments of interest, specifically, any comparisons to pembrolizumab as the comparison arm in KEYNOTE-045 consists of a combination of treatments that cannot be considered similar enough to either of the three individual treatments that comprise investigator's choice for this to be a common comparator (for instance, treating investigator's choice as docetaxel monotherapy for network connectivity). For this reason, a NMA was not conducted.

4.10.13 Programming language

Not applicable

4.10.14; 4.10.15; 4.10.16 Results of analysis and results of statistical assessment of heterogeneity

Not applicable

4.10.17 Justification for the choice of random or fixed effects model

Not applicable

4.10.18 and 4.10.19 Heterogeneity between results of pairwise comparisons and inconsistencies between direct and indirect evidence

Not applicable

4.11 Non-randomised and non-controlled evidence

4.11.1 - Non-controlled evidence

Not applicable

4.12 Adverse reactions

4.12.2 Adverse reactions reported in RCTs listed in section 4.2

KEYNOTE-45 Adverse reactions[16, 17]

Safety and tolerability were assessed by clinical and statistical review of all relevant parameters including AEs and laboratory test abnormalities during the treatment period up to the data cut-off date of 07-Sep-2016. The All-Patients-as-Treated (APaT) population was used for the analysis of safety data in this trial. The APaT population consisted of all randomised subjects who received at least 1 dose of study treatment (i.e., n=521 subjects; 266 in the pembrolizumab arm and 255 in the control arm).

- *Extent of exposure*

The duration of exposure was measured from the date of the first dose to the date of last dose. Overall, exposure to pembrolizumab was approximately twice as long as exposure to the chemotherapy agents in the control arm (Table 50). The durations of exposure (median months on therapy) for the APaT population were 3.45 months for the pembrolizumab arm compared with 1.54 months in the control arm (paclitaxel: 1.45 months; docetaxel: 1.43 months; vinflunine: 2.10 months) (Table 51).

Of the 266 subjects in the pembrolizumab arm, 95 (35.7%) received treatment for ≥6 months and 43 (16.2%) received treatment for ≥12 months. In contrast, of the 255 subjects in the control arm, only 29 (11.4%) received treatment for ≥6 months and 3 (1.2%) received treatment for ≥12 months (Table 52).

Table 50: Summary of drug exposure - All subjects (APaT population)

	Control	Pembrolizumab
	N=255	N=266
Time on Therapy (months)		
Mean	2.74	5.60
Median	1.54	3.45
SD	2.71	5.37
Range	0.03 to 14.19	0.03 to 20.04
Number of Administrations		
Mean	4.74	8.81
Median	3.00	6.00
SD	3.71	7.61
Range	1.00 to 20.00	1.00 to 30.00

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Table 51: Summary of drug exposure (with breakdown of control group) - All subjects (APaT population)

	Paclitaxel	Docetaxel	Vinflunine	Pembrolizumab
	N=84	N=84	N=87	N=266
Time on Therapy (months)				
Mean	2.92	2.12	3.17	5.60
Median	1.45	1.43	2.10	3.45
SD	3.05	2.02	2.87	5.37
Range	0.03 to 14.19	0.03 to 10.48	0.03 to 12.02	0.03 to 20.04
Number of Administrations				
Mean	5.00	3.90	5.30	8.81
Median	3.00	3.00	4.00	6.00
SD	4.16	2.75	3.96	7.61
Range	1.00 to 20.00	1.00 to 14.00	1.00 to 17.00	1.00 to 30.00

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Table 52: Clinical trial exposure by duration - All subjects (APaT population)

Duration of Exposure	Control		Pembrolizumab	
	n	(%)	n	(%)
> 0 m	255	100.0	266	100.0
≥ 1 m	184	72.2	213	80.1
≥ 3 m	83	32.5	139	52.3
≥ 6 m	29	11.4	95	35.7
≥ 12 m	3	1.2	43	16.2

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date +1.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

- *Adverse Events (AEs)*

Table 53 displays an overview of the numbers and percentages of subjects in the APaT population who had AEs up to 30 days and Serious AEs (SAEs) up to 90 days after the last dose of study medication. Adverse events were collected over a longer period of time for the pembrolizumab arm as compared to SOC given the almost double mean exposure to pembrolizumab as compared to SOC.

Subjects in the pembrolizumab arm experienced, in general, fewer AEs compared with subjects in the control arm, demonstrating that pembrolizumab has a favourable tolerability in the target population.

Overall, 93.2% of subjects in the pembrolizumab arm experienced at least 1 AE compared with 98.0% of subjects in the control arm. Importantly, fewer subjects in the pembrolizumab arm compared with the control arm, respectively, experienced drug-related AEs (60.9% vs 90.2%), Grade 3 to 5 AEs (52.3 vs 62.7%), Grade 3 to 5 drug-related AEs (15.0% vs 49.4%) and drug-related AEs leading to treatment discontinuation (5.6% vs 11.0%) (Table 53).

Reports of SAEs were comparable for subjects in the pembrolizumab and control arms, but fewer subjects in the pembrolizumab arm had drug-related SAEs compared with subjects in the control arm (10.2% vs 22.4%).

Overall, a similar percentage of subjects in both treatment arms experienced a drug-related AE with a fatal outcome: 1.5% in the pembrolizumab arm and 1.6% in the control arm.

Table 53: AE summary - All subjects (APaT population)

	Control		Pembrolizumab	
	n	(%)	n	(%)
Subjects in population	255		266	
with one or more adverse events	250	(98.0)	248	(93.2)
with no adverse event	5	(2.0)	18	(6.8)
with drug-related† adverse events	230	(90.2)	162	(60.9)
with toxicity grade 3-5 adverse events	160	(62.7)	139	(52.3)
with toxicity grade 3-5 drug-related adverse events	126	(49.4)	40	(15.0)
with serious adverse events	104	(40.8)	104	(39.1)
with serious drug-related adverse events	57	(22.4)	27	(10.2)
who died	8	(3.1)	13	(4.9)
who died due to a drug-related adverse event	4	(1.6)	4	(1.5)
discontinued‡ due to an adverse event	32	(12.5)	22	(8.3)
discontinued due to a drug-related adverse event	28	(11.0)	15	(5.6)
discontinued due to a serious adverse event	12	(4.7)	15	(5.6)
discontinued due to a serious drug-related adverse event	10	(3.9)	9	(3.4)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA V19.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

The most commonly reported AEs (reported in ≥20% of subjects in ≥1 of the treatment arms) were fatigue, anaemia, constipation, nausea, decreased appetite, alopecia, asthenia, and pruritus:

- In the pembrolizumab arm, the AEs observed in ≥20% of the subjects, and their prevalence in the control arm were, respectively: fatigue (25.9% vs 33.7%), pruritus (23.3% vs 5.5%), decreased appetite (21.1% vs 20.8%), and nausea (20.7% vs 28.6%).

- In the control arm, additional AEs observed in ≥20% of the subjects were as follows (pembrolizumab vs control frequency): alopecia (0.8% vs 38.8%), anaemia (17.3% vs 35.7%), constipation (18.8% vs 31.8%), and asthenia (11.3% vs 20.8%).

Analyses of subjects with AEs by decreasing incidence (incidence ≥ 10% in one or more treatment groups) in the APaT population, are presented below in Table 54.

Table 54: KEYNOTE-045 Subjects with AEs by decreasing incidence (incidence ≥10% in one or more treatment groups) - All subjects (APaT population)

	Control		Pembrolizumab	
	n	(%)	n	(%)
Subjects in population	255		266	
with one or more adverse events	250	(98.0)	248	(93.2)
with no adverse events	5	(2.0)	18	(6.8)
Fatigue	86	(33.7)	69	(25.9)
Anaemia	91	(35.7)	46	(17.3)
Constipation	81	(31.8)	50	(18.8)
Nausea	73	(28.6)	55	(20.7)
Decreased appetite	53	(20.8)	56	(21.1)
Alopecia	99	(38.8)	2	(0.8)
Diarrhoea	48	(18.8)	43	(16.2)
Asthenia	53	(20.8)	30	(11.3)
Pruritus	14	(5.5)	62	(23.3)
Urinary tract infection	34	(13.3)	39	(14.7)
Vomiting	34	(13.3)	39	(14.7)
Pyrexia	33	(12.9)	36	(13.5)
Abdominal pain	34	(13.3)	34	(12.8)
Oedema peripheral	40	(15.7)	26	(9.8)
Back pain	21	(8.2)	37	(13.9)
Cough	18	(7.1)	38	(14.3)
Dyspnoea	23	(9.0)	33	(12.4)
Arthralgia	30	(11.8)	24	(9.0)
Haematuria	20	(7.8)	30	(11.3)
Pain in extremity	28	(11.0)	21	(7.9)
Rash	16	(6.3)	29	(10.9)
Neutropaenia	43	(16.9)	0	(0.0)
Neutrophil count decreased	38	(14.9)	1	(0.4)
Neuropathy peripheral	31	(12.2)	1	(0.4)
Peripheral sensory neuropathy	28	(11.0)	2	(0.8)

Every subject is counted a single time for each applicable specific adverse event.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA V19.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

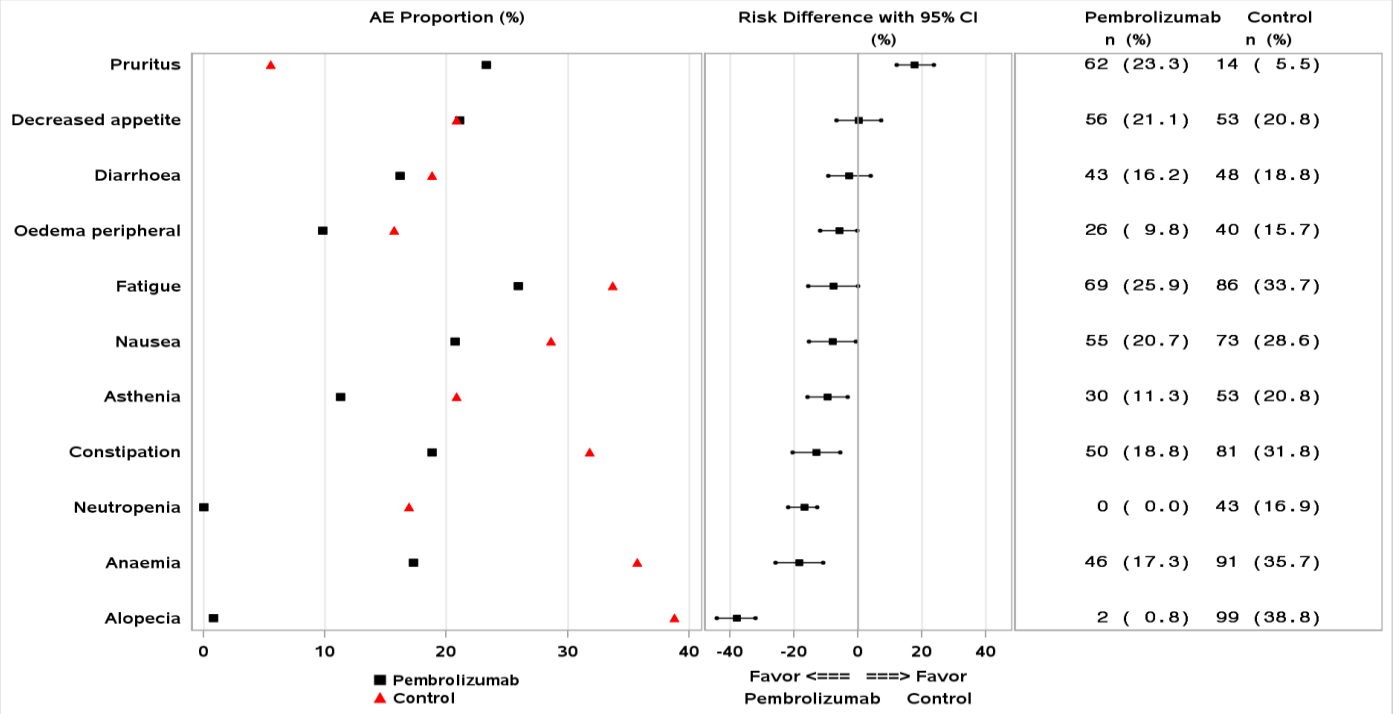
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Among the AEs observed in ≥15% of subjects in the 1 or more treatment arms, all, with the exception of pruritus, were reported in a lower or similar frequency among the subjects receiving pembrolizumab versus control (Figure 31). The observed frequency of pruritus is consistent with the previously described frequency of pruritus AEs with pembrolizumab. Of note, the observed frequency of urinary tract infection and hematuria was greater than the previously described frequency with pembrolizumab. Upon medical review, those events were deemed unlikely to be related to pembrolizumab, and more likely related to the underlying

disease condition and associated procedures. Among the AEs observed in ≥20% of subjects in the control arm, all were reported in higher or similar frequency compared with the subjects receiving pembrolizumab.

Figure 31: KEYNOTE-045 - Between-treatment comparisons in AEs: Selected AEs (incidence >=15% in one or more treatment groups) and sorted by risk difference of pembrolizumab (266) vs. control (255) - All subjects (APaT population)



MedDRA V19.0 preferred terms Neoplasm progression, Malignant neoplasm progression and Disease progression not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Appendix 15 provides a detailed summary of the incidence, number of episodes and duration of episodes of grade 3-5 AEs and grade 2-5 diarrhoea AEs in the KEYNOTE-045 population.

- *Drug-related AEs*

Adverse events considered by the Investigator to be "possibly," "probably," or "definitely" related to the study treatment are combined into the category drug-related AEs. Table 55 displays the number and percentage of subjects with drug-related AEs (incidence ≥10%) by decreasing incidence (based on the total incidence) in the APaT population. Fewer subjects in the pembrolizumab arm experienced drug-related AEs compared with the control arm, once again demonstrating that pembrolizumab has a favourable tolerability in the target population. The number of subjects who experienced a drug releated AE in each arm of the study was as follows: 162 (60.9%) in the pembrolizumab arm and 230 (90.2%) in the control arm.

The most commonly reported drug-related AEs (reported in ≥10% of subjects in one of the treatment arms) were: fatigue, alopecia, nausea, anaemia, decreased appetite, pruritus, constipation, diarrhoea, asthenia, neutropaenia, neutrophil count decreased, peripheral sensory neuropathy, and neuropathy peripheral:

- In the pembrolizumab arm, the drug-related AEs observed in ≥10% of the subjects, and their prevalence in the control arm were, respectively: fatigue (13.9% vs 27.8%), nausea (10.9% vs 24.3%), and pruritus (19.5% vs 2.7%).

- In the control arm, additional drug-related AEs observed in ≥10% of the subjects were as follows (pembrolizumab vs control): alopecia (0.0% vs 37.6%), anaemia (3.4% vs 24.7%), decreased appetite (8.6% vs 16.1%), constipation (2.3% vs 20.4%), diarrhoea (9.0% vs 12.9%), asthenia (5.6% vs14.1%) neutropaenia (0.0% vs 15.3%), neutrophil count decreased (0.4% vs 14.1%), peripheral sensory neuropathy (0.8% vs 11.0%), and neuropathy peripheral (0.4% vs 10.6%).

Among the drug-related AEs observed in ≥10% of the subjects on pembrolizumab, with the exception of pruritus, all were reported in a lower or similar frequency among the subjects receiving pembrolizumab versus control. Pruritus has been previously identified as an adverse drug reaction for pembrolizumab. Among the AEs observed in ≥10% of subjects in the control arm, all were reported in higher or similar frequency compared with the subjects receiving pembrolizumab.

Table 55: KEYNOTE-045 - Subjects with drug-related AEs by decreasing incidence (incidence ≥5% in one or more treatment groups) - All subjects (APaT population)

	Control		Pembrolizumab	
	n	(%)	n	(%)
Subjects in population	255		266	
with one or more adverse events	230	(90.2)	162	(60.9)
with no adverse events	25	(9.8)	104	(39.1)
Fatigue	71	(27.8)	37	(13.9)
Alopecia	96	(37.6)	0	(0.0)
Nausea	62	(24.3)	29	(10.9)
Anaemia	63	(24.7)	9	(3.4)
Decreased appetite	41	(16.1)	23	(8.6)
Pruritus	7	(2.7)	52	(19.5)
Constipation	52	(20.4)	6	(2.3)
Diarrhoea	33	(12.9)	24	(9.0)
Asthenia	36	(14.1)	15	(5.6)
Neutropaenia	39	(15.3)	0	(0.0)
Neutrophil count decreased	36	(14.1)	1	(0.4)
Vomiting	25	(9.8)	12	(4.5)
Rash	9	(3.5)	22	(8.3)
Peripheral sensory neuropathy	28	(11.0)	2	(0.8)
Neuropathy peripheral	27	(10.6)	1	(0.4)
Arthralgia	17	(6.7)	8	(3.0)
Pyrexia	8	(3.1)	17	(6.4)
Stomatitis	21	(8.2)	4	(1.5)
Mucosal inflammation	17	(6.7)	3	(1.1)
White blood cell count decreased	19	(7.5)	1	(0.4)
Oedema peripheral	19	(7.5)	0	(0.0)
Febrile neutropaenia	18	(7.1)	0	(0.0)
Dysgeusia	14	(5.5)	3	(1.1)
Pain in extremity	13	(5.1)	3	(1.1)
Hypothyroidism	0	(0.0)	15	(5.6)

Every subject is counted a single time for each applicable specific adverse event.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

- *Drug-related Grade 3 to 5 AEs*

Table 56 displays the number of subjects with drug-related Grade 3 to 5 AEs (incidence ≥5% in one or more treatment groups), and shows that fewer subjects in the pembrolizumab arm experienced drug-related Grade 3 to 5 AEs compared with the control arm (15.0% vs 49.4%, respectively).

The most commonly reported drug-related Grade 3 to 5 AEs (reported in ≥5% of subjects in one of the treatment arms) were neutropaenia, neutrophil count decreased, anaemia, febrile neutropaenia, and white blood cell decreased.

In the pembrolizumab arm, no drug-related Grade 3 to 5 AEs were observed in ≥5% of subjects. In further detailed analysis of the data, the drug-related Grade 3 to 5 AEs reported in ≥1% of subjects in the pembrolizumab arm were pneumonitis (n=4, 1.5%), AST increased (n=3, 1.1%), diarrhoea (n=3, 1.1%), and fatigue (n=3, 1.1%) (See Appendix 16).

In the control arm, the drug-related Grade 3 to 5 AEs observed in ≥5% of the subjects were as follows (pembrolizumab versus control): neutropaenia (0% vs 13.3%), neutrophil count decreased (0.4% vs 12.2%), anaemia (0.8% vs 7.8%), febrile neutropaenia (0.0% vs 7.1%), and white blood cell decreased (0.4% vs 5.1%).

Among the drug-related Grade 3 to 5 AEs observed in ≥1% in the pembrolizumab arm, all are either known adverse drug reactions to pembrolizumab or common AEs in the target population. Notably, among the drug-related Grade 3 to 5 AEs observed in ≥5% of subjects in the control arm, all were reported in a frequency of less than 1% of subjects in the pembrolizumab arm.

Table 56: Subjects with drug-related grade 3-5 AEs by decreasing incidence (incidence ≥5% in one or more treatment groups) - All subjects (APaT population)

	Control		Pembrolizumab	
	n	(%)	n	(%)
Subjects in population	255		266	
with one or more adverse events	126	(49.4)	40	(15.0)
with no adverse events	129	(50.6)	226	(85.0)
Neutropaenia	34	(13.3)	0	(0.0)
Neutrophil count decreased	31	(12.2)	1	(0.4)
Anaemia	20	(7.8)	2	(0.8)
Febrile neutropaenia	18	(7.1)	0	(0.0)
White blood cell count decreased	13	(5.1)	1	(0.4)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

- *Drug-related serious AEs (SAEs)*

Table 57 shows that the incidence of drug-related SAEs, as assessed by the Investigators, in subjects in the pembrolizumab arm was half than that reported for subjects in the control arm (10.2% vs 22.4%).

In the pembrolizumab arm, the drug-related SAEs observed in ≥1% of subjects and their prevalence in the control arm, were respectively: pneumonitis (1.9% vs 0) and colitis (1.5% vs 0).

In the control arm, the drug-related SAEs occurring in ≥1% of the subjects were as follows (pembrolizumab versus control): febrile neutropenia (0.0% vs 5.9%), constipation (0.0% vs 2.7%), anemia (0.0% vs 2.0%), intestinal obstruction (0.0% vs 2.0%), neutropenia (0.0% vs 2.0%), urinary tract infection (0.0% vs 1.6%), and neutrophil count decreased (0.0% vs 1.2%).

Table 57: Subjects With Drug-related Serious Adverse Events Up to 90 Days After Last Dose (Incidence >0% in One or More Treatment Groups) - All Subjects (APaT Population)

	Control		Pembrolizumab	
	n	(%)	n	(%)
Subjects in population	255		266	
with one or more adverse events	57	(22.4)	27	(10.2)
with no adverse events	198	(77.6)	239	(89.8)
Blood and lymphatic system disorders	**28**	**(11.0)**	**0**	**(0.0)**
Anaemia	5	(2.0)	0	(0.0)
Febrile neutropenia	15	(5.9)	0	(0.0)
Leukopenia	1	(0.4)	0	(0.0)
Neutropenia	5	(2.0)	0	(0.0)
Normochromic normocytic anaemia	1	(0.4)	0	(0.0)
Pancytopenia	2	(0.8)	0	(0.0)
Thrombocytopenia	1	(0.4)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**1**	**(0.4)**
Adrenal insufficiency	0	(0.0)	1	(0.4)
Gastrointestinal disorders	**20**	**(7.8)**	**5**	**(1.9)**
Colitis	0	(0.0)	4	(1.5)
Constipation	7	(2.7)	0	(0.0)
Diarrhoea	1	(0.4)	2	(0.8)
Ileus	2	(0.8)	0	(0.0)
Ileus paralytic	2	(0.8)	0	(0.0)
Intestinal obstruction	5	(2.0)	0	(0.0)
Large intestinal obstruction	1	(0.4)	0	(0.0)

Nausea	1	(0.4)	0	(0.0)
Neutropenic colitis	1	(0.4)	0	(0.0)
Subileus	1	(0.4)	0	(0.0)
Vomiting	1	(0.4)	0	(0.0)
General disorders and administration site conditions	**5**	**(2.0)**	**3**	**(1.1)**
Death	1	(0.4)	1	(0.4)
Fatigue	1	(0.4)	1	(0.4)
Influenza like illness	0	(0.0)	1	(0.4)
Malaise	1	(0.4)	0	(0.0)
Mucosal inflammation	1	(0.4)	0	(0.0)
Pyrexia	1	(0.4)	0	(0.0)
Hepatobiliary disorders	**1**	**(0.4)**	**0**	**(0.0)**
Jaundice	1	(0.4)	0	(0.0)
Infections and infestations	**10**	**(3.9)**	**2**	**(0.8)**
Lung infection	0	(0.0)	1	(0.4)
Pneumocystis jirovecii infection	1	(0.4)	0	(0.0)
Pneumonia	1	(0.4)	1	(0.4)
Sepsis	2	(0.8)	0	(0.0)
Septic shock	1	(0.4)	0	(0.0)
Upper respiratory tract infection	1	(0.4)	0	(0.0)
Urinary tract infection	4	(1.6)	0	(0.0)
Investigations	**4**	**(1.6)**	**2**	**(0.8)**
Alanine aminotransferase increased	0	(0.0)	1	(0.4)
Aspartate aminotransferase increased	0	(0.0)	1	(0.4)
Neutrophil count decreased	3	(1.2)	0	(0.0)
Platelet count decreased	1	(0.4)	0	(0.0)
Transaminases increased	0	(0.0)	1	(0.4)
Metabolism and nutrition disorders	**3**	**(1.2)**	**1**	**(0.4)**
Decreased appetite	1	(0.4)	0	(0.0)
Dehydration	1	(0.4)	0	(0.0)
Fluid retention	1	(0.4)	0	(0.0)
Hyponatraemia	0	(0.0)	1	(0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.4)**
Malignant neoplasm progression	0	(0.0)	1	(0.4)
Nervous system disorders	**1**	**(0.4)**	**1**	**(0.4)**
Encephalopathy	0	(0.0)	1	(0.4)
Posterior reversible encephalopathy syndrome	1	(0.4)	0	(0.0)
Renal and urinary disorders	**3**	**(1.2)**	**4**	**(1.5)**
Acute kidney injury	2	(0.8)	0	(0.0)
Autoimmune nephritis	0	(0.0)	1	(0.4)
Nephritis	0	(0.0)	1	(0.4)
Renal failure	1	(0.4)	0	(0.0)

Renal injury	0	(0.0)	1	(0.4)
Urinary tract obstruction	0	(0.0)	1	(0.4)
Reproductive system and breast disorders	**0**	**(0.0)**	**1**	**(0.4)**
Female genital tract fistula	0	(0.0)	1	(0.4)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.8)**	**7**	**(2.6)**
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.4)
Dyspnoea	1	(0.4)	0	(0.0)
Interstitial lung disease	0	(0.0)	1	(0.4)
Pneumonitis	0	(0.0)	5	(1.9)
Pulmonary hypertension	1	(0.4)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**1**	**(0.4)**
Rash maculo-papular	0	(0.0)	1	(0.4)
Vascular disorders	**1**	**(0.4)**	**0**	**(0.0)**
Deep vein thrombosis	1	(0.4)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA V19.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

- *Summary of deaths*

Overall, 4.9% (n=13) of subjects in the pembrolizumab arm and 3.1% (n=8) of subjects in the control arm had AEs that resulted in death within 90 days of the last dose (Table 58).

Review of the fatal pneumonitis event in the pembrolizumab arm indicated that the information in the case is consistent with the previously described characterization of immune-mediated pneumonitis with pembrolizumab. Upon medical review of the available information for the remaining AEs with a fatal outcome in subjects receiving pembrolizumab, the conclusion was they were deemed unlikely related to pembrolizumab; these were thought to be more likely related to either malignant neoplasm progression, infections (common among subjects with cancer), or related to complication of surgery for gastrointestinal perforation. No new safety signal was identified upon review of these fatal events.

Table 58: Subjects with AEs resulting in death up to 90 days after last dose (incidence >0% in one or more treatment groups) - All subjects (APaT population)

	Control		Pembrolizumab	
	n	(%)	n	(%)
Subjects in population	255		266	
with one or more adverse events	8	(3.1)	13	(4.9)
with no adverse events	247	(96.9)	253	(95.1)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.4)**
Gastrointestinal perforation	0	(0.0)	1	(0.4)
General disorders and administration site conditions	**4**	**(1.6)**	**2**	**(0.8)**
Death	4	(1.6)	1	(0.4)
General physical health deterioration	0	(0.0)	1	(0.4)
Infections and infestations	**4**	**(1.6)**	**5**	**(1.9)**
Atypical pneumonia	0	(0.0)	1	(0.4)
Pneumonia	1	(0.4)	3	(1.1)
Sepsis	2	(0.8)	0	(0.0)
Septic shock	1	(0.4)	0	(0.0)
Urosepsis	0	(0.0)	1	(0.4)
Metabolism and nutrition disorders	**0**	**(0.0)**	**2**	**(0.8)**
Cachexia	0	(0.0)	2	(0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.4)**
Malignant neoplasm progression	0	(0.0)	1	(0.4)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(0.4)**
Urinary tract obstruction	0	(0.0)	1	(0.4)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(0.4)**
Pneumonitis	0	(0.0)	1	(0.4)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA V19.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

- *Adverse Events of Special Interest*

Table 59 displays the subjects with AEOSI (incidence >0% in one or more treatment groups) by AEOSI category. AEs of special interest (AEOSI) are immune-mediated events and infusion-related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab. A pre-specified list of preferred terms (PTs) was developed for assessing AEOSIs, based on ongoing monitoring of the pembrolizumab safety profile during the development program. These PTs are considered to be clinically equivalent to the immune-mediated events and infusion-related reactions. All pre-specified AE terms were included in the assessment of frequency and nature of AEOSIs for pembrolizumab, regardless of causality as reported by Investigators.

There were 45 (16.9%) subjects in the pembrolizumab arm with 1 or more AEOSIs (Table 59). In general, the frequency and severity of each AEOSI observed during the trial were similar to the previously described characterization of the safety profile of pembrolizumab. No indication-specific AEOSI was identified (new immune-mediated event causally associated with pembrolizumab). Outcomes for subjects with AEOSIs are shown in (Table 60).

Table 59: Subjects with AEOSI (incidence > 0% in one or more treatment groups) - All subjects (APaT population)

	Control		Pembrolizumab	
	n	(%)	n	(%)
Subjects in population	255		266	
with one or more adverse events	19	(7.5)	45	(16.9)
with no adverse events	236	(92.5)	221	(83.1)
Adrenal Insufficiency	**0**	**(0.0)**	**1**	**(0.4)**
Adrenal insufficiency	0	(0.0)	1	(0.4)
Colitis	**1**	**(0.4)**	**6**	**(2.3)**
Colitis	1	(0.4)	5	(1.9)
Enterocolitis	0	(0.0)	1	(0.4)
Hyperthyroidism	**1**	**(0.4)**	**10**	**(3.8)**
Hyperthyroidism	1	(0.4)	10	(3.8)
Hypothyroidism	**3**	**(1.2)**	**17**	**(6.4)**
Hypothyroidism	3	(1.2)	17	(6.4)
Infusion Related Reactions	**10**	**(3.9)**	**2**	**(0.8)**
Hypersensitivity	2	(0.8)	1	(0.4)
Infusion related reaction	8	(3.1)	1	(0.4)
Myositis	**1**	**(0.4)**	**0**	**(0.0)**
Myositis	1	(0.4)	0	(0.0)
Nephritis	**0**	**(0.0)**	**2**	**(0.8)**

Autoimmune nephritis	0	(0.0)	1	(0.4)
Nephritis	0	(0.0)	1	(0.4)
Pneumonitis	**1**	**(0.4)**	**11**	**(4.1)**
Interstitial lung disease	1	(0.4)	1	(0.4)
Pneumonitis	0	(0.0)	10	(3.8)
Severe Skin Reactions	**3**	**(1.2)**	**2**	**(0.8)**
Jaundice	1	(0.4)	0	(0.0)
Dermatitis exfoliative	0	(0.0)	1	(0.4)
Drug eruption	1	(0.4)	0	(0.0)
Pruritus	1	(0.4)	0	(0.0)
Rash	0	(0.0)	1	(0.4)
Thyroiditis	**0**	**(0.0)**	**2**	**(0.8)**
Autoimmune thyroiditis	0	(0.0)	1	(0.4)
Thyroiditis	0	(0.0)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA V19.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Table 60: Subject with AEOSI adverse events by outcome (incidence > 0% in one or more treatment groups) - All subjects (APaT population)

		Control		Pembrolizumab	
	Outcome	n	(%)	n	(%)
Subject in population		255		266	
With one or more adverse events	Overall	19	(7.5)	45	(16.9)
	Fatal	0	(0.0)	1	(0.4)
	Not Resolved	5	(2.0)	19	(7.1)
	Resolved	13	(5.1)	20	(7.5)
	Resolving	0	(0.0)	2	(0.8)
	Sequelae	1	(0.4)	2	(0.8)
	Unknown	0	(0.0)	1	(0.4)

Every Subject is counted once for the AE outcome,with the order: Fatal>NotResolved>Resolving>Unknown>Sequelae>Resolved.
Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.
If the same preferred terms are reported more than once for the same subject, the outcome of the last occurrence is reported.
Grades are based on NCI CTCAE version 4.0.
Control arm is investigator<s choice of paclitaxel, docetaxel or vinflunine. (Database Cut-off Date: 07SEP2016)

4.12.3 Studies that report additional adverse reactions to those reported in section 4.2

The search strategy used to identify studies which reported AEs was consistent with that described in section 4.1 (see Appendix 2). No additional studies were identified in addition to those described in sections 4.2 and 4.7.

4.12.4 Brief overview of the safety of the technology in relation to the decision problem

The safety data from KEYNOTE-045 demonstrated that pembrolizumab is well tolerated in the target population, and offers favourable tolerability in comparison to SOC chemotherapy regimens in the target population.

This conclusion is supported by the following safety findings:

- A smaller proportion of subjects in the pembrolizumab arm experienced at least 1 AE (93.2%) compared with subjects in the control arm (98.0%)
- Fewer subjects in the pembrolizumab arm (60.9%) experienced drug-related AEs compared with the control arm (90.2%)
- Fewer subjects in the pembrolizumab arm (52.3%) experienced Grade 3 to 5 AEs compared with the control arm (62.7%)
- Fewer subjects in the pembrolizumab arm (15.0%) experienced Grade 3 to 5 drug-related AEs compared with the control arm (49.4%)
- There was a lower frequency of drug-related AEs leading to treatment discontinuation in the pembrolizumab arm (5.6%) compared with the control arm (11.0%)

Although reports of SAEs were comparable for subjects in the pembrolizumab and control arms, fewer subjects in the pembrolizumab arm had drug-related SAEs compared with subjects in the control arm (10.2% vs 22.4%).

Urinary tract infection and hematuria events were observed in a frequency not previously observed with pembrolizumab. Upon medical review, there was insufficient evidence for causality and the events were deemed most likely related to the underlying medical condition or to procedures commonly performed in the target population, such as urinary diversion.

In general, the frequencies and severity of each AEOSIs observed during the trial were similar to the previously described characterisation of the safety profile of pembrolizumab

No new safety risk was observed in association with pembrolizumab in the target population.

In summary, the data from KEYNOTE-045 underscore the safety profile of pembrolizumab relative to chemotherapy in subjects with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Statement of principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

In totality, the efficacy and safety results from IA2 of KEYNOTE-045[16, 17] are robust and demonstrate substantial, clinically meaningful benefit of pembrolizumab for OS, ORR, DOR, and QoL, combined with a more favourable tolerability compared with control (which comprised of investigator's choice SOC chemotherapy: paclitaxel, docetaxel or vinflunine) in patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy.
Based on the results of the pre-specified interim analysis (IA2), an independent Data Monitoring Committee (DMC) recommended that the trial be stopped early on the basis that it had met its primary endpoint. Patients continue to be followed-up up for survival outcomes.

A summary of the main clinical effectiveness findings from KEYNOTE-045 is provided below:

- **Pembrolizumab 200mg Q3W significantly prolongs OS and results in higher ORR and longer duration of response compared to SOC chemotherapy**

The OS results from KEYNOTE-045 are robust and demonstrated substantial, clinically meaningful benefit of pembrolizumab compared with control in all subjects, regardless of PD-L1 status (Section 4.7).

In the overall population, pembrolizumab significantly prolonged OS compared with control (HR = 0.73; p=0.002), with median OS of 10.3 months in the pembrolizumab arm versus 7.4 months in the control arm, thereby demonstrating a survival benefit in a population with a high unmet need. The OS curves cross and then began to separate after month 3, with continuous separation over the course of follow-up. Notably, the pembrolizumab curve began to flatten and a plateau was developing along the tail of the survival curve. This suggests patients have

the potential for long lasting survival benefit from pembrolizumab treatment. Subgroup analyses results were remarkably consistent with the primary findings, providing further evidence of the survival benefit of pembrolizumab over control among several important subgroups, including the specific Investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine).

Treatment with pembrolizumab, however, did not prolong PFS compared with control (HR = 0.98; p=0.416). Despite the lack of RECIST 1.1 PFS benefit, KM estimates show separation in favour of pembrolizumab after 6 months with a plateau in the tail of the curve, suggesting a meaningful benefit for some subjects from 6 months onward.

Pembrolizumab resulted in a statistically significant and clinically meaningful improvement in confirmed ORR versus the control arm (21.1% vs 11.4%, p=0.0010). As of the data cut-off date, the median response duration had not been reached for pembrolizumab, whereas it was 4.3 months for the control arm. The DOR rates at 12 months were 68% for pembrolizumab versus 35% for the control arm. This further underscores the substantial, durable treatment effect of pembrolizumab as a treatment option for patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy.

Efficacy findings in the CPS ≥10% and CPS ≥1% subgroups were in general consistent with the findings in the overall population. The available data underscore the substantial treatment effect of pembrolizumab when administered for patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy.

Post-hoc sub-group analyses focusing on as assessment of the efficacy of pembrolizumab versus only those SOC chemotherapy regimens of relevance to the UK (paclitaxel and docetaxel) show that versus each individual chemotherapy regimen, pembrolizumab demonstrated a trend towards better efficacy that SOC. Although the results were not statistically significant, this is not unexpected given the small sample sizes in each subgroup. Consequently the p-values should be interpreted as purely exploratory and within the context of the results in the overall population (Section 4.8).

- **Pembrolizumab 200mg Q3W improves HRQoL compared to SOC chemotherapy**

The improved benefit as assessed by OS, ORR, and response duration for pembrolizumab as compared with control in the KEYNOTE-045 population is corroborated by improvements in health status/QoL measures. Subjects treated with pembrolizumab had significantly better health status/QoL compared with subjects treated with chemotherapy (as demonstrated by the higher EORTC QLQ-C30 global health status/QoL score over time) and a longer time to deterioration in the pembrolizumab arm compared with control.

Results from EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses; while the EQ-5D visual analog score (Table 45) and the EQ-5D Utility scores (Table 46) were stable over time for subjects in the pembrolizumab arm, a worsening of these scores was observed in the SOC chemotherapy group.

- **Pembrolizumab 200mg Q3W has a favourable AE profile and is more tolerable in the patient population of interest, compared with SOC chemotherapy**

The results from KEYNOTE-045 consistently demonstrate that pembrolizumab has a more favourable tolerability profile compared to control in the target population. This conclusion is supported by the observation that subjects in the pembrolizumab arm experienced a lower frequency of AEs (93.2% vs 98.0%), drug-related AEs (60.9% vs 90.2%), Grade 3 to 5 AEs (52.3% vs 62.7%), drug-related Grade 3 to 5 AEs (15% vs 49.4%), drug-related SAEs (10.2% vs 22.4%), and drug-related AEs leading to treatment discontinuation (5.6% vs 11.0%) than did subjects in the SOC chemotherapy arm, regardless of ECOG, sex, and age subgroups. Fewer subjects in the pembrolizumab arm compared with the control arm discontinued study treatment due to adverse event (10.9% vs 15.7 %,), withdrawal by subject (1.1% vs 11.4%), or physician decision (2.3% vs 10.6%).

No new safety risk was observed in association with pembrolizumab. No new immune-mediated adverse events were identified during KEYNOTE-045. The analysis of AEOSIs for pembrolizumab demonstrated that the frequency and nature in the target population is consistent with the previously described safety profile of pembrolizumab. Overall, the frequencies of AEs, SAEs, drug-related AEs, and fatal AEs are either consistent with previous experience with pembrolizumab or considered related to the underlying medical condition (advanced/unresectable or metastatic urothelial carcinoma) of the target population.

4.13.2 Discussion of the strengths and limitations of the clinical evidence base for the technology

Internal Validity

KEYNOTE-045[16, 17] is a multicentre, randomised, open-label phase III trial of pembrolizumab 200mg Q3W versus control (which comprised of investigator's choice SOC chemotherapy: paclitaxel, docetaxel or vinflunine), in patients with metastatic or locally advanced/unresectable urothelial cancer that had recurred or progressed following platinum-containing chemotherapy. Randomisation was stratified by ECOG Performance Scale (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months [90 days]).

The co-primary efficacy endpoints were OS and PFS. Both are clinically relevant endpoints that were directly referenced in the final scope for this appraisal and the decision problem. The endpoints selected are consistent with those used in studies of other therapeutic agents in the population of advanced urothelial cancer. The definition of progression when evaluating the co-primary endpoint of PFS in KEYNOTE-045 followed an established response evaluation criteria (RECIST 1.1) in the primary efficacy analysis, in line with European guidance.[75]

HRQoL was an exploratory endpoint of the KEYNOTE-045 study, with changes from baseline in patients treated with pembrolizumab compared to patients treated with control recorded using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC-QLQC30 (see section 5.4).

Although KEYNOTE-045 was conducted as an open-label study, the independent radiologists who performed the central imaging review were blinded to treatment assignment, in order to minimise bias. The treatment arms were generally well balanced by all baseline characteristics, with the exception that slightly more subjects in the pembrolizumab arm were in the ≥65 years of age (61.1% vs 54.0%), ECOG-PS = 0 (44.1% vs 39%) and in the never smokers (38.5% vs 30%) subgroups compared with the control arm.

External validity

KEYNOTE-045[16, 17] is a global study conducted in 120 academic medical centres in 29 countries. 50 out of the 120 sites were in Europe, and the study included 4 patients from the 2 UK study sites.

Baseline characteristics of patients enrolled in KEYNOTE-045 were as expected for patients with advanced urothelial cancer. The majority of patients were male, ≥65 year of age, white, and former or current smokers (Table 17). Nevertheless, subgroup analyses confirm the benefit of pembrolizumab versus SOC in patients of all histologies.

With regards to risk factors, the majority of subjects in both arms had an ECOG-PS of 1, had visceral metastasis (including 34.3% with liver metastases), baseline haemoglobin ≥10 g/dL, and had completed prior therapy ≥3 months before being randomised to this trial. The treatment arms were generally well balanced by all baseline characteristics.

The observed safety profile of pembrolizumab in KEYNOTE-045 was consistent with that seen previously with pembrolizumab for the treatment of other types of tumours.[7-13]

Life expectancy of people with advanced Urothelial cancer in England

Full details concerning the life expectancy of UK patients with advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy, have been provided in section 3.4 of the submission and are summarised in

Table 61 below. Information concerning the estimated number of people with the particular therapeutic indication for which the technology is being appraised is also presented in section 3.4.

Please note that according to the new CDF TA process the criterion of small patient population does no longer apply.[76]

Table 61: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: Patients with advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy, have a short life expectancy with median survival measured in only a few months.[77, 78]
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	Pembrolizumab offers an extension to life of at least 3 months compared to UK SoC: • In KEYNOTE-045, the median OS for pembrolizumab arm was 10.3 (95% CI, 8.0, 11.8) months compared to 6.9 (95% CI, 5.3, 8.1) months for UK SOC (using 2-stage model for adjustment) • The average number of months of life gained with pembrolizumab as estimated by the economic model is 32.5 months compared to 19 months with UK SOC

4.14 Ongoing studies

Results provided in this submission are from the second interim analysis (IA2) of KEYNOTE-045,[16, 17] which had a data cut-off date of 07-Sept-2016. Based on the results of this pre-specified interim analysis, an independent Data Monitoring Committee (DMC) met on 18-October-2016 and recommended that the trial be stopped early. Although the trial was stopped early on the basis of meeting its primary endpoint, patients continue to be followed-up for survival outcomes. At the time of IA2, the study protocol permitted patients in the control arm to receive an alternative therapy after their trial treatment stopped. Following the DMC review of IA2, the study protocol has been revised as per the DMC recommendation in order to add a built in cross-over phase to allow patients in the control arm the opportunity to receive pembrolizumab upon disease progression.

5. Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Strategies used to retrieve cost-effectiveness studies relevant to decision-making in England

Relevant cost-effectiveness studies from the published literature were identified through a systematic literature search carried out between the 6th and 7th August 2015, and updated in December 2016. A detailed search strategy is provided in Appendix 23. The target population in this submission is patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy. However, the scope of the review was broadened to patients with advanced or metastatic patients with urothelial cancer irrespective of therapy line, in order to identify all relevant data that could inform the development and population of the model. Electronic database searches and additional hand-searches were restricted to the last 10 years, as older cost data may not be considered representative of the current economic environment.

The first stage in the review was to identify all relevant economic evidence for the comparator treatments by implementing comprehensive searches. The following research questions were posed in accordance with the decision problem:

- What is the cost-effectiveness of comparator therapies to pembrolizumab in treating patients with advanced or metastatic urothelial cancer, following platinum-containing chemotherapy?
- What is the health-related quality of life (in terms of utilities) associated with advanced or metastatic urothelial cancer, following platinum-containing chemotherapy?
- What are the resource requirements and costs associated with the treatment of advanced or metastatic urothelial cancer, following platinum-containing chemotherapy?

A comprehensive literature search relative to these three research questions was carried out using several databases and is presented in Appendix 17:

- MEDLINE and MEDLINE In-process (using Embase.com) - 1995 to 2016
- EconLit: No limit
- EMBASE (using Embase.com) – 1995 to 2016
- The Cochrane Library, including NHS EED and HTA databases – 1995 to 2016

Manual searches were also performed in the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), American Urological Association conference proceedings and International Society for Pharmacoeconomics and Outcomes Research (ISPOR), with additional papers identified from the reference list of included papers. The manual searches were limited to the most recent 2 years. A bibliographic search of the relevant, published systematic reviews, economic models and HTAs was also conducted to ensure that all studies of relevance to the review had been captured in the initial searches.

In addition to the formal literature search and manual searches, the National Institute for Health and Care Excellence (NICE) website was searched during the updated search in December 2016 to identify relevant information from previous submissions not otherwise captured.

All retrieved studies were reviewed by two independent researchers and assessed against the eligibility criteria set out in the final protocol and presented in Table 62 below.

Table 62: Inclusion and exclusion criteria for cost-effectiveness studies

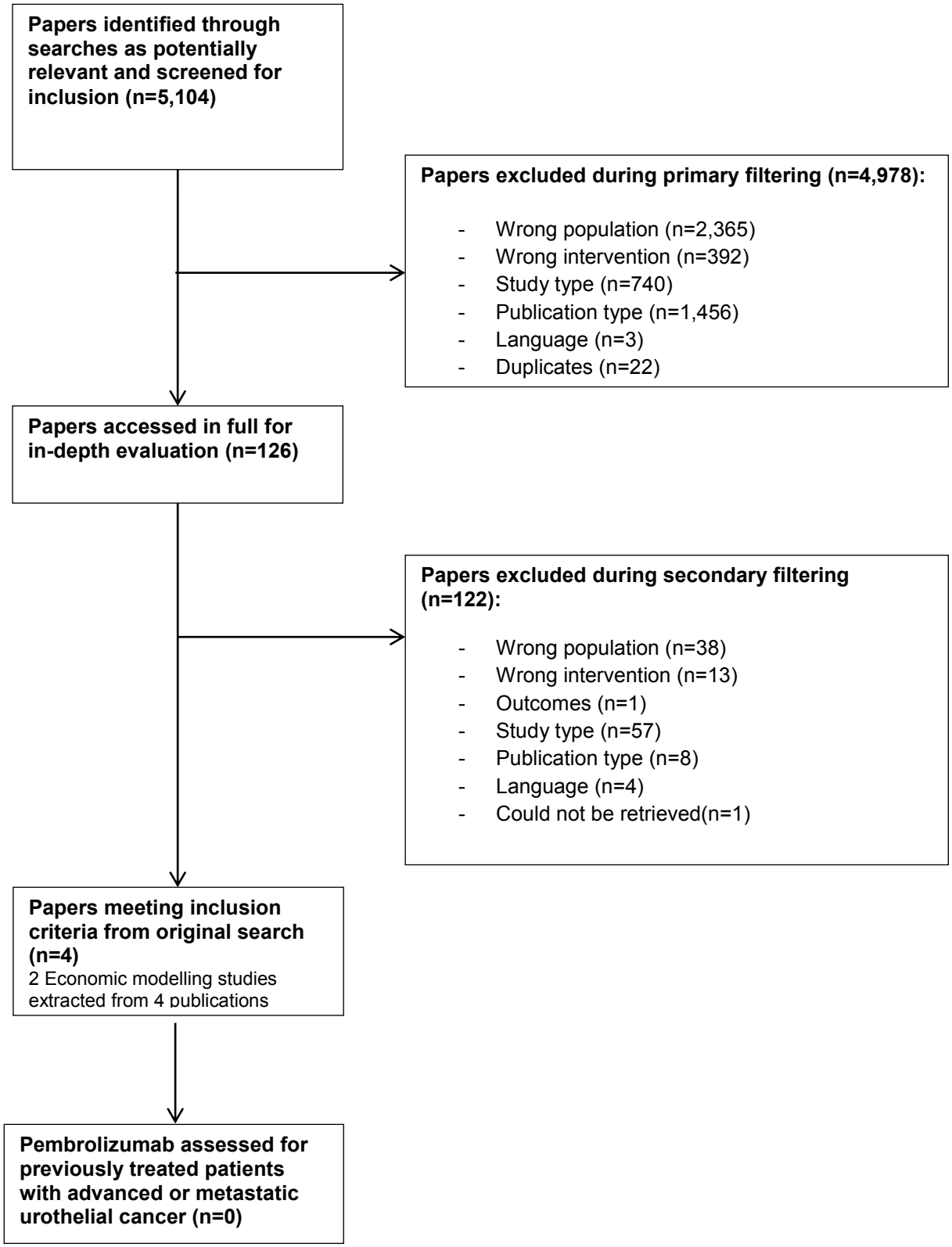
Criteria	Inclusion	Exclusion	Rationale
Population	Adult (age ≥18 years) patients with advanced or metastatic urothelial cancer	• Healthy volunteers • Patients under the age of 18 • Disease other than advanced or metastatic urothelial cancer	The relevant patient population
Intervention/ Comparator	Studies comparing pembrolizumab vs. any other pharmacological treatment	Non-drug treatments (e.g. surgery, radiotherapy)	To allow all papers with relevant pharmacological interventions to be captured
Outcomes	Studies including a comparison of benefits and costs between the intervention and comparator arms. Results should be expressed in incremental costs and QALYs, or any other measure of effectiveness reported together with costs	Cost-only outcomes	To identify relevant cost-effectiveness studies
Study type	Full economic evaluation comparing at least two interventions in terms of: • cost-consequence • cost-effectiveness • cost-utility • cost-benefit evaluations	Burden of illness studies, Cost-minimisation and Budget impact analysis	To identify relevant cost-effectiveness studies

Criteria	Inclusion	Exclusion	Rationale
Publication type	Economic evaluations	Letters, editorials and review studies	To identify primary study articles
Time limit	Studies published in last 10 years will be included	Studies published before 2005	To ensure recent economic models are included and limit the number of studies identified to those most relevant to the decision problem
Language	Studies for which a full text version is available in English	Not available in English	To ensure the studies can be correctly understood and interpreted
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed The study's data and results must be extractable	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated Studies that fail to present extractable results	To ensure • data can be extractable • methods can be replicated • results can be validated
Key: QALYs, Quality adjusted life years.			

5.1.2 Brief description of identified cost-effectiveness studies

Of a total of 5,104 potentially relevant papers or abstracts identified for the three SLRs, no cost-effectiveness studies assessing pembrolizumab for patients with advanced or metastatic urothelial cancer were found that met all the inclusion criteria. Thus, a summary list of published cost-effectiveness studies has not been compiled. The PRISMA flow diagram is presented in Figure 32.

Figure 32: PRISMA diagram – Economic evaluation review*



Key: n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

*From the updated search conducted in December 2016, 342 additional hits were identified, none of them was included.

5.1.3 Complete quality assessment for each relevant cost-effectiveness study identified

This is not applicable as no cost-effectiveness study meeting all the inclusion criteria was identified, indicating a de novo cost-effectiveness model is required to assess the cost-effectiveness of pembrolizumab compared with the relevant comparators.

5.2 De novo analysis

5.2.1 Patient population

The patient population included in the economic evaluation consisted of patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy. This is in line with the anticipated licenced indication and with the NICE final scope.[33]

The main body of clinical evidence was derived from the KEYNOTE-045 study, which included advanced or metastatic patients with urothelial cancer who have been previously treated.[16]

The baseline characteristics of the patients included in the model are presented in Table 63.

Table 63. Baseline characteristics of patients included in the model

Patient Characteristics	Mean	Measurement of uncertainty and distribution	Reference / Source
Average age	65.5	-	KEYNOTE-045 CSR [16]
Proportion male	74.2%	-	KEYNOTE-045 CSR[16]
Average BSA (m^2)*	1.90	SD = 0.20	KEYNOTE-045 CSR[16]

*These values refer to patients recruited from European sites participating in KEYNOTE-045.

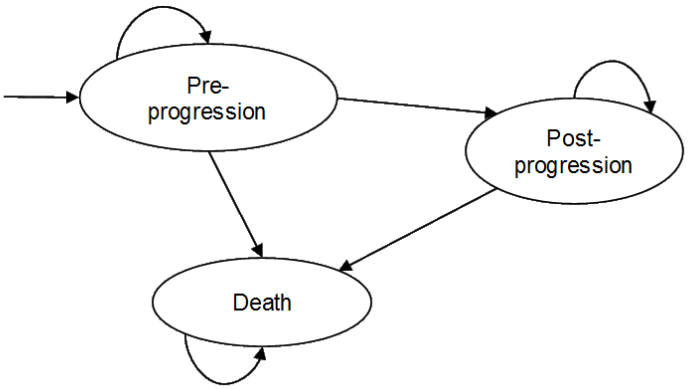
5.2.2 Model structure

Consistent with the majority of economic models previously developed for recent NICE oncology submissions,[51, 79] a de-novo economic analysis was built as a 'partitioned-survival' area-under-the-curve model. The model consisted of three health states: pre-progression, post-progression, and death (see Figure 33). This approach was also in line with the clinical endpoints assessed in KEYNOTE-045[16], in which progression free survival (PFS) and overall survival (OS) where assessed as primary endpoints. A cycle length of one week was considered sufficient to reflect the patterns of treatment administration and the transitions to disease progression and death. In line with previous oncology submissions, a half-cycle correction was implemented to mitigate bias.[79, 80]

Health states were mutually exclusive, meaning that patients could only be in one state at a time. All patients started in the pre-progression state. Transitions to the death state could occur from either pre-progression or post-progression, while death was an 'absorbing state'. Patients could not transition to an improved health state (i.e. from post-progression to pre-progression).

Disease progression was defined per RECIST v1.1 as assessed by BICR, which was the primary endpoint in KEYNOTE-045. [16, 81]

Figure 33. Model structure



The partitioned-survival model was developed by fitting survival curves to trial data for PFS and OS to facilitate extrapolation of trial outcomes. The area underneath the OS curve represented the proportion of patients that were still alive (both in pre-progression and post-progression) at different points in time, while the proportion of patients in the pre-progression state were identified by the patients located underneath the PFS curve. The area between the PFS and the OS represented the proportion of post-progression patients, i.e. those who were in the 'post progression' health state.

The definition of the health states used in the model was based on the definitions conventionally used in oncology clinical trials and, specifically, the ones used in the KEYNOTE-045 trial:

- Progressive disease was defined following the RECIST 1.1 criteria, i.e., at least a 20% increase in the sum of diameters of target lesions, and an absolute increase of at least 5 mm, or appearance of one or more new lesions. [82]
- Non-progressive disease reflected patients being alive and not in progressive disease (which included patients with complete response, partial response, and stable disease).
- Death (absorbing health state).

In the base case, pembrolizumab is compared with UK standard of care (UK SOC), i.e. investigator's choice of paclitaxel or docetaxel and results are expressed in terms of the incremental cost per QALY.

5.2.3 Key features of the de novo analysis

Table 64: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	35 years	Lifetime horizon for the defined population (NICE reference case[83]
Cycle length	1 week	Sufficient to model the patterns of treatment administration, transitions to disease progression and OS. In line with a recent NICE submission in Oncology.[79] [84]
Half-cycle correction	Yes	In line with previous submissions and to mitigate bias[79, 80]
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[83]
Discount of 3.5% for utilities and costs	Yes	NICE reference case[83]
Perspective (NHS/PSS)	Yes	NICE reference case[83] Please note that the costs to the NHS were included, but PSS costs have not been considered due to the unavailability of data to incorporate this into the model.
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.4 Intervention technology and comparators

The intervention (i.e. pembrolizumab) was applied in the model as per the anticipated licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]). The anticipated licence states that pembrolizumab is to be administered until disease progression or unacceptable toxicity. The KEYNOTE-045 protocol established that treatment should continue until radiologic disease progression, toxicities leading to discontinuation, physician's decision or 24 months of uninterrupted treatment with pembrolizumab.

It is anticipated that pembrolizumab will be considered as an option for adults with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy. The NICE final scope specifies the following treatment regimens as relevant comparators:[33]

- Retreatment with 1st line platinum-containing chemotherapy (in patients whose disease has had an adequate response)
- Docetaxel

- Paclitaxel

As described in section 4.10, an indirect treatment comparison using a NMA was not feasible as based on the available evidence identified during the systematic literature review process, a connected network could not be formed linking pembrolizumab to UK comparators of interest. Therefore, the cost-effectiveness analysis was limited to comparator regimens included in the KEYNOTE-045 trial. Post-hoc subgroup analyses of the data from KEYNOTE-045 was conducted, to focus only on comparators of relevance to England (i.e. paclitaxel and docetaxel, excluding the non-recommended by NICE vinflunine). The results of these analyses are presented in Section 4.8.

In the base case, pembrolizumab was compared to UK SOC, i.e. physicians' choice of docetaxel or paclitaxel, based on the distribution of the regimens observed in KEYNOTE-045 in order to be consistent with the efficacy inputs of the model. A scenario analysis is presented in which the cost of UK SOC is based on the UK market share of docetaxel and paclitaxel (Table 65).

Table 65. Distribution of patients according to KEYNOTE-045 vs. market shares

Regimens	KEYNOTE-045 (base case)	UK market shares*
Docetaxel	51.1%	74%
Paclitaxel	48.9%	26%
% Total	100%	100%

*UK market shares were re-adjusted by excluding platinum-containing chemotherapy regimens

Source: Ipsos 2016. Data on file.[21]

Docetaxel and paclitaxel do not have marketing authorisation in the UK for the indication under consideration; their use is therefore off-label in this setting. The dosing and administration frequencies for the comparator regimens were taken from the KEYNOTE-045 trial,

The comparisons assessed in the cost-effectiveness model are presented in

Table **66**.

Table 66. Intervention and comparators according to the different types of analyses assessed in de novo cost-effectiveness model

Population	Intervention and comparators	OS for comparator arm			
	Pembrolizumab vs.	ITT unadjusted	Two-stage	RPSFT	IPCW
ITT	UK SOC (docetaxel and paclitaxel)	✓	✓	✓	✓
	Docetaxel	✓	×	✓	✓
	Paclitaxel	✓	×	✓	×
ITT – histology subgroup	UK SOC (docetaxel and paclitaxel) ▪ Predominant transitional cell carcinoma ▪ Pure transitional cell carcinoma	✓	×	×	×
PD-L1 positive (CPS≥1%)	UK SOC (docetaxel and paclitaxel)	✓	×	✓	✓
PD-L1 strongly positive (CPS≥10%)	UK SOC (docetaxel and paclitaxel)	✓	×	✓	×

5.2.5 Discontinuation rules

In KEYNOTE-045, patients were to continue pembrolizumab until radiographic disease progression as determined by the investigator/site radiologist, unacceptable toxicity or a maximum of 24 months of uninterrupted treatment with pembrolizumab.[16] In the cost-effectiveness model, the survival estimates of OS and PFS are based on KEYNOTE-045 data, thus reflecting the within-trial maximum treatment duration.

Based on clinical expert opinion, it was assumed that up to a maximum of 6 cycles were administered to reflect the UK clinical practice for the treatment regimens included under this comparator.

5.3 Clinical parameters and variables

5.3.1 Overall method of modelling survival

In order to include only comparator regimens that are relevant to UK clinical practice, the primary data source for the SOC arm in the economic model was a post-hoc analysis of KEYNOTE-045 clinical trial,

As described in Section 4.8 and Appendix 10, some patients in the UK SOC arm, i.e. investigator's choice of paclitaxel or docetaxel, switched over to anti-PDL1 treatments following disease progression. Therefore, three statistical methods were applied in order to adjust for treatment switching: the RPSFT, the simplified 2-stage method and the IPCW. Table 67 summarises the results of OS analyses for pembrolizumab vs. UK SOC.

Table 67: Summary Results of OS Analyses

Switching adjustment correction method	Pembrolizumab vs. UK SOC		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT	[redacted]	[redacted]	[redacted]
Simplified two-stage[$]	[redacted]	[redacted]	[redacted]
RPSFT[¶]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]

¶ Re-censoring applied to all control patients
§ No Re-censoring applied
** P-value retained from ITT analysis by design*
†: Bootstrap p-value

A summary of the median OS in the pembrolizumab and UK SOC arm, with and without various treatment switching correction methods applied, is summarised below in Table 68.

Table 68: Analysis of median OS using Two-stage, RPSFT and IPCW methods

Switching correction method	Median OS (months) (95% CI)
UK SOC (no correction)	[redacted]
UK SOC - Simplified two-stage correction (no re-censoring)	[redacted]
UK SOC – RPSFT correction	[redacted]
UK SOC – IPCW correction	[redacted]

In summary, the three methods adjusting for switchover in the UK SOC arm provide treatment estimates that are larger (HR in a range of [redacted] to [redacted]) than the ITT estimate (HR=[redacted]). The IPCW method is likely to be biased due to the small sample size.The post-progression treatment of pembrolizumab estimated through the 2-stage methodology (acceleration factor of 3.86, 95% CI [1.79, 11.68]) was compared with the overall effect of pembrolizumab adjusted for switching (acceleration factor of 1.44, 95% CI [1.14, 1.82]). Although this comparison may be prone to some bias, it suggests that there is numerical evidence against the common treatment assumption that justifies the 2-stage approach. Therefore, based on the trial characteristics, the switching mechanism, the proportion of patients switching and the clinical validity of the outputs obtained,[60] the two-stage adjustment was found to be the most appropriate method for this adjustment. The assumptions required for it to be valid (i.e. potential to switch determined by disease progression and potential confounders measured until this point) were met.

OS extrapolation

The follow-up period in KEYNOTE-045 was shorter than the time horizon of the economic model. Therefore, extrapolation of the OS and PFS was required for the area-under-the-curve (AUC) partitioned survival approach.

The guidance from the NICE DSU was followed to identify base case parametric survival models for OS and PFS.[85] In summary, the steps that were followed include:

1. Testing the proportional hazard (PH) assumption – To assess whether joint or separate statistical models were more appropriate for the pembrolizumab and UK SOC treatment arms. Visual inspection of the OS and PFS KM curves confirmed that the PH assumption does not hold as the survival curves for pembrolizumab and UK SOC cross.

2. Separate survival models were then explored. Models were separately fitted to each arm using data from the relevant treatment arm. Following the recommendation from the DSU, the same functional form was selected for the parametric models according to that fitting the overall data most closely.

3. Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to help identify the most plausible survival models.

4. Lastly, the choice of base case parametric models was validated in terms of clinical plausibility of both short-term and long-term extrapolations.

5.3.2 Modelling overall survival

To adjust OS for switching in the UK SOC arm, a simplified two-stage approach[60, 85] was identified as the most appropriate method, as mentioned in section 4.8. The OS KM curve for UK SOC adjusted for treatment switching using the two-stage model compared to the unadjusted OS is shown in

Figure **34** below.

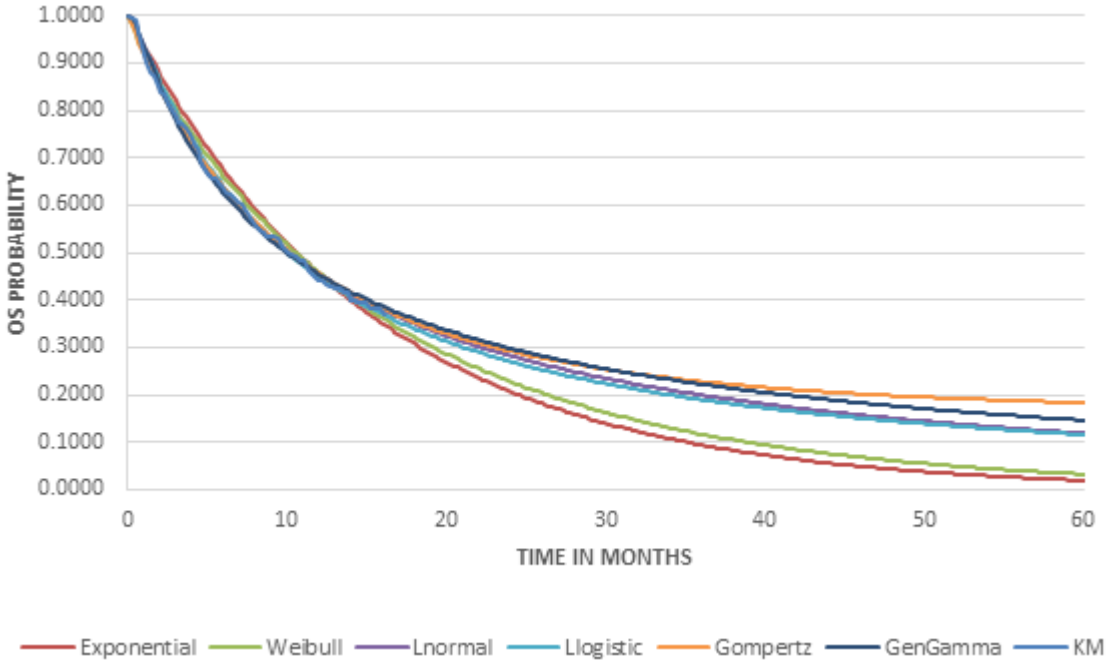
Figure 34. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis for pembrolizumab vs UK SOC

[redacted]

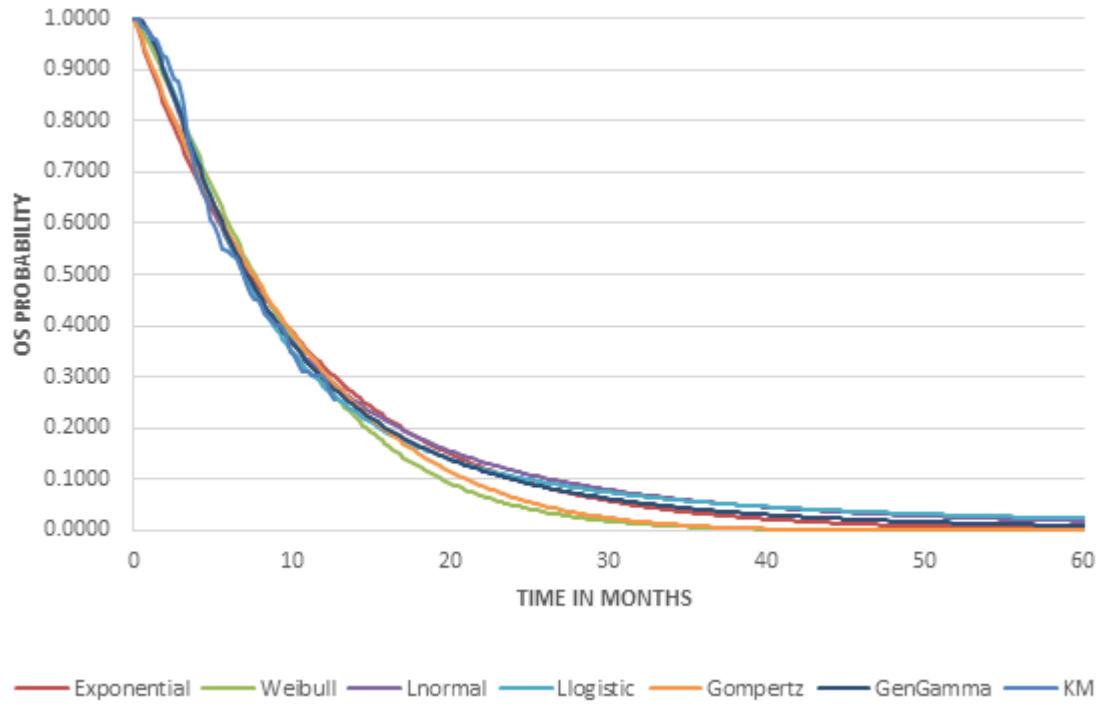
Since the PH assumption did not hold, separate models were fitted based on the individual patient data from KEYNOTE-045.[85] The fitted separate standard parametric curves are presented in Figure 35.

Figure 35. Fitted separate standard parametric curves for the OS of pembrolizumab (A) and UK SOC (B)

A) Separate fitted curves for pembrolizumab



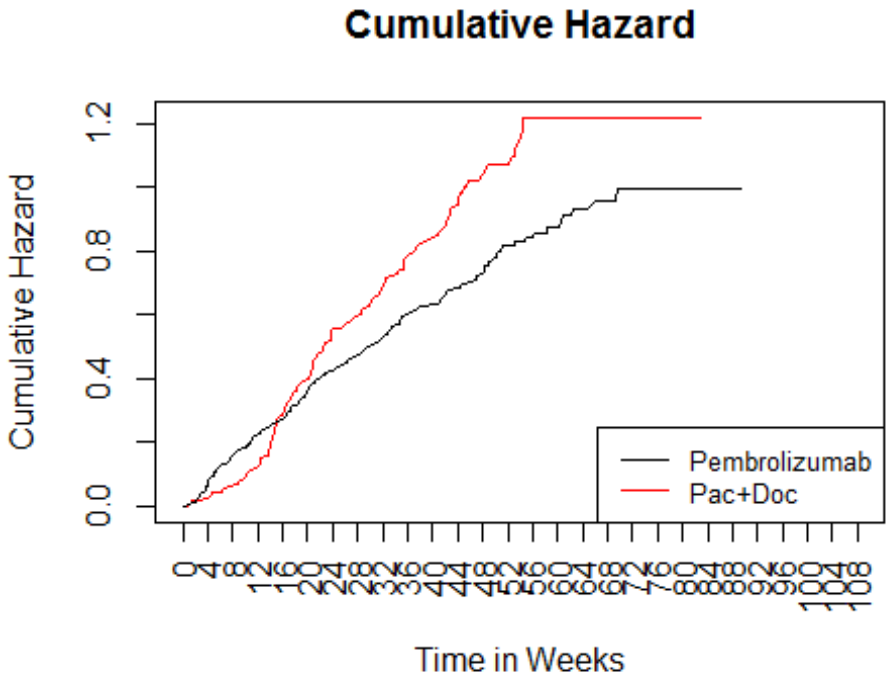
B) Separate fitted curves for UK SOC(adjusted using two-stage approach)



The cumulative hazard plot (see **Error! Reference source not found.**) demonstrates that the change in hazard is not constant over time (i.e. the OS curves start separating from week 24,

while there is a more clear change in the slope after around 40 weeks). This supports that a piecewise model is more appropriate than the use of single parametric curves. Given the precedence of the use of 2-phase piecewise models (KM plus parametric approach) in recent NICE oncology appraisals,[79, 86]; we decided to implement a 2-phase piecewise model as the most appropriate method to extrapolate OS.

Figure 36. Cumulative hazard plot of OS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and UK SOC based on KEYNOTE-045



For the UK SOC parametric adjustment, the curves presenting the closest statistical fit to the data (i.e. generalized gamma distribution followed by gompetz) resulted in an overestimation of the OS at 5 years (i.e. approximately 17% and up to 24%), which is well above the approximately 9-11% OS rate reported by the Cancer Research UK for patients with stage IV bladder cancer.[44] These were therefore discarded as clinically implausible whereas the log-normal distribution projected 7.8% OS rate at 5 years, which is closest to the available OS estimates. Particularly given that the patient population under consideration also includes patients with transitional cell carcinoma of renal pelvis and urether for whom there is evidence of poorer prognosis (see section 3.4).

For the pembrolizumab arm, the log-normal curve is the closest statistical fit to the data based on the AIC statistic whereas the exponential curve is the closest based on BIC. However, the exponential curve underestimates the UK SOC arm with only 0.3% OS rates at 5 years. Therefore this was discarded as clinically implausible.

Table 69. Fitted exponential curves for the fully fitted parametric approach for OS

Fitted Function	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC
Exponential	339.1	342.1	165.1	167.1
Weibull	340.5	346.4	165	169.1
Gompertz	338.1	344	160.4	164.5
Llogistic	339.4	345.3	163.7	167.7
Lnormal	337.5	343.4	161.8	165.9
GenGamma	338.5	347.3	160.2	166.3

For the 2-phase piecewise approach, the two-phase parametric models were fitted using a 40-week cut-off point. The fitted 2-phase piecewise models are presented in Figure 37. These provide a good balance of KM data to be used directly in the first phase and enough remaining KM data to be used to fit a log-normal curve in the second phase. Additionally, it results in a plausible visual fit.

Figure 37. OS KM curves vs. fitted 2-phase piecewise models for the OS of pembrolizumab and UK SOC (2-stage adjustment applied) based on KEYNOTE-045

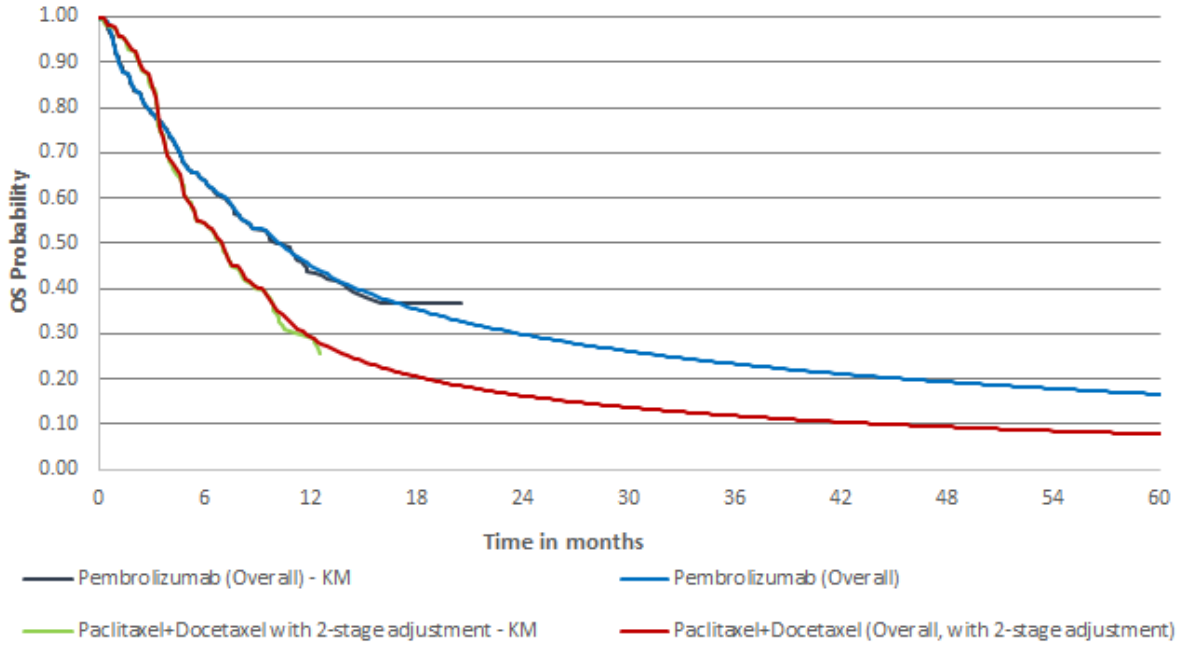


Table 70. Fitted log-normal curves for the 2-phase piecewise approach for OS

	Log-normal curve parameters	
40-weeks cut-off	Pembrolizumab	UK SOC (2-stage adjusted)
Intercept	4.4613	3.6962
Scale	0.6498	0.6814

5.3.3 Modelling progression free survival

Based on the trial protocol of KEYNOTE-045, the first tumour assessment was performed at week 9 and then every 6 weeks thereafter. This resulted in a protocol-driven drop of PFS between weeks 0 and 9, which did not allow the fitting of a full parametric curve. As a consequence, the KM data were used directly until week 21 (3rd assessment) of the model time horizon and parametric functions were fitted from then onwards. The 21-week cut-off point was selected based on the clear separation of the curves observed in the cumulative hazard plot (see Figure 38). To identify the most plausible PFS curves among the standard parametric curves, the guidance from the NICE DSU[85] was followed (please see section 5.3.1).

The PH assumption did not hold as the KM PFS curves for pembrolizumab and UK SOC cross. Therefore, separate models were used based upon the pembrolizumab and UK SOC data for the projection of the PFS using a 2-part piecewise extrapolation. Following DSU guidance[87], only similar types of parametric curves for OS and PFS (with 'type' defined as the same parametric distribution) were considered for the pembrolizumab and UK SOC arms.

Figure 38. Cumulative hazard plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and UK SOC based on KEYNOTE-045

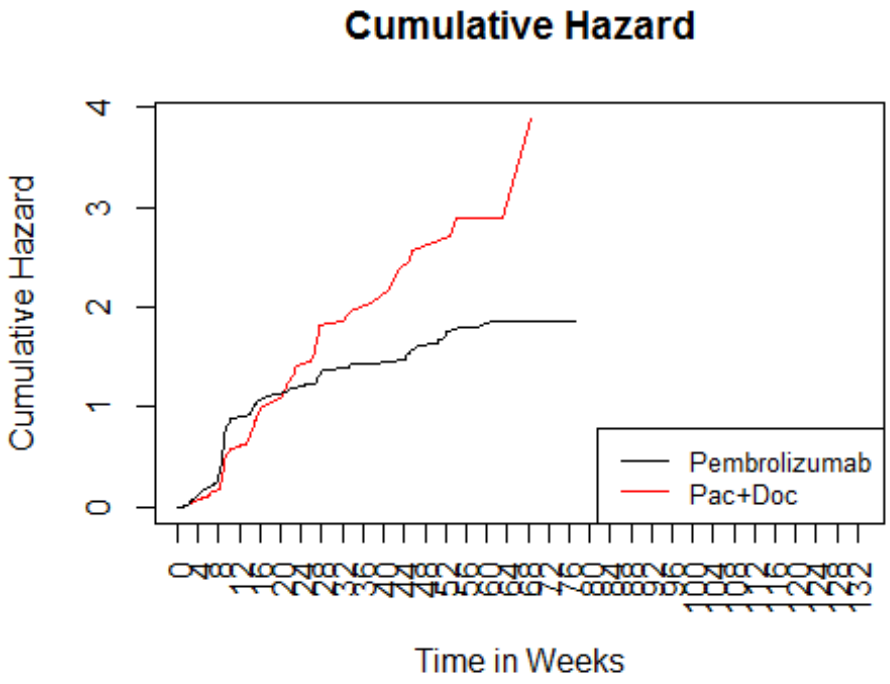


Table 71 reports the AIC/BIC statistics for the second part of the PFS two-part fit for pembrolizumab based on KEYNOTE-045 PFS data. An exponential distribution was the best

fit to the pembrolizumab PFS data based both on AIC/BIC criteria and visual fit (see Figure 39). For UK SOC, there is no clear best statistical fit, with the Weibull distribution presenting the lowest BIC value while the generalized gamma the lowest AIC value. Based on visual inspection (see Figure 40), all distributions are very close. Consequently, the exponential curve was selected for the extrapolation of PFS for UK SOC to maintain consistency with the best fit identified for pembrolizumab.

Table 71. Goodness-of-fit measures for PFS defined per RECIST v1.1 as assessed by BICR, with cut-off at 21 weeks, for pembrolizumab and UK SOC based on KEYNOTE-045

	Pembrolizumab		UK SOC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	339	341.4	154.1	155.4
Weibull	340.7	345.5	150.6	153.1
Gompertz	340.2	345	155.9	158.4
Llogistic	340.2	344.9	153.6	156.1
Lnormal	339.9	344.6	153.4	155.9
GenGamma	341.8	348.9	149.8	153.6
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria.				

Figure 39. PFS KM curve vs. fitted 2-phase piecewise models according to the PFS defined per RECIST v1.1 as assessed by BICR, with cut-off at 21 weeks, for pembrolizumab based on KEYNOTE-045

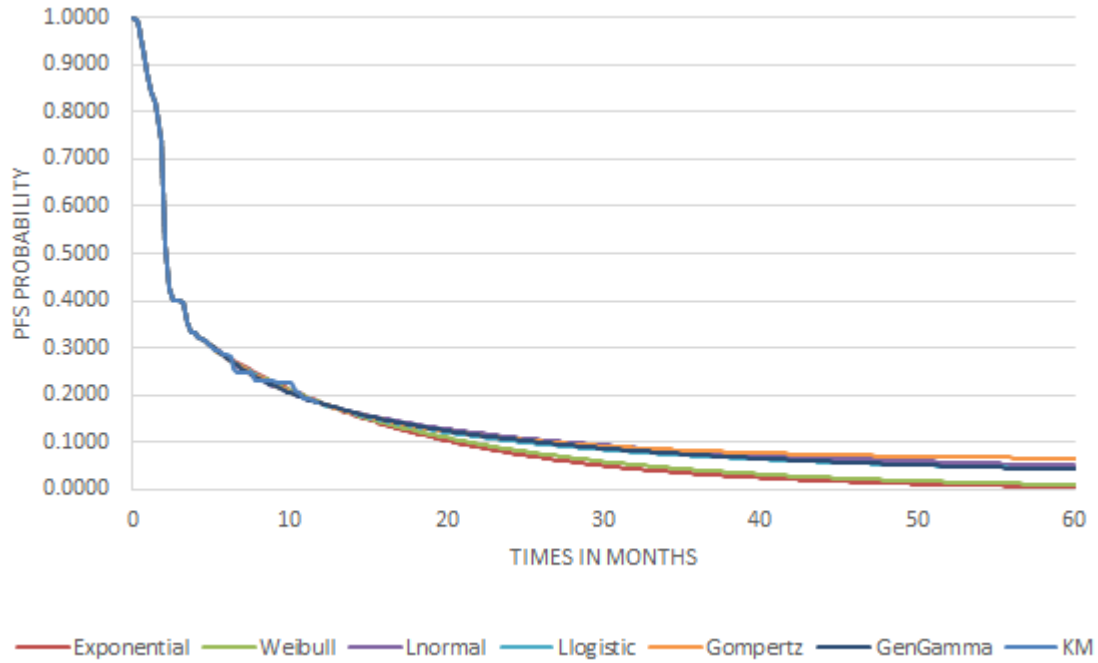
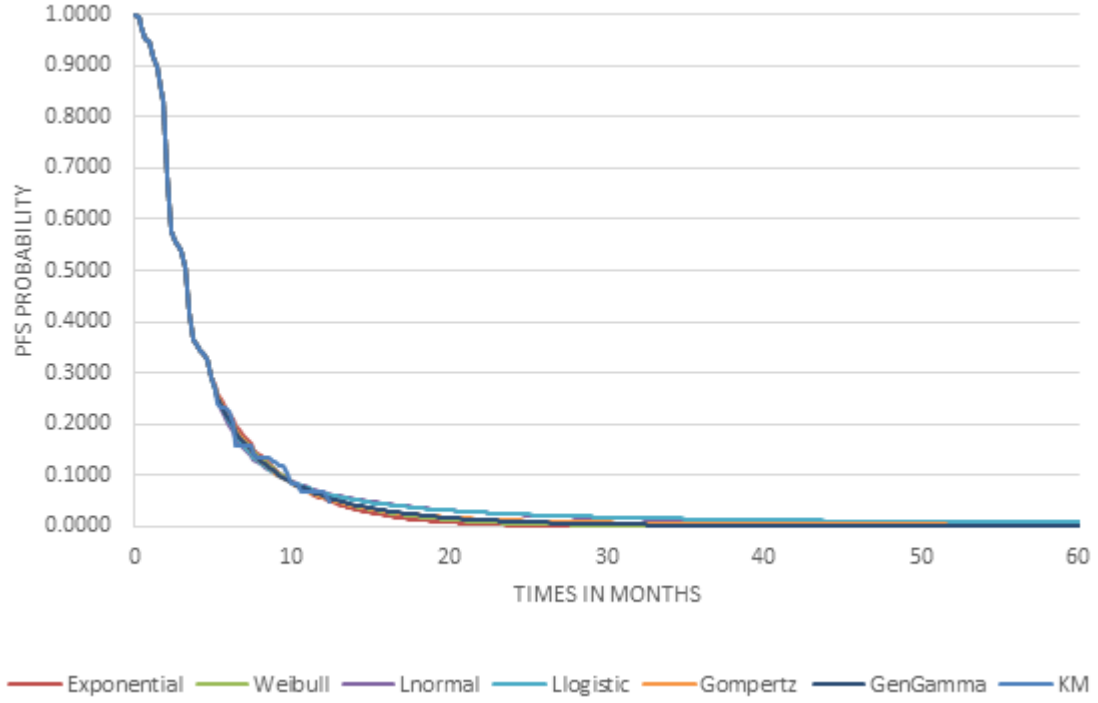
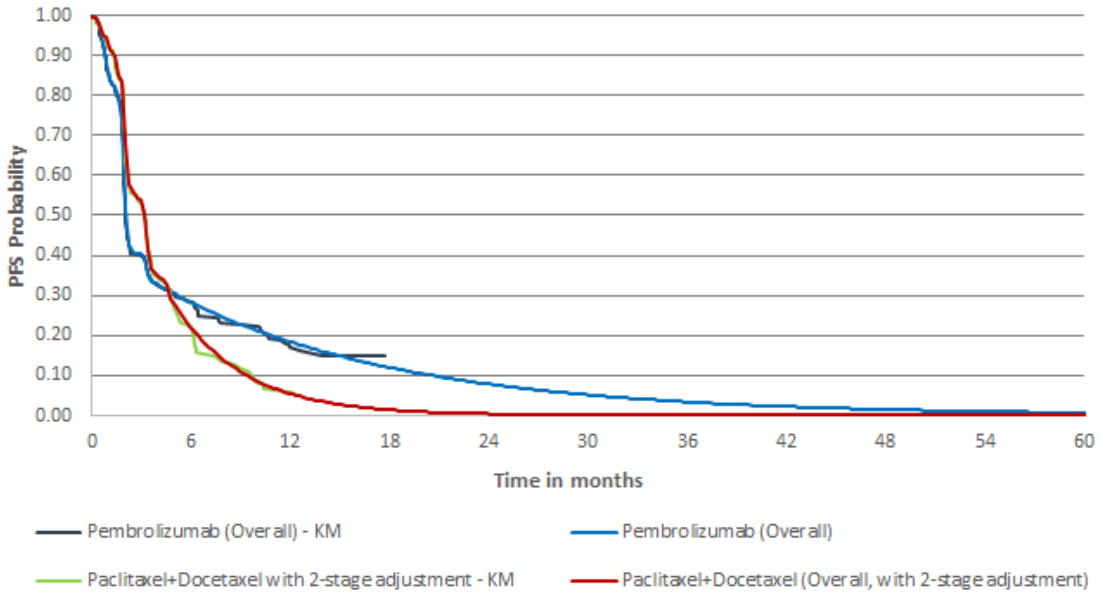


Figure 40. PFS KM curve vs. fitted 2-phase piecewise models according to the PFS defined per RECIST v1.1 as assessed by BICR, with cut-off at 21 weeks, for UK SOC based on KEYNOTE-045



The modelled PFS curves based on the approach above are presented in Figure 41 below.

Figure 41. Fitted base case 2-phase piecewise models according to the PFS of pembrolizumab and UK SOC based on KEYNOTE-045



5.3.5 Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm, with two exceptions:

- Diarrhoea Grade 2 is also included to be consistent with previous NICE appraisals.[79, 86]

- Febrile neutropaenia (with a 2% incidence in the UK SOC arm) is also included as clinicians have suggested that this AE has significant impact on quality of life and costs. The inclusion of febrile neutropaenia is also consistent with recent NICE appraisal.[79]

The approach to identify the relevant AEs to be included in the economic model was previously validated by clinical experts.

The incidence of AEs was taken from the KEYNOTE-045 trial for each treatment arm (see Table 72). It should be noted that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. The unit cost and the disutility associated with the individual AEs were assumed to be the same for all treatment arms, therefore the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 72. This was consistent with the methods used in previous oncology submissions[79, 80] and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting.

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm. AE-related disutilities were considered as part of the base case since this was the preferred approach by the committee appraising pembrolizumab in NICE TA428.[79]

Table 72. Grade 3+ AE rates for AEs included in the economic model based on KEYNOTE-045 data (Incidence >5% in one or more treatment arms)

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for UK SOC (Grade 3+)
Anaemia	8.3%	11.9%
Febrile neutropenia	0.0%	4.76%
Neutropenia	0.0%	11.9%
Diarrhoea	5.3%	5.36%
Fatigue	3.8%	5.95%
Neutrophil count decreased	0.4%	14.29%
White blood cell count decreased	0.4%	5.95%
Pneumonia	2.6%	4.17%
Hypophosphatemia	0.80%	3.57%

5.3.6 Subsequent treatment

Given the advanced nature of the disease and the lack of data on multiple lines of therapy beyond second-line treatment, only one line of subsequent therapy is modelled. Data from KEYNOTE-045 was used to estimate the proportion of patients in each treatment arm receiving different types of subsequent therapy. The list of subsequent therapies is presented in Appendix 21.

In the economic model, patients in the progressed disease health state were assumed to incur the costs of subsequent therapies as observed in the KEYNOTE-045 trial but with the clinical benefit, if any, being part of the analysis derived from KEYNOTE-045. This is to ensure that the relevant cost of treatment for a progressed patient is accurately represented. A mean duration of 2 cycles was applied to all subsequent treatments, which is based on the NICE TA272.[51] For the UK SOC arm, since a switching adjustment was implemented as part of the OS projections adjusting by the effect of anti-PD-1/anti-PD-L1 agents, the cost related to these therapies was not accounted for in the model. Scenario analysis using unadjusted OS estimates and inclusion of the treatment and administration costs of anti-PD-1/anti-PD-L1 received by patients as subsequent therapies is presented in section 5.8.3.

5.3.7 Inputs from clinical experts

The long-term OS extrapolation estimated by the model (i.e. 5-year and 10-year OS rates) was validated with clinical experts.

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 (HRQoL) was evaluated in the KEYNOTE-045 trial using the EuroQoL EQ-5D-3L (see sections 4.3 and 4.7 above). The estimated utilities were used in the cost-effectiveness model as evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case.[83]

In KEYNOTE-045, the EQ-5D questionnaire was administered at treatment cycles 1, 2, 3, 4 and every second cycle thereafter for as long as patients were on treatment. Additionally, it was administered at the discontinuation visit, and 30 days after (during the Safety Follow-up visit). The EQ-5D analyses presented below are based on the FAS population for the pembrolizumab and the control arms of the trial. EQ-5D questionnaires administered to the vinflunine arm of the KEYNOTE-045 trial were also included in order to maximise the data for analysis.[16]

When estimating utilities, two approaches were considered:

- Estimation of utilities based on time-to-death.

  This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. The approach has been used previously in the estimation of HRQoL in NSCLC patients receiving palliative radiotherapy[88] and in advanced melanoma patients.[89-91] Time to death was demonstrated as more relevant than progression-based utilities since with more health states offering a better HRQoL data fit.[79, 84, 89-91]

  Based on KEYNOTE-045 EQ-5D data, time to death was categorised into the following groups:

  - 360 or more days to death
  - 180 to 360 days to death
  - 90 to 180 days to death
  - 30 to 90 days to death
  - Under 30 days to death.

  EQ-5D scores collected within each time category were used to estimate mean utility associated with that category. The analyses of the intervals related to time to death lower than 360 days included only patients with observed death dates. The justification to exclude patients whose death dates were censored was that their EQ-5D values could not be linked to their time-to-death category. However, for the category of 360 or more days to death, patients with censored death date of 360 days or longer were also included since their EQ-5D data related to a survival of at least 360 days, independent of when the death date was censored.

- Estimation of utilities based on progression-free and progressed disease states.

  Another approach, commonly seen in oncology economic modelling literature, is to define health states based on time relative to disease progression. This approach generates results to fit the health states modelled. However, in KEYNOTE-045, utility data was collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further. Therefore, the utility data for post-progression is very limited as it is usually collected directly after progression, thereby missing the utility data as patients' HRQoL deteriorates when getting closer to death. This leads to an overestimation of the utility in the post-progression state.

  Following this approach, the date of progression was determined from the RECIST version 1.1 using blinded independent central review (BICR).

  - To estimate utilities for the progression-free health state, EQ-5D scores collected at all visits before the progression date were used.
  - Utilities for the progressive state were based on the EQ-5D scores collected at all visits after the progression date.

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab and control arms), and pooled for both arms. In addition, 95% confidence intervals were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested.

The level of EQ-5D compliance through time is presented in Table 73.

Table 73. Compliance of EQ-5D by visit and by treatment (FAS Population)

Treatment Visit	Category	Pembrolizumab	Control
		N = 266	N = 254
		n (%)	n (%)
Baseline	Expected to complete questionnaires	266	254
	Completed	260	243
	Compliance(completed per protocol)*	97.7%	95.7%
Week 3	Expected to complete questionnaires	260	246
	Completed	238	219
	Compliance(completed per protocol)*	91.5%	89.0%
Week 6	Expected to complete questionnaires	230	218
	Completed	215	199
	Compliance(completed per protocol)*	93.5%	91.3%
Week 9	Expected to complete questionnaires	216	202
	Completed	200	176
	Compliance(completed per protocol)*	92.6%	87.1%
Week 15	Expected to complete questionnaires	179	134

Treatment Visit	Category	Pembrolizumab	Control
		N = 266	N = 254
		n (%)	n (%)
	Completed	157	118
	Compliance(completed per protocol)*	87.7%	88.1%
Week 21	Expected to complete questionnaires	143	83
	Completed	127	73
	Compliance(completed per protocol)*	88.8%	88.0%
Week 27	Expected to complete questionnaires	118	57
	Completed	105	46
	Compliance(completed per protocol)*	89.0%	80.7%
Week 33	Expected to complete questionnaires	95	33
	Completed	85	27
	Compliance(completed per protocol)*	89.5%	81.8%
Week 39	Expected to complete questionnaires	85	14
	Completed	76	12
	Compliance(completed per protocol)*	89.4%	85.7%
Week 45	Expected to complete questionnaires	73	12
	Completed	60	11
	Compliance(completed per protocol)*	82.2%	91.7%
Week 51	Expected to complete questionnaires	56	9
	Completed	47	6
	Compliance(completed per protocol)*	83.9%	66.7%
Week 57	Expected to complete questionnaires	45	3
	Completed	8	2
	Compliance(completed per protocol)*	17.8%	66.7%

*Compliance is the proportion of subjects who completed the PRO questionnaire among those who are expected to complete it at each time point (excludes those missing by design).
Missing by design includes: death, discontinuation, translations not available, and no visit scheduled.
(Database Cut-off Date: 07 Sep 2016).

UK preference-based scores were used for all patients analysed from the KEYNOTE-045 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique.[92]

A diagnostic analysis conducted to compare baseline EQ-5D utility scores, collected at the first visit (treatment cycle 1), showed that there was no significant difference in baseline utilities across the two treatment arms, i.e. pembrolizumab and control arm. Based on this analysis, utilities were similar in pembrolizumab and control treatment groups at baseline. There were no statistically significant or clinically meaningful differences in EQ-5D scores by treatment arm; therefore, the scores from the pooled treatment group were used.

The estimated utilities are presented in Table 74 and Table 75 below.

Table 74: EQ-5D health utility scores by time-to-death

Time to Overall Survival (days)	Pembrolizumab					Control (Paclitaxel, Docetaxel and Vinflunine)					Pembrolizumab and Control Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥360*	77	259	0.765	0.017	(0.731, 0.799)	43	132	0.804	0.015	(0.773, 0.835)	120	391	0.778	0.013	(0.753, 0.803)
[180, 360)	51	158	0.686	0.022	(0.643, 0.728)	64	190	0.699	0.015	(0.670, 0.728)	115	348	0.693	0.013	(0.668, 0.718)
[90, 180)	75	158	0.566	0.025	(0.517, 0.615)	84	171	0.612	0.022	(0.569, 0.654)	159	329	0.590	0.016	(0.557, 0.622)
[30, 90)	63	106	0.457	0.037	(0.384, 0.529)	84	151	0.446	0.032	(0.384, 0.509)	147	257	0.451	0.024	(0.403, 0.498)
<30	29	35	0.336	0.077	(0.180, 0.493)	26	29	0.311	0.082	(0.143, 0.480)	55	64	0.325	0.056	(0.214, 0.436)

† n=Number of patient with non-missing EQ-5D score
‡ n=Number of records with non-missing EQ-5D score
*This time-to-death category includes the records of the patients whose death dates were observed or censored ≥ 360 days after the report of EQ-5D scores. Other categories only include the records of patients with an observed death date.

Table 75: EQ-5D health utility scores by progression status

	Pembrolizumab					Control (Paclitaxel, Docetaxel and Vinflunine)					Pembrolizumab and Control Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	234	907	0.757	0.009	(0.740, 0.775)	228	714	0.698	0.01	(0.679, 0.718)	462	1621	0.731	0.007	(0.718, 0.744)
Progressive	178	488	0.680	0.015	(0.650, 0.709)	142	254	0.565	0.023	(0.520, 0.611)	320	742	0.641	0.013	(0.615, 0.666)

† n=Number of patients with non-missing EQ-5D score
‡ n=Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included

5.4.2 Mapping

Not applicable as HRQoL was derived from the KEYNOTE-045 EQ-5D data.

5.4.3 Systematic searches for relevant HRQoL data

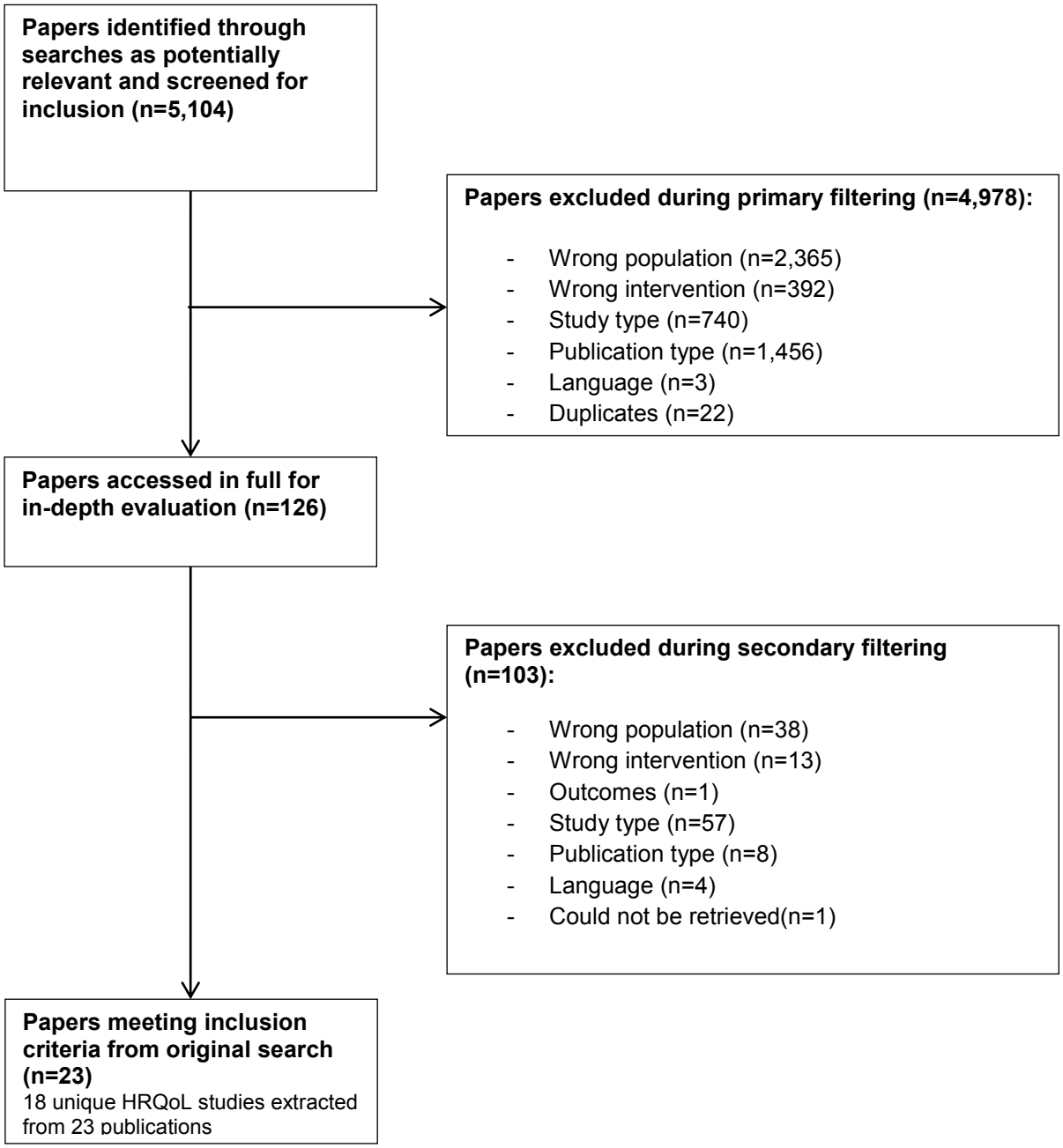
The relevant HRQoL data from the published literature were identified through a systematic literature search carried out during the period of 6th and 7th August 2015 and updated in December 2016, for patients with advanced or metastatic urothelial cancer, regardless of whether they were previously treated with platinum-containing chemotherapy (see Appendix 17 for more details). The objective was to identify HRQoL (in terms of utilities) associated with advanced or metastatic urothelial cancer, in line with the research question posed in section 5.1.

A comprehensive literature search was carried out using the databases presented in section 5.1.1. The electronic database searches for utility studies were not limited by any specific publication year or date. Conference searches were also performed to identify potentially relevant conference abstracts or posters of interest (see section 5.1.1). These searches were restricted to abstracts published during the last 2 years

Appendix 17 provides details of the search strategies for HRQoL and utilities along with the eligibility criteria set out in the final protocol.

Systematic database searches identified 5,104 records for economic modelling studies, cost and resource use studies and HRQoL studies. Twenty three publications were identified as HRQoL studies from a total of 126 potentially eligible publications recognised in these SLRs. Six studies were linked to the other included studies and HRQoL data from 18 studies were extracted.
The search was updated in December 2016 to identify new studies published since the initial searches were conducted. Six additional studies were identified from this search.

Figure 42: PRISMA Diagram: HRQoL and Utility studies*



Key: HRQoL, Health-related quality of life.

*From the updated search conducted in December 2016, 382 additional hits were identified, six were included and are not accounted for in the above PRISMA diagram.

5.4.4 Provide details of the studies in which HRQoL was measured

Please see Appendix 18 for the details of the identified studies.

5.4.5 Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

The majority of the studies and the HTA submission identified do not use EQ-5D data, using mainly EORTC QLQ-C30 questionnaire.[51, 93-96] The results presented focus either on the impact on HRQoL by treatment group[97-100] or on specific symptoms of the disease such as pain and fatigue.[94, 101-103]

None of the studies or the HTA submission identified from the SLR estimated utilities as a function of time until death. Whereas, the pre- and post- progression utility values from the KEYNOTE-045 trial are in line with the utilities observed in the TA272. In both the analysis from KEYNOTE-045 and the utilities presented in TA272, the pre-progression EQ-5D values are higher than post-progression values, suggesting a worsening of HRQoL after disease progression.[51] However the utility values presented in NICE TA272 were mapped from EORTC QLQ-C30 questionnaire using a regression model based on US cancer patients.[51] The approach was not considered appropriate by the ERG and there is considerable uncertainty around the estimates.

5.4.6 Describe how adverse reactions affect HRQoL

The impact of AEs on HRQoL was assessed by examining the EQ-5D health utilities of patients who experienced AEs (grade 3-5) compared to those who did not experience AEs in the progression-free health state.

For this assessment, the time points associated with grade 3-5 AEs for each patient were identified. EQ-5D scores collected at these time points were then used to estimate the utility of the progression-free state with grade 3-5 AEs. EQ-5D scores collected at other time points were used to estimate the utility associated with the progression-free health state in the absence of grade 3-5 AEs. The utility values for patients experiencing grade 3-5 AEs were significantly lower (0.635; 95% CI: 0.600, 0.670) than those of patients not experiencing grade 3-5 AEs (0.752; 95% CI: 0.738, 0.766; see Table 76).

It has been assumed for the purposes of the modelling that any impact of AEs on HRQoL will be expressed in terms of a disutility of AEs applied based on AE incidence rates and the corresponding mean duration (i.e. 13.9 days of duration across grade 3+ AEs, as estimated from KEYNOTE-045).

Table 76: Utility values for individuals with and without Grade 3+ AEs in the KN045 clinical trial

	Pembrolizumab					Control (Paclitaxel, Docetaxel and Vinflunine)					Pembrolizumab and Control Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression -Free with Grade3+ AE	51	110	0.586	0.032	(0.523, 0.649)	89	176	0.666	0.021	(0.625, 0.707)	140	286	0.635	0.018	(0.600, 0.670)
Progression -Free w/o Grade3+ AE	209	797	0.781	0.009	(0.764, 0.798)	187	538	0.709	0.011	(0.686, 0.731)	396	1335	0.752	0.007	(0.738, 0.766)

5.4.7 Definition of the health states in terms of HRQoL in the cost-effectiveness analysis.

EQ-5D analyses based on KEYNOTE-045 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-progression health state. However, due to the limited records at the post-progression health state, progression related utilities do not show a large difference between pre- and post-progression utilities, indicating that progression status is unlikely to be sufficiently reflective of changes in quality of life. When time-to-death was considered, HRQoL decreased over time as patients progressed closer to death. To capture HRQoL more appropriately, the time-to-death utility values were further divided into five categories (i.e. 360 or more days to death, 180 to 360 days to death, 90 to 180 days to death, 90 to 30 days to death or under 30 days to death).

5.4.8 Clarification on whether HRQoL is assumed to be constant over time in the cost-effectiveness analysis

A constant value for HRQoL is applied in each cycle taking. An age-related utility decrement of 0.0045 is applied per year, from the age of 65 until 75, to reflect the natural decrease in utility associated with increasing age.[104]

The annual age-related utility decrement applied in the model is based on the age and gender-specific UK general population utility norms presented by Kind et al.[104], which reported average utility values for males and females under 25, 25-34, 35-44, 45-54, 55-64, 65-74 and 75+ respectively. It was assumed that the utilities for 75+ reported by Kind et al. (0.75 and 0.71 for males and females, respectively) apply to all patients who are 75 years and above. Therefore, no further age-related decrement in utility was applied in the model for patients aged over 75 years. This means that patients aged 75 and above had the same age-related utility decrement in the cost-effectiveness model.

5.4.9 Description of whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states

Not applicable.

5.4.10 Description of how and why health state utility values used in the cost-effectiveness analysis have been adjusted, including the methodologies used

The health state utility values have not been amended; however, as explained above, a yearly utility decrement applies as patients get older.

5.4.11 Identification of any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

No health effects on patients were excluded from the cost effectiveness analysis. HRQoL in the base case is based upon time to death as the utility values derived from the KEYNOTE-045 trial were more sensitive than the pre-and post- progression utility values. Progression-based utilities are presented in scenario analysis.

5.4.12 Summary of utility values chosen for the cost-effectiveness analysis

The utility values chosen for the cost-effectiveness model are presented in Table 77.

Table 77: Summary of utility values for cost-effectiveness analysis

	Utilities**		Reference in submission (section and page number)	Justification
	Mean	95% CI		
By time-to-death (days) - 5 categories				
≥360*	0.761	(0.650, 0.873)	Section 5.4.1 Table 74 Page 193	Utility values from KEYNOTE-045[16]
[180, 360)	0.693	(0.668, 0.718)		
[90, 180)	0.59	(0.557, 0.622)		
[30, 90)	0.451	(0.403, 0.498)		
<30	0.325	(0.214, 0.436)		
Progression based utilities				
Progression-Free	0.731	(0.718, 0.744)	Section 5.4.1 Table 74 Page 193	Alternative utility values from KEYNOTE-045[16]
Progressed	0.641	(0.615, 0.666)		

** This group also includes patients whose death dates were censored and report EQ-5D ≥ 360 days.*
*** Utilities from KEYNOTE-045 are pooled utilities*

5.4.13 Details of clinical expert assessment of the applicability of the health state utility values available

The applicability of the selected health state utility values was not assessed by clinical experts as these values were consistent with the NICE reference case.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Parameters used in the cost effectiveness analysis

A summary of the variables used in the cost estimation is presented in Appendix 19.

5.5.2 Resource identification, measurement and valuation studies

The type of costs considered in the economic model included the drug and administration costs related to the intervention and comparator, including the costs related to subsequent therapies (see section 5.5.5), the monitoring and management of the disease (see section 5.5.6), the management of adverse events (AEs) (see section 5.5.7), and the costs related to terminal care (see section 5.5.6). In addition, for subgroup analysis and patients with PD-L1 expression, the cost of testing for PD-L1 expression was included (see section 5.5.5).

A comprehensive literature search was conducted on the 6th and 7th of August 2015 to identify costs and resource use in the treatment and on-going management of metastatic or locally advanced/unresectable urothelial cancer patients. The population criteria considered in the systematic review included patients with locally advanced or metastatic urothelial cancer. The search was limited to only include studies published since 2005, as older cost data may not be considered representative of the current economic environment.

The literature search was updated in December 2016 to identify costs and resource use in the treatment and on-going management of metastatic or locally advanced/unresectable urothelial cancer; this included a manual search of an additional electronic database (NICE Website). While the scope of the searches was broad only studies from UK NHS perspective where finally included in the SLR results.

The searches conducted for resource use data and the selection criteria followed for the identification and inclusion of relevant studies are provided in Appendix 17.

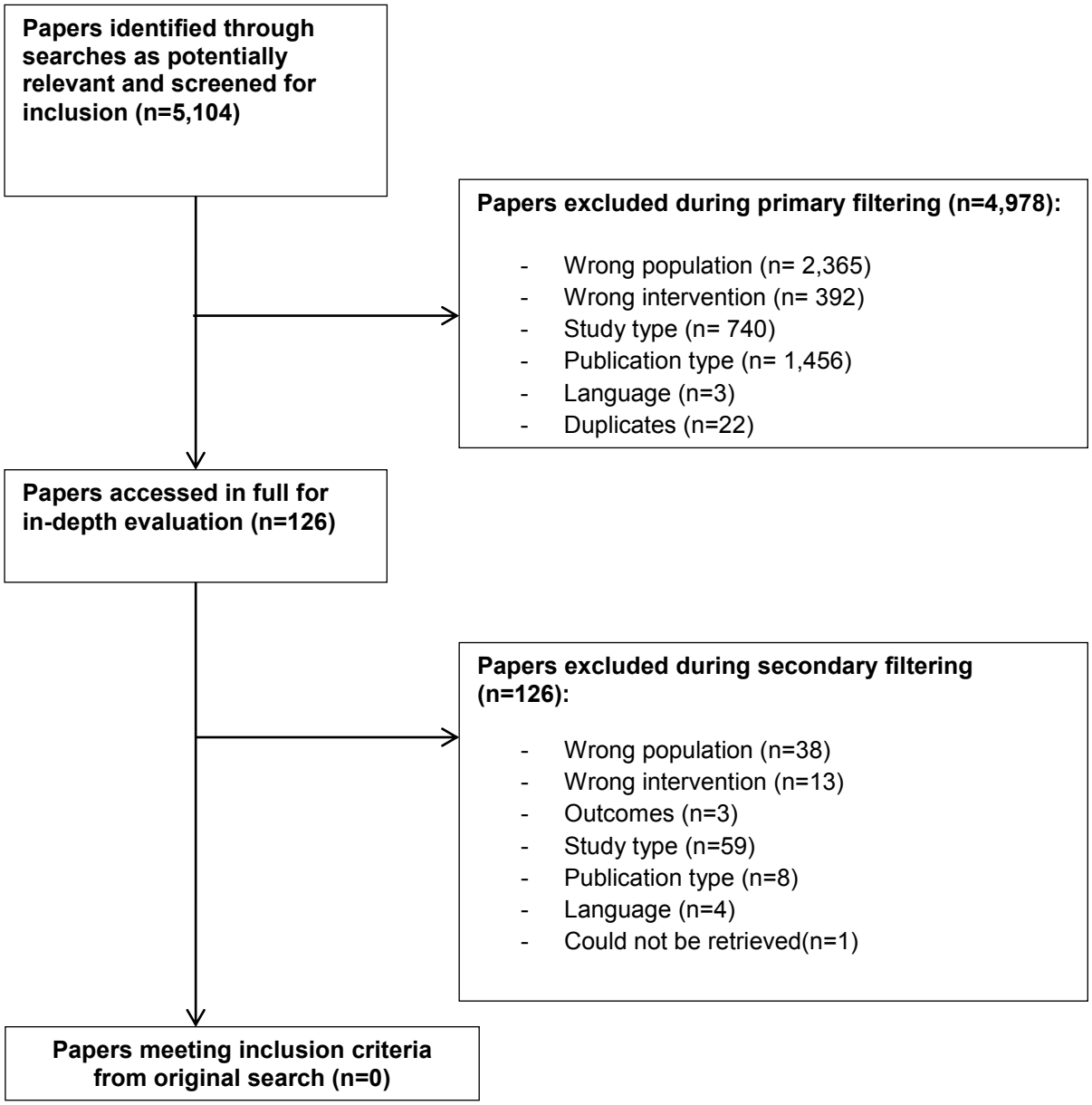
The systematic database searches identified 5,104 records for economic modelling studies, cost and resource use studies and HRQoL studies. Of the 126 publications identified, none were included for data extraction.

From the updated search strategy, 342 additional hits were identified and one publication was included for data extraction. The study included for extraction is an HTA submission for vinflunine for patients with advanced or metastatic transitional cell cancer of the urothelial tract, submitted to NICE in 2010.[51] It has provided resource use data for the treatment and

management of patients with transitional cell carcinoma of the urothelial tract which has been used within our cost-effectiveness model (please see Appendix 20).

The final resource use and costs inputs applied in the model are presented in sections 5.5.4 to 5.5.7 with details and rationale for the sources used.

Figure 43: PRISMA diagram for included cost and resource use studies*



Key: HTAD, Health Technology Assessment Database; NHS EED, NHS Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

* From the updated search conducted in December 2016, 342 additional hits were identified; 1 was included and is not accounted for in the above PRISMA diagram

5.5.3 Use of NHS reference costs or payment-by-results (PbR) tariffs

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab. Details about the cost estimation of treatment with pembrolizumab in terms of acquisition and administration are reported below. As previously agreed with NHS England (personal communication, 9th December 2014) for the single technology assessment (STA) submission of pembrolizumab for advanced melanoma,[105] the administration cost of pembrolizumab can be reflected through NHS Reference Cost code SB12Z[106], since this corresponds to the administration of a simple therapy (i.e. involving the administration of only one agent without IV anti-emetics), with the infusion lasting less than one hour.

5.5.4 Input from clinical experts

The above costing approach was previously validated with clinical experts in previous HTA submissions of pembrolizumab.[79, 84]

5.5.5 Intervention and comparators' costs and resource use

Drug costs

The drug acquisition costs per treatment are presented below, with the unit costs for comparator regimens being taken from the latest electronic market information tool (eMit)[107] published on December 2016, which provides information about prices for generic drugs based on the average price paid by the NHS over the last four months.

Pembrolizumab

As per the anticipated licence, the model uses a 200mg fixed dose of pembrolizumab, administered as a 30-minute IV infusion every three weeks (Q3W) (see the Summary of Product Characteristics [SmPC] in Appendix 1). The list price of a 100mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100mg vials using the list price. [redacted]

Comparators

Drug acquisition costs for individual drugs included in the UK SOC arm were taken from eMit[107] When multiple vial/package sizes were available, the least expensive price per mg was applied as a conservative assumption. The costs of concomitant medications for patients

receiving docetaxel or paclitaxel were not taken into consideration as the costs are trivial and unlikely to affect the results.

Dosing for the individual comparator regimens was based on the KEYNOTE-045 protocol[81], as those regimens are not currently licensed for the indication under consideration. Drug costs per administration were calculated based on the body surface area (BSA), which was estimated to be 1.90m^2 based on a weighted average BSA from the male and female patients recruited at European sites in KEYNOTE-045.[16] As a conservative assumption, full vial sharing (i.e. no wastage) is assumed for the administration of all comparator drugs.

Table 78: Dosing, frequency of infusion and unit costs per administration for comparator drugs

Drug	Dosing per administration	Frequency of administration	Total dose	Cost per mg	Cost per administration (assuming no wastage)	Reference for dosing	Reference for drug costs
Docetaxel	75mg/m^2	Q3W	142.5mg	£0.13	£18.09	KEYNOTE-045	eMit[107]
Paclitaxel	175mg/m^2	Q3W	332.5mg	£0.07	£23.81	KEYNOTE-045	eMit[107]

* Q3W, every three weeks

Number of administrations required, unit costs and total drug costs per treatment per cycle

As per the anticipated licence, patients treated with pembrolizumab are expected to be treated until disease progression is confirmed. However, in line with the KEYNOTE-045 protocol, a stopping rule has been implemented whereby patients do not receive therapy beyond 24 months.[81] To estimate the duration of treatment in the pembrolizumab and comparator arms, time on treatment (ToT) data from KEYNOTE-045 was used, to reflect both early discontinuation caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some patients may receive until confirmation of progression.

Separate parametric curves were fitted to the patient level treatment duration data from KEYNOTE-045 to represent ToT in the economic model (see Figure 44 and Figure 45). AIC/BIC based tests combined with visual inspection were used to select the best-fitted parametric distributions. The function with the lowest AIC/BIC is Weibull for pembrolizumab, and GenGamma for UK SOC (see Table 79). The modelled ToT curves based on the approach above are presented in Figure 46 below

Table 79: Goodness of fit measures for ToT

	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	1923.8	1927.4	1133.1	1136.3
Weibull	**1870.5**	**1877.7**	1126.8	1133.1
Gompertz	1890.9	1898.1	1134.1	1140.4
Log-logistic	1885	1892.2	1167.2	1173.5
Log-normal	1899.8	1906.9	1177.1	1183.3
GenGamma	1872.1	1882.8	**1122.2**	**1131.6**

Figure 44. Standard parametric curves for ToT of pembrolizumab

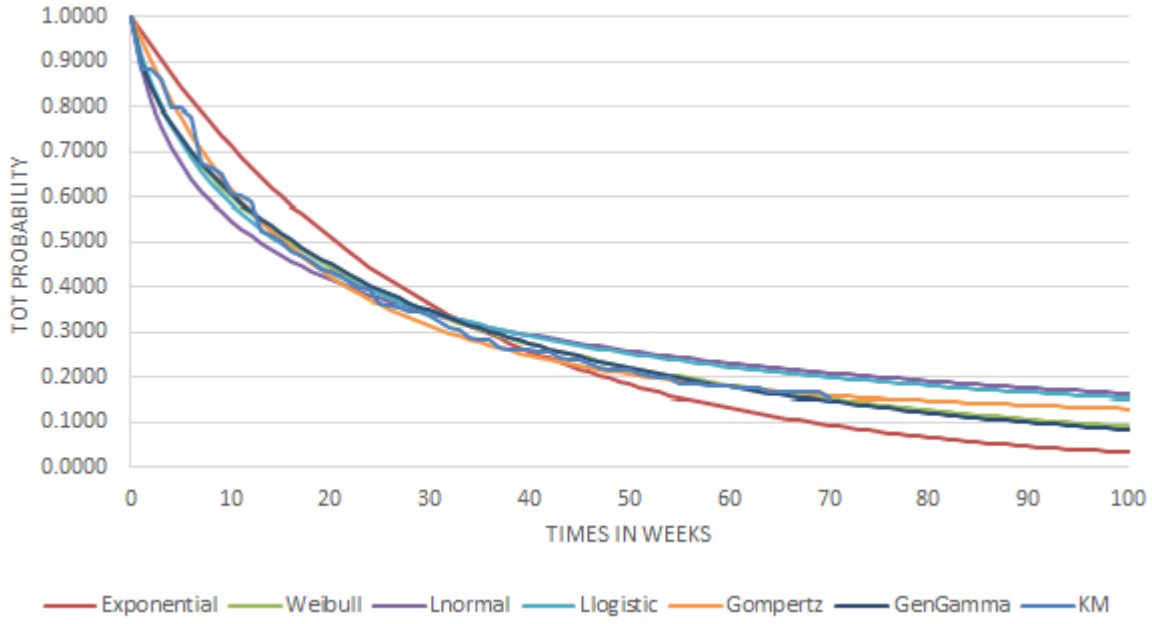


Figure 45. Standard parametric curves for ToT of UK SOC

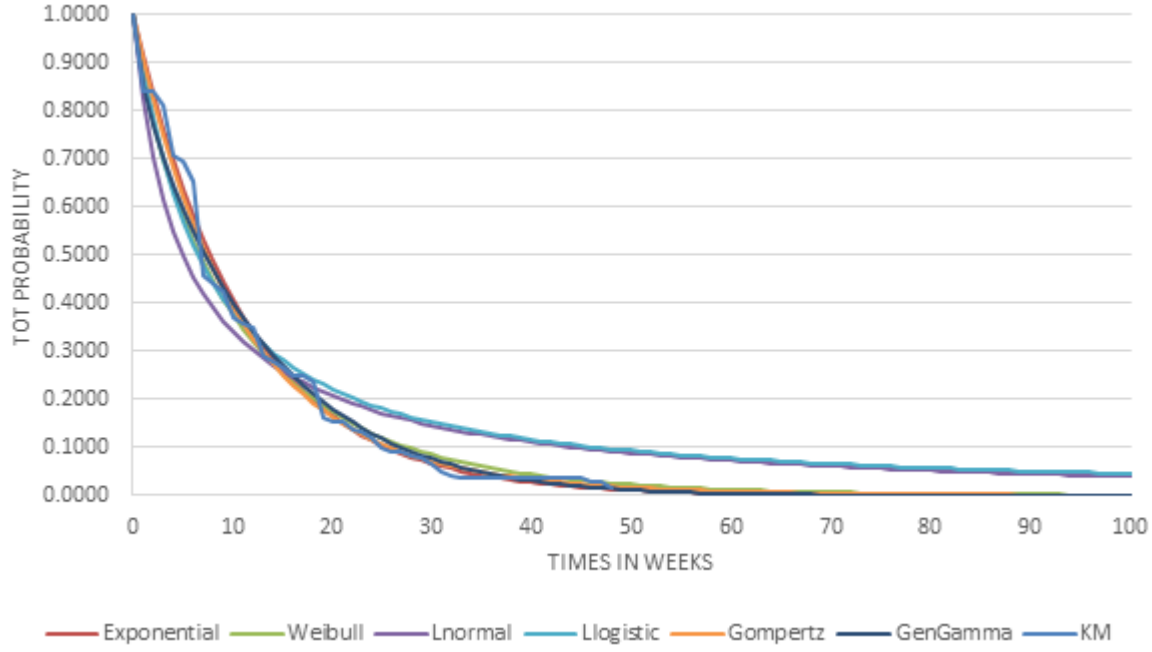
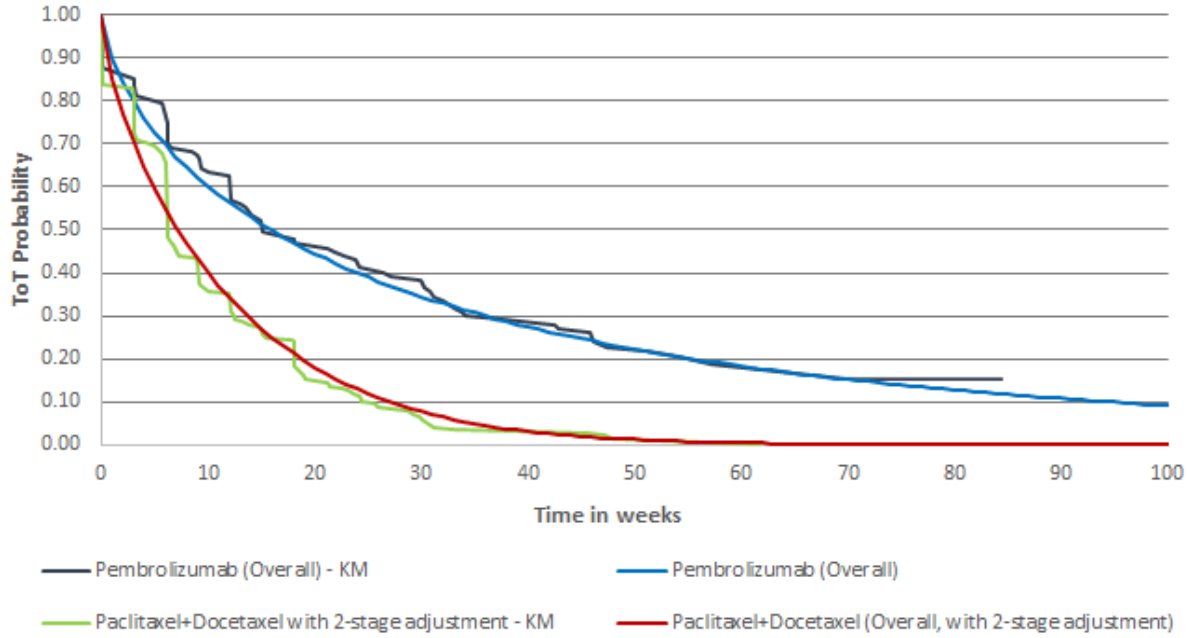


Figure 46. Standard parametric curves for TOT of pembrolizumab and UK SOC



In the base case, a maximum treatment duration of 35 cycles (i.e., 24 months) was assumed for pembrolizumab, in line with the KEYNOTE-045 protocol.[81] A maximum treatment duration of 18 weeks (i.e. 6 cycles for the UK SOC administrated every 3 weeks) was used for the comparator therapies to reflect the clinical practice in England. The average number of cycles received per patient in KEYNOTE-045 was 5.00 cycles for paclitaxel and 3.90 cycles for docetaxel.

For patients on treatment, adjustments were made based on the actual proportion of a full treatment dose that, on average, patients receive within each 3-week treatment cycle in KEYNOTE-045. For this, data regarding dose intensity occurring within KEYNOTE-045 was analysed, showing that on average the dose intensity was 100.42% for patients on pembrolizumab, 102.75% for patients on docetaxel and 100.02% for patients on paclitaxel. These estimates are not in line with those observed in previous KEYNOTE trials or considered to be realistic in clinical practice where dose intensity will always be below 100% related to delayed doses and 'holidays' due to AEs. Therefore a conservative 100% dose intensity has

been applied in the cost-effectiveness model, with no further adjustment on clinical outcomes in the model.

Administration costs

Pembrolizumab

Given the time required for the administration of pembrolizumab is 30 minutes, the Healthcare Resource Groups (HRG) code for SB12Z*: Deliver simple parenteral chemotherapy at first attendance* based on the latest NHS reference costs 2015-2016 was used to reflect administration costs for pembrolizumab. The assumption had been previously agreed with NHS England (personal communication, 9th December 2014) for previous NICE submissions of pembrolizumab.

Docetaxel

The time required per administration is 60 minutes every 3 weeks. As stated in the Referenced Cost Guidance 2014-2015 and referenced in the ERG report for TA389,[108, 109] for single chemotherapy agents considered to require up to 60 minutes infusion time, the cost of SB12Z: *Deliver simple parenteral chemotherapy at first attendance* is appropriate therefore this code has been used to reflect administration of docetaxel.[106].

Paclitaxel

The time required per administration of paclitaxel is 3 hours every 3 weeks. As stated in the Referenced Cost Guidance 2014-2015 and referenced in the ERG report for TA389,[108, 109], for single chemotherapy agents considered to require more than 120 minutes infusion time the cost of SB14Z: *Deliver complex chemotherapy, including prolonged infusion treatment at first attendance* at is appropriate, therefore this code has been used to reflect administration of paclitaxel.[106]

Table 80. Administration costs of pembrolizumab, docetaxel and paclitaxel[106]

	Type of administration required	NHS code	Cost
Pembrolizumab	Simple chemotherapy	SB12Z	£253.32
Docetaxel	Simple chemotherapy	SB12Z	£253.32
Paclitaxel	Complex chemotherapy	SB14Z	£406.63

Costs associated with subsequent therapies received by patients after treatment discontinuation

The average cost of subsequent treatment is calculated by weighting the proportions of patients receiving each subsequent treatment and the unit cost of each subsequent treatment (See Section 5.3.6. and Appendix 21), assuming an average duration of 2 cycles (based on NICE TA272).[51] This weighted cost was applied during 2 cycles to patients who moved to the post-progression health state.

5.5.6 Health-state unit costs and resource use

The published data exploring in detail the resource use associated with patients with previously treated urothelial cancer is limited. Consequently the main source of resource utilisation per health state used in this submission is the vinflunine NICE submission (TA272) while the resource use associated with terminal care was based on the study by Brown et al (2013).[51, 110]

Monitoring and disease management costs

There are three health states included in the model - Progression free (PFS), post-progression and death.

Patients incur disease management costs whilst they remain on treatment, and potentially longer. Table 81 shows the resource use for monitoring and disease management in the progression free health state and the post-progression health state.

Table 82 presents the unit costs for individual resource use items, which were updated based on the latest NHS reference costs 2015-2016 and the Personal and Personal and Social Services Research Unit (PSSRU) 2016 report.[106, 111] The estimated monitoring and disease management costs per month were £154.61 and £136.07 respectively for the pre-progression and post-progression periods.

Table 81: Resource use frequency for progression-free and progressed health states[51]

Resource	Pre-Progression (per month)	Post-Progression (per month)	Reference
GP home consultation	1	1	TA 272
Community nurse specialist visit	4	4	
Health home visitor	1	1	

Dietician	1	1	
Consultant led oncologist follow-up visit	1	0	
Non consultant led oncologist follow-up visit	0	1	

* GP, general practitioner, TA, Technology Appraisal.

Table 82. Unit costs of disease monitoring and supportive care[106, 111]

Resource	Cost	Source
GP home visits	£91.26	Per patient contact lasting 11.4 minutes per home visit + 12-minutes travel time per visit (PSSRU 2015), £3.90 per minute of patient contact (PSSRU 2016).
Community nurse specialist	£76.00	Cost per hour of patient-related work (PSSRU 2015), Inflated to 2016 using the HCHS index 2015/2016.
Health home visitor	£77.01	Mean average cost for face-to-face contact for a Health Visitor (PSSRU 2015) Inflated to 2016 using the HCHS index 2015/2016.
Dietician	£33.00	Cost per working hour, band 5 (PSSRU 2015)
Consultant led oncologist	£167.08	NHS Reference Costs 2015-16, outpatient attendances service code 370
Non-consultant oncologist follow up	£86.44	NHS Reference Costs 2015-16, outpatient attendances service code 370

* GP, general practitioner; PSSRU, Personal Social Services Research Unit; HCHS, Hospital and Community Health Services index.

Cost of terminal care

A one-off cost is applied to those patients at death to reflect the cost of terminal care. The data for the cost and resource use of urothelial cancer patients in terminal care is limited; the cost of terminal care is based on Brown et al which is not specific to any particular cancer type. Clinical advice suggested that due to their propensity to bleed, patients with urothelial cancer receive radiotherapy at end of life; therefore, this cost has also been included. This is also in line with the palliative care in TA272.[51] The resource consumption reflects treatment received in various care settings and is based on values taken from the ONS and also referenced in TA374.[112] Resource use is based on values from TA277 and costs have been updated to reflect 2016 costs.[51, 106]

The estimated one-off terminal cost was £7,252.82 and is assumed to be the same for all treatment arms (see Table 83).

Table 83. Unit costs of terminal care patients

Resource	Number of consumption	Unit cost	% of patients in each setting	Total cost	Reference (resource use)	Reference (unit cost)
Community nurse specialist visit (per hour)	28 hours	£76	27%	£1,447.25	Appendix 1 of NICE guideline CG81,[113], Marie curie report[114]	Per patient contact lasting 11.4 minutes per home visit + 12-minutes travel time per visit (PSSRU 2015), £3.30 per minute of patient contact (PSSRU 2016).
GP Home visit	7.00 visits	£91.26	27%		Marie Curie Report[114]	Cost per hour of patient-related work (PSSRU 2015), Inflated to 2016 using the HCHS index 2015/2016.
Macmillan nurse	50.00 hours	£50.69	27%		Marie Curie report[114]	Macmillan nurse: 66.7% of community nurse cost (assumption as per Brown et al).
Drugs and equipment	As required	-	27%		Marie Curie report[114]	-
Terminal care in hospital	1 episode (9.66 days)	£3,345	56%	£1,866.51	Marie Curie report[114]	National Schedule of Reference Costs Year: 2015-16 - All NHS trusts and NHS foundation trusts. Non-elective long-stay. Ureteric or Bladder Disorders, without Interventions, with CC Score 5+. LB19E (average length of stay)
Terminal care in hospice	1 episode	£4,181.25	17%	£706.53	Marie Curie report[114] Assumption 25% increase on hospital IP care	National Schedule of Reference Costs Year: 2015-16 - All NHS trusts and NHS foundation trusts. Non-elective long-stay. Ureteric or Bladder Disorders, without Interventions, with CC Score 5+. LB19E (average length of stay) 25% increase on hospital inpatient care. Assumption as per Brown et al.
Radiotherapy	5.88	£550.20	100%	£3232.43	NICE TA272[51]	NHS Reference costs Year: 2015-16 - SC46Z and SC22Z - Outpatient
Total cost	**£7252.82**					

* GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HCHS, Hospital and Community Health Service; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups

5.5.7 Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section 5.3.5. The approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in section 5.4.6.

The resource use related to the management of AEs were mainly derived from the Brown et al study.[110] All unit costs were taken from the latest NHS Reference Costs 2015/16, and when the codes where not similar, the unit costs were inflated to 2015/16 prices using the hospital and community health services (HCHS) index published by PSSRU for 2016.[106, 111] Table 84 below presents only the unit costs per AE that costing was applied in the cost-effectiveness model.

Table 84: Unit cost per AE used in the de novo model[106, 111]

Adverse event	Cost	Assumption
Anaemia	£1,315.94	NHS reference costs 2015-2016: SA01K,J,H and G, Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia. Weighted cost of non-elective long stay, short stay and day case
Febrile neutropenia	£2,641.80	The NICE Decision Support Unit report on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2015/16 prices using the HCHS index.
Neutropenia	£70.80	It is assumed that 10% of patients require hospital treatment, each requiring two episodes during chemotherapy. Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions.
Diarrhoea	£919.84	It is assumed that a typical patient will have two hospital admissions, corresponding to NHS Reference costs 2015-16. FZ91M Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 as a non-elective short-stay episode, each costing £459.52.
Fatigue	£2,499.99	It is assumed that a typical patient will have one hospital admission during chemotherapy, corresponding to WH52A Follow-Up Examination for Malignant Neoplasm, with Interventions as a non-elective long-stay episode of 8–9 days.
Neutrophil count decreased	£70.80	Assumed to be the same as neutropenia.
White blood cell count decreased	£70.80	Assumed to be the same as neutropenia.
Hypophosphataemia	£1,212.89	NHS reference costs 2015-2016: KC05G,H,J,K,L,M,N Fluid or Electrolyte Disorders. Weighted cost of non-elective long stay, short stay and day case
Pneumonia	£1,751.08	NHS reference costs 2015-2016: DZ11K-V Lobar, Atypical or Viral Pneumonia. Weighted cost of non-elective long stay, short stay and day case

*NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HCHS, Hospital and Community Health Service; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups

5.5.8 Miscellaneous unit costs and resource use

There are no additional costs included in the model apart from those outlined in the previous sections.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Tabulated variables included in the cost-effectiveness analysis

A table summarising the full list of variables applied in the economic model is presented in Appendix 19.

Additionally, Table 85 below presents a summary of the clinical inputs and data sources used in the economic model.

Table 85. Summary of clinical inputs and data sources used in the economic model

Clinical evidence and source	Brief description	Use in the model
KEYNOTE-045[16]	Multicentre open-label, randomised, phase 3 trial of pembrolizumab 200 mg Q3W (n=272) versus control (n=270) in adults with previously treated advanced or metastatic urothelial cancer In the cost-effectiveness section the analysis was based on the sub-population of subjects pre-assigned by investigator to docetaxel or paclitaxel pre-randomisation (n=182) and pembrolizumab (n=188)	• Used to derive the baseline patient characteristics (including average age, the proportion of males and weighted average BSA). • Patient level data were used to fit OS, PFS and ToT parametric curves for both pembrolizumab and UK SOC arms. • Patient level data from the UK SOC arm was used to perform treatment switching adjustments for the UK SOC OS. • OS KM data were used to model OS in the first phase of the OS before parametric curves were applied. • PFS KM data were used to model PFS in the first 21 weeks before parametric curves were applied. • Patient level data were used to calculate the actual proportion of a full treatment dose that, on average, patients receive within each 3-week treatment cycle. • EQ-5D data collected in the trial were used to derive health state utility values (time-to-death utility values) used in the model. • Used to derive the incidence of grade 3+ AEs and grade 2 diarrhoea and febrile neutropaenia (all grades) for both pembrolizumab and UK SOC. • Used to derive the proportion of patients receiving subsequent treatments for both pembrolizumab and UK SOC.
General population mortality[115]	Latest national life table in England & Wales providing age- and gender-specific general population mortality.	Applied throughout the modelled time horizon as background mortality (i.e., general population mortality is applied when modelled mortality is lower than the gender- and age-matching general population mortality).

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible

The base-case cost-effectiveness analysis reflects the NICE reference case as closely as possible.

5.6.3 List of all assumptions used in the de novo economic model with justifications for each assumption

Table 86 summarises the assumptions used in the economic model.

Table 86: List of assumptions used in the economic model

Area	Assumption	Justification
Treatment pathway	Once patients progress they receive subsequent therapies as experienced by patients in KEYNOTE-045.	The use of subsequent treatments as observed in KEYNOTE-045 trial is consistent with the OS efficacy inputs used in the model, which are based on patients receiving these subsequent treatments. Patients in the UK SOC arm are assumed not to receive pembrolizumab when a treatment switching adjustment is implemented in the cost-effectiveness model, since their OS efficacy estimates are adjusted to control for the impact of crossing over to pembrolizumab. An alternative approach was used as part of sensitivity analyses to reflect more closely the costing related to SOC therapies as administered in UK clinical practice.
Time horizon	35 years	The average age of patients in the model is 65.5. A lifetime horizon is in line with NICE reference case.[83]
Efficacy	Use adjusted KM data for the first 40 weeks from KEYNOTE-045 trial to model OS for pembrolizumab and UK SOC	The 2-phase piecewise method (KM plus parametric approach) has been used in previous HTA submissions.[79, 86] For the first 40 weeks OS KM data provides robust and reliable estimate and at that point patient numbers are sufficient to implement parametric fitting based on KEYNOTE-045 data. The standard parametric curves do not provide good visual fit compared to the 2-phase piecewise method. The cumulative hazard plot also suggests that a piecewise model is preferred.

Area	Assumption	Justification
HRQoL	The quality of life of patients is appropriately captured by considering time to death utilities	Clinical opinion suggests there is a decline in HRQL in the final months of life of patients which may not appropriately be captured solely through the use of progression-based health state. This was supported by the feedback provided by the ERG of previous NICE oncology submissions, which supported the use of a disutility associated to the terminal stage. Given the limitations of the progression-based approach to reflect appropriately utilities post-progression, a time to death approach was considered in the base case. In sensitivity analyses, the impact of considering an alternative approach (i.e. progression-based only) was considered. However, it was deemed to be less relevant due to limitations in the amount of data collected post-progression
Safety	The incidence of AEs from KEYNOTE-045 trial was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-045 trial (i.e. grade 3-5 AEs (incidence≥5% in one or more treatment groups, considering any grade)). The same method and criteria were applied in a recent NICE oncology appraisal of pembrolizumab. (79)

5.7 Base-case results

5.7.1 Base-case cost effectiveness analysis results

The results of the economic model are presented in Table 87 below. In the base case analysis, the estimated mean overall survival was 2.71 years with pembrolizumab and 1.59 years with UK SOC. At the end of the 35-year time horizon there were 0.2% patients still alive in the pembrolizumab cohort and 0.1% in the UK SOC cohort. Patients treated with pembrolizumab accrued 1.95 QALYs compared to 1.09 among patients in the UK SOC cohort.

5.7.2 Base-case incremental cost effectiveness analysis results

Table 87 below presents the base case incremental cost-effectiveness results, incorporating the PAS. The results show pembrolizumab to be cost-effective compared to UK SOC when considering a willingness to pay threshold of £50,000 per QALY. The corresponding incremental-cost-effectiveness ratio (ICER) when pembrolizumab is compared to UK SOC was £45,861. This ICER should be considered in the context of pembrolizumab being an end of life technology that presents an innovative nature (see Section 2.5 and Section 4.13).

Table 87: Base-case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£20,820	1.59	1.09	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,233	0.86	£45,861
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

5.7.3 Clinical outcomes from the model

In Table 88 the outcomes of the pembrolizumab and UK SOC arms of the KEYNOTE-045 trial, have been compared to the outcomes from the model. The model estimates similar percentages of patients in pre-progression and surviving at different points in time to those reported in the KEYNOTE-045 trial (see Table 88), suggesting that, for the trial period, the model is able to replicate the results of KEYNOTE-045.

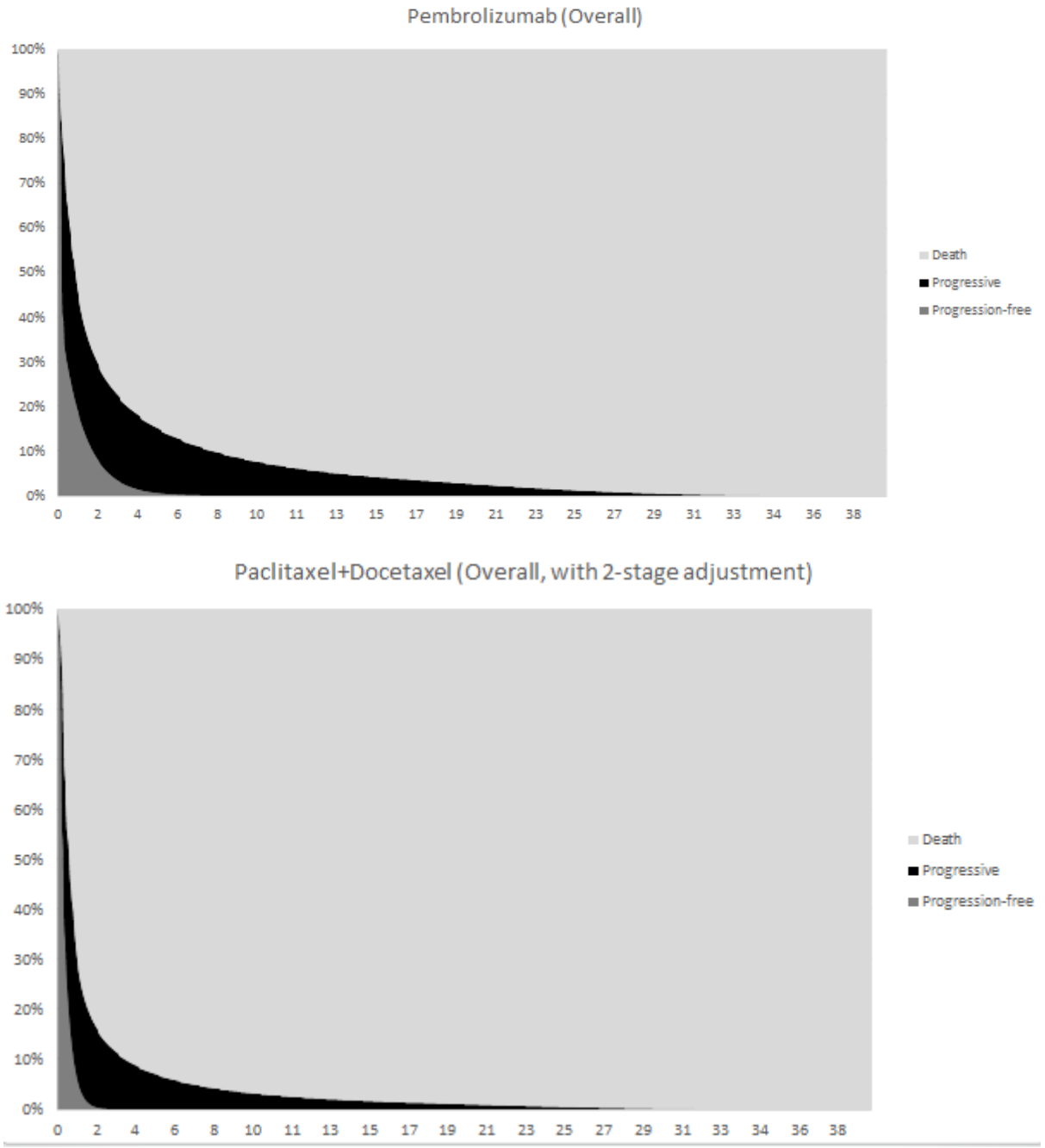
Table 88: Comparison of model and trial outcomes

	Pembrolizumab		UK SOC	
Outcome	**Base case**	**KEYNOTE-045**	**Base case**	**KEYNOTE-045**
Median PFS (months)	2.3	2.1	3.4	3.2
6-month PFS	28.6%	28.8%	22.8%	22.7%
Median OS (months)	10.3	10.3	7.1	6.9
6-month OS	64.1%	63.9%	54.8%	54.5%
1-year OS	45.5%	43.9%	29.6%	30.2%
2-year OS	30.0%	-	16.4%	-
5-year OS	16.7%	-	7.8%	-
10-year OS	9.9%	-	4.2%	-

5.7.4 Markov traces

Figure 47 below illustrates how patients move through the model states over time when treated with pembrolizumab or UK SOC, respectively. The diagrams show that patients spend longer in the pre-progression health state on pembrolizumab compared the UK SOC and that patients also survive for longer.

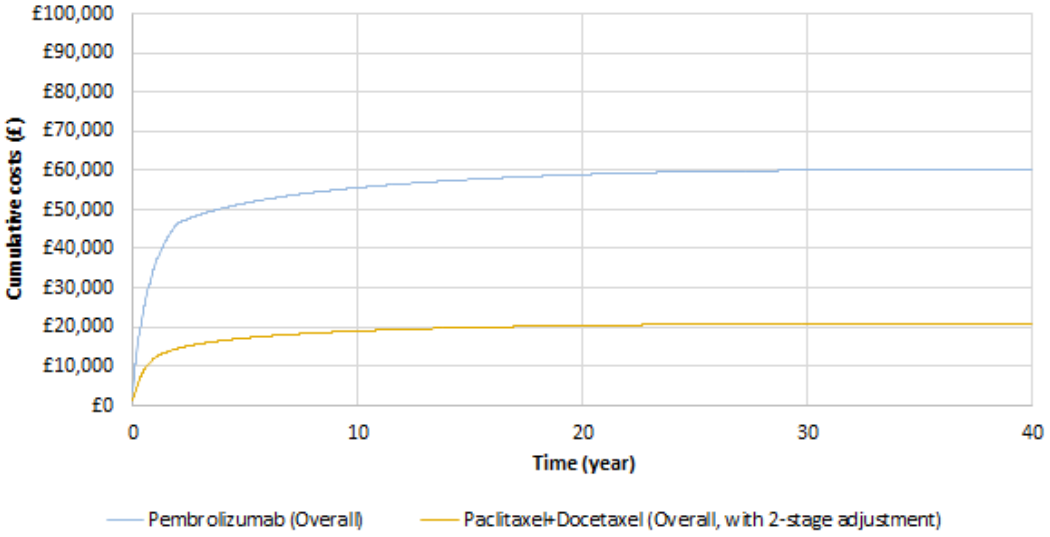
Figure 47: Markov trace for pembrolizumab and UK SOC

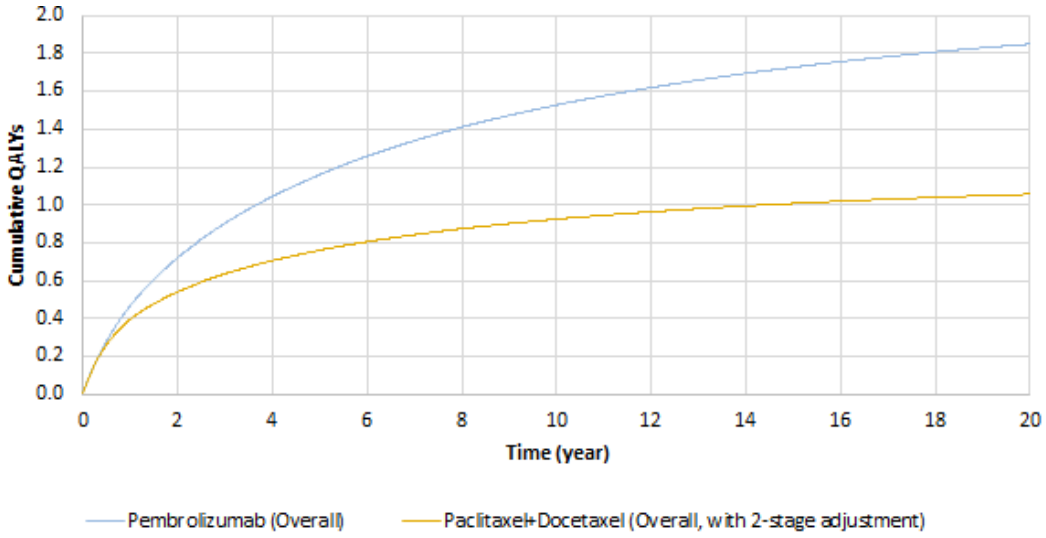


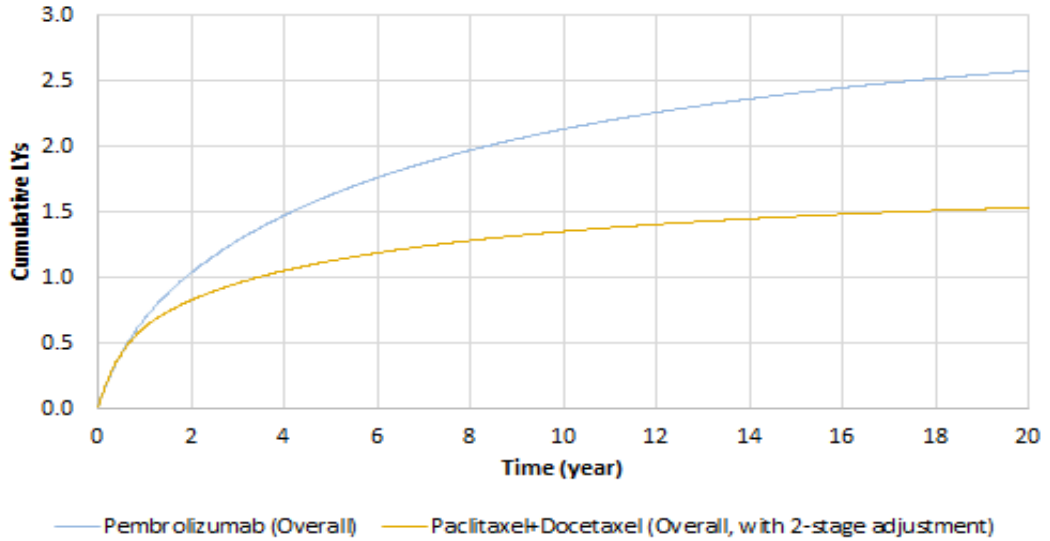
5.7.5 Accrual of costs, QALYs and LYs over time

Figure 48 shows how the costs, QALYs and life years accumulate over time, respectively. In the base case, QALYs are accrued over time according to the time to death utilities approach, as previously reported (see sections 5.2.2 and 5.4).

Figure 48: Cumulative costs, QALYs and LYs over time







5.7.6 Disaggregated results of the base case incremental cost effectiveness analysis

Table 89 shows the disaggregated life years by health state. This shows that patients on pembrolizumab spend longer in both the pre- and post-progression health states compared to patients receiving UK SOC. Table 90 shows that the majority of costs in the pembrolizumab cohort are associated with treatment.

Table 89: Disaggregated life-years by health state (discounted)

	Pre-progression	Post-progression	Total
Pembrolizumab	0.60	2.12	2.71
UK SOC	0.38	1.21	1.59

Table 90: Summary of predicted resource use by category of cost

	Pembrolizumab	UK SOC	Incremental	Absolute increment	% absolute increment
Drug acquisition cost	£30,283	£71	£30,212	£30,212	74.31%
Drug administration cost	£2,652	£1,116	£1,536	£1,536	3.78%
Disease management cost	£19,837	£11,639	£8,197	£8,197	20.16%
Post-discontinuation cost	£294	£407	-£113	£113	0.28%
Terminal care cost	£6,679	£6,967	-£287	£287	0.71%
AE cost	£309	£620	-£311	£311	0.76%
Total	**£60,053**	**£20,820**	**£39,233**	**£40,656**	**100%**

5.8 *Sensitivity analyses*

5.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 26.

Table 91: Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£20,971	1.10	-	-	-
Pembrolizumab	£60,359	1.96	£39,387	0.86	£45,826
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 91, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 49 and Figure 50.

The cost-effectiveness acceptability curve shows that there is an approximately 58% probability of pembrolizumab to be cost-effective when compared to UK SOC at the £50,000 per QALY threshold.

Figure 49: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

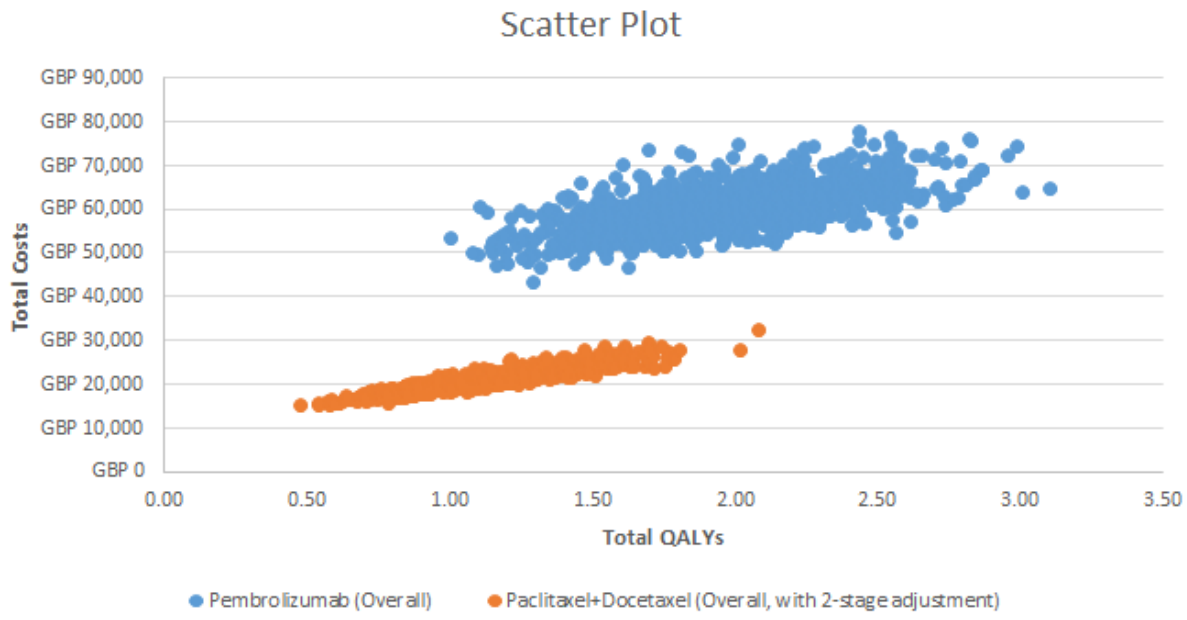
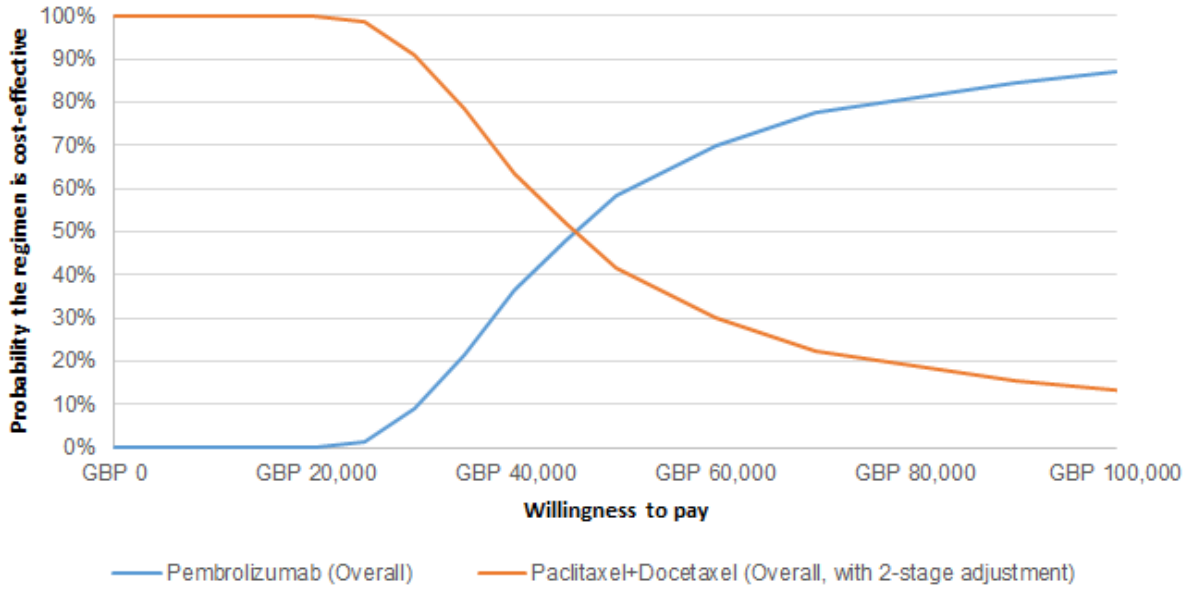


Figure 50: Cost-effectiveness acceptability curve (results discounted, with PAS)



5.8.2 Deterministic sensitivity analysis

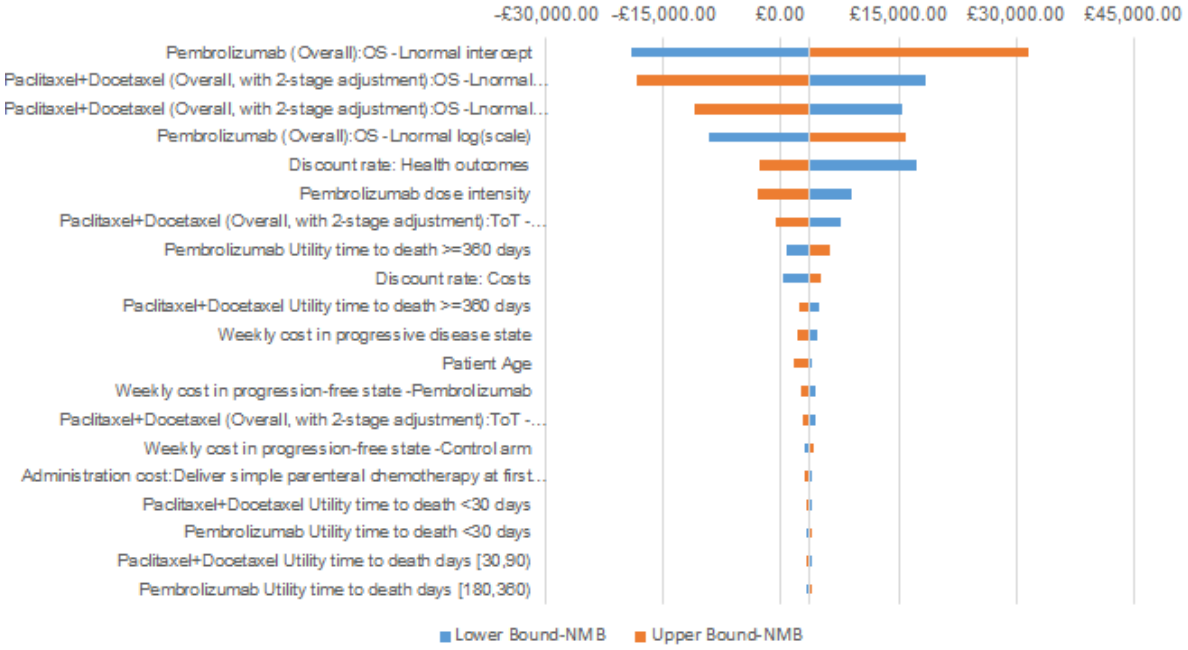
Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

- Baseline characteristics (i.e. body surface area)
- Administration costs
- Costs of the PD-L1 test
- Resource utilisation
- Proportion of patients actually receiving the expected dose
- Subsequent treatment costs and mean duration of subsequent treatment
- Health-state related costs when on active treatment, when no active treatment and for terminal care
- Health-state utility values
- Proportion of patients experiencing AEs for pembrolizumab and UK SOC
- Costs of AEs
- Duration of AEs
- Parameters of the parametric curves fitted to OS, PFS and ToT.
- Discount rate (0% and 6%)

The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab vs. UK SOC are presented in Figure 51 below. These are presented with the PAS for pembrolizumab.

The inputs that most affect the ICERs are those related to the extrapolation of the OS (i.e. the parameters of the log normal distribution used for extrapolation), followed by the discount rate for health outcomes, assumptions around time on treatment and dose intensity considered to estimate the cost of UK SOC and pembrolizumab, respectively; and the utility values for long-term survivors (see Figure 51).

Figure 51: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables (discounted results, with PAS)



5.8.3 Scenario analyses

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions:

- Impact of implementing different treatment switching adjustments (scenario 1), including:
    - No adjustment (scenario 1.a)
    - RPSFT adjustment (scenario 1.b)
    - IPCW adjustment (scenario 1.c)
- Alternative cut-off for the estimation of the exponential curve in the second phase of the piecewise approach used to extrapolate OS (scenario 2):
    - Considering a 24-week cut-off (scenario 2.a), time at which the OS KM curves for pembrolizumab and UK SOC started separating. The validity of this approach is questionable given that it does not allow full use of the OS KM data. Since a more clear change in slope occurs later at week 40, a more appropriate approach is that presented in the base case, whereby accurate KM data are used up to week 40 to maximise the use of the trial data and to reduce the period to which extrapolation is to be applied.

- Considering a 32-week cut-off (scenario 2.b). This approach was not considered to be appropriate because it did not make optimal use of the OS KM data and it did not fit the data.

- Alternative cut-off for the estimation of the parametric curve in the second phase of the piecewise approach used to extrapolate PFS (scenario 3):
  - Considering an 15-week cut-off (i.e. second radiologic assessment; scenario 3.a)
  - Considering a 27-week cut-off (i.e. fourth radiologic assessment; scenario 3.b).
- Using a different parametric function to extrapolate UK SOC PFS (since Gen gamma seemed a better fit than Exponential in terms of AIC/BIC statistics, although Exponential was used in the base case to be consistent with the parametric approach used for pembrolizumab; scenario 4).
- Assessing the impact of the half-cycle correction (scenario 5).
- Assuming the distribution of patients across different combination chemotherapies administered as part of UK SOC reflects UK market shares (scenario 6).
- Using progression-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-045 (scenario 7).
- Using utilities derived per treatment arm instead of pooled utilities from KEYNOTE-045 (scenario 8):
  - With the time to death approach (scenario 8.a)
  - With the progression-based approach (scenario 8.b)
- Removing the age-related disutilities (scenario 9).

Table 92: Results from the scenario analyses

All population										
		Pembrolizumab			UK SOC			Pembrolizumab vs UK SOC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case		£60,053	2.71	1.95	£20,820	1.59	1.09	£39,233	0.86	£45,861
Scenario 1.a	Switchover – ITT (no adjustment)	£60,053	2.71	1.95	£24,545	1.92	1.34	£35,508	0.61	£58,448
Scenario 1.b	Switchover- RPSFT adjustment	£60,053	2.71	1.95	£15,829	0.86	0.54	£44,224	1.41	£31,413
Scenario 1.c	Switchover- IPCW adjustment	£60,053	2.71	1.95	£21,896	1.74	1.21	£38,157	0.74	£51,785
Scenario 2.a	OS cut-off – 24 weeks	£60,027	2.71	1.95	£17,214	1.06	0.70	£42,813	1.25	£34,207
Scenario 2.b	OS cut-off – 32 week	£63,642	3.24	2.34	£20,524	1.54	1.06	£43,118	1.28	£33,651
Scenario 3.a	PFS cut-off – 15 weeks	£60,039	2.71	1.95	£20,821	1.59	1.09	£39,217	0.86	£45,843
Scenario 3.b	PFS cut-off – 27 weeks	£60,050	2.71	1.95	£20,822	1.59	1.09	£39,228	0.86	£45,855
Scenario 4	UK SOC PFS extrapolation based on gen. gamma	£60,341	2.71	1.95	£20,830	1.59	1.09	£39,510	0.86	£46,185
Scenario 5	No half cycle correction	£59,575	2.70	1.94	£20,725	1.58	1.09	£38,850	0.86	£45,403
Scenario 6	UK SOC as for UK market shares	£60,053	2.71	1.95	£20,696	1.59	1.09	£39,357	0.86	£46,006
Scenario 7	Utilities – Progression based (pooled)	£60,053	2.71	1.74	£20,820	1.59	1.02	£39,233	0.72	£54,672
Scenario 8.a	Utilities – Time to death (per treatment arm)	£60,053	2.71	1.92	£20,820	1.59	1.13	£39,233	0.79	£49,736
Scenario 8.b	Utilities – Progression-based (per treatment arm)	£60,053	2.71	1.84	£20,820	1.59	0.92	£39,233	0.91	£42,890
Scenario 9	No age-related disutilities	£60,053	2.71	2.00	£20,820	1.59	1.11	£39,233	0.88	£44,448

5.8.4 Summary of sensitivity analyses results

The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 58%.

One-way sensitivity analyses showed that the inputs that most affect the ICER are those related to the extrapolation of the OS (i.e. the parameters of the log normal distribution used for extrapolation), the discount rate for health outcomes, parameters on extrapolation of time on treatment, dose intensity and the utility values for long-term survivors.

Scenario analysis showed that the cost-effectiveness of pembrolizumab is resilient to the sources of uncertainty assessed, including: selection of cut-points for PFS and OS extrapolation, utility values for shorter term survivors, distribution of market shares, and assumptions around age-related disutilities. The two scenarios evaluating different adjustment methods for treatment switching, i.e. no adjustment and IPCW adjustment, as well as, the scenario on utilities by progression status are the only outliers.

5.9 Subgroup analysis

5.9.1 Types of subgroups that are not considered relevant

The results of the clinical analyses on the subgroups of patients with advanced or metastatic urothelial cancer by individual comparator regimen, by histology and those by PD-L1 expression are presented in Appendix 22. The subgroup analyses have been conducted because they were pre-specified in the protocol and in the final scope. However, due to the small number of patients per subgroup, the results should be interpreted with caution as there is uncertainty around the estimates.

5.9.2 Analysis of subgroups

Further details on the statistical analyses of these subgroups are presented in section 4.8 and in Appendices 11 and 22.

5.9.3 Definition of the characteristics of patients in the subgroup

See section 4.8 and Appendices 11 and 22.

5.9.4 Description of how the statistical analysis was carried out

See section 4.8 and Appendices 11 and 22.

5.9.5 Results of subgroup analyses

See Appendix 22.

5.9.6 Identification of any obvious subgroups that were not considered

Not applicable.

5.10 Validation

5.10.1 Methods used to validate and quality assure the model

Clinical benefit

Comparing the model outcomes to clinical trial outcomes

The outcomes of the pembrolizumab and the UK SOC arms of the KEYNOTE-045 trial have been compared to the outcomes from the model. For more details comparing the results generated from the model to the outcomes from the model please refer to section 5.7.3.

Cross validation

The model has been adapted in order to compare the outcomes of the model with the outcomes of a cost-effectiveness model in patients with NSCLC. The following steps were undertaken:

1. Using identical base case settings and inputs
2. The drug administration cost was used as fixed cost
3. Parametric curve fitting: KM data and Point estimates used from NSCLC model
4. ToT of comparator: Survival data values with any distribution added to NSCLC model, as there no parametric fitting of distribution for ToT for comparator
5. Sensitivity Analysis with discount rate, time horizon, Utility approach, maximum treatment duration & parametric distributions of OS, PFS and ToT
6. The results were compared. The outcomes of the two models matched identically in terms of cost, efficacy and overall outcomes.

Expert validation

The model has been validated by an external health economist. Professor Martin Hoyle is a leading expert in health economic practice and methodology development in the UK and Director of PenTAG. Please refer to Appendix 30 for the methodology employed for the model validation.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab for the treatment of patients with advanced or metastatic urothelial cancer. The economic evaluation reflects patients assessed in KEYNOTE-045 and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

No study assessing the cost-effectiveness of pembrolizumab for the target population specified above was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

5.11.2 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the advanced or metastatic urothelial cancer population eligible for pembrolizumab as per the anticipated licence. As mentioned previously (see section 5.3.1), the KEYNOTE-045 trial, which assessed patients in line with the anticipated licenced indication, was used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab as second line therapy.

5.11.3 Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KEYNOTE-045 and the de novo economic evaluation are reflective of patients with advanced or metastatic urothelial cancer in the UK.
- The economic model structure is consistent with other oncology models submitted to NICE.
- The resource utilitisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab.

- Extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs.

- The OS projections of the model were validated against available UK sources to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

5.11.4 Strengths and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model.

- OS: Head-to-head data from the KEYNOTE-045 trial comparing pembrolizumab to UK SOC was used in the economic evaluation.

- Treatment switching adjustments: The two-stage adjustment method was deemed to be the most appropriate to adjust for the effect of switching to pembrolizumab from the UK SOC arm within KEYNOTE-045.

- Cut-off points for OS and PFS extrapolation: One of the strengths for this submission is that different time points for extrapolation of PFS and OS confirms the cost-effectiveness of pembrolizumab compared to UK SOC.

- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-045 data. Five time categories were used for the time-to-death approach.

- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 24 months, i.e. 35 cycles, as defined as part of the KEYNOTE-045 protocol.

- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice.

Extensive sensitivity analyses were conducted to inform the uncertainty around the above, which helped in understanding what key variables could potentially have a major impact on the cost-effectiveness results.

Since the approaches taken for modelling are, mostly conservative, the results presented here support the conclusion that, within the context of innovative end-of-life therapies, pembrolizumab is a cost-effective therapeutic option for the treatment of patients with previously treated advanced or metastatic urothelial cancer.

5.11.5 Further analyses

See section 4.14.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

There are no further factors relating to the decision problem which are relevant to the NHS but fall outside of the remit of the assessment.

6.2 Number of people eligible for treatment in England

In total, 502 patients with locally advanced/unresectable or metastatic urothelial cancer who have undergone previous treatment are estimated to be eligible for treatment with pembrolizumab in 2017 (see Table 93 below). The steps followed to estimate these values are described below.

Table 93: Number of previously treated, advanced/unresectable or metastatic urothelial cancer patients eligible for treatment with pembrolizumab in second line

	Year 1	Year 2	Year 3	Year 4	Year 5
	2017	2018	2019	2020	2021
Number of patients	502	510	517	524	532

The incidence rate of urothelial cancer per 100,000 people for England in 2014 was obtained from the Office of National Statistics; the value reflects the combined incidence rates of bladder, renal pelvis and ureter cancers as well as other malignant neoplasms of the urinary organs [52]. Using the ONS rates with a weighted average of the annual rate change of bladder cancer incidence obtained from Mistry et al., the incidence of urothelial cancer was calculated as a proportion of the total population of England in 2015[42, 115]. A weighted average of the annual change in the number of cases of bladder cancer from Mistry et al was then applied to this value to calculate the population of urothelial cancers in England for the following years.

In 2017 10,205 new cases bladder, renal pelvis and ureter cancers as well as other malignant neoplasms of the urinary organs are expected to occur. The proportion of cases expected to be transitional in histology is 90% (9,185 patients) and 14% of patients will be diagnosed with stage IV (1,286 patients)[29, 31]. Approximately 95% of these patients are expected to receive first line therapy (1225 patients) and 41% of these will go on to be treated at the second line (502 patients)[116].

Table 94: Estimates of incident population

	England	Sources
Rate of renal pelvis cancer per 100,000	1.15	Cancer Registration Statistics, ONS 2014[52]
Rate of ureter cancer per 100,000	1.10	Cancer Registration Statistics, ONS 2014[52]
Rate of bladder cancer per 100,000	15.65	Cancer Registration Statistics, ONS 2014[52].
Rate of malignant neoplasm of other urinary organs	0.35	Cancer Registration Statistics, ONS 2014[52]
Annual rate increase of bladder cancer incidence	-0.76%	Weighted average of annual incidence growth rate for bladder cancer, for males and females, and 2014 incidence of bladder cancer, for males and females[42, 52].
Annual case increase of bladder cancer incidence	1.44%	Weighted average of annual change in number of cases of bladder cancer, for males and females, and 2014 incidence of bladder cancer, for males and females [42, 52].
Rate of urothelial cancer as a proportion of bladder cancer	90%	Cancer Research UK 2016[29]
Proportion of patients with stage IV disease	14%	Cancer Research UK 2016[31]
Proportion of patients treated in 1L	95%	MSD Data on file (2016)[116]
Proportion of patients treated 1L that go on to be treated in 2L	41%	MSD Data on file (2016)[116]

Based on the estimated PD-1 class share (MSD internal forecasting), we have estimated the maximum number of patients eligible for pembrolizumab in the 2nd line that could receive pembrolizumab. We have not broken this down further to shares for individual drugs within the class for transparency purposes (Table 95).

Table 95: Estimated number of patients stage IV urothelial cancer receiving 2L treatment per year

	Year 1	Year 2	Year 3	Year 4	Year 5
	2017	2018	2019	2020	2021
Estimated class share PD-1 class	29%	70%	70%	70%	70%
Total stage IV patients eligible for treatment with pembrolizumab in 2L	146	357	362	367	372

6.3 Assumptions that were made about current treatment options and uptake of technologies

The budget impact compares two alternative scenarios:

- The existing treatment scenario in current clinical practice (i.e. without pembrolizumab), where patients can be treated with the comparators included in this submission, of either docetaxel or paclitaxel.
- The new treatment scenario (with pembrolizumab assumed to be used as part of clinical practice).

The main assumptions formulated to estimate the number of patients eligible to receive pembrolizumab in 2L are:

- The budget impact model considers the following costs: treatment pre-progression, administration and management of AEs.
- A total of 39% of patients with stage IV urothelial cancer will be eligible for treatment with pembrolizumab in 2L.
- Patients treated with pembrolizumab receive the anticipated licensed dose of 200 mg for an average of 5.6 months (i.e. for 8.81 cycles), as reported in KEYNOTE-045.
- The population considered in the budget impact analysis is reflective of the population in KEYNOTE-045, described below:
  - The stage of disease in the population (i.e. stage IV)
  - Patients have previously received chemotherapy treatment
  - The mean treatment duration (see Table 96)
  - The frequency of adverse events in each arm of the trial
- The weighting of docetaxel and paclitaxel as standard of care were based on the most up to date market shares for the treatment of stage IV urothelial cancer at 2L between these two treatments, which were 74% and 26% respectively.
- No patients are assumed to be treated through clinical trials
- Only the costs related to pre-progression is considered as part of the budget impact estimation (i.e. for simplification, it is assumed that after progression costs will be similar independent of the subsequent therapies administered).
- It is assumed that pembrolizumab is introduced in the market in 2017.

Table 96. Time on treatment and number of administrations

	Pembrolizumab 200 mg Q3W	Docetaxel	Paclitaxel
Time on therapy (months)	5.60	2.21	2.92
Number of administrations (cycles)	8.81	3.90	5.00
Sources	KEYNOTE-045[16]		

6.4 Assumptions that were made about market shares in England

We have assumed that all eligible patients will get treatment with pembrolizumab in second line once pembrolizumab is introduced into the market and after a positive recommendation by NICE. This reflects, therefore, the maximum number of patients that could be expected to receive pembrolizumab.

6.5 Other significant costs associated with treatment that may be of interest to commissioners

Technology costs and other significant costs associated with treatment with pembrolizumab are identical to those assumed in the cost-effectiveness model and are described in section 5.5.

6.6 Unit costs assumed and how they were calculated

All unit costs considered here estimate the annual budget to the NHS in England and are based upon the ones included in the economic in section 5.5.

6.7 Estimates of resource savings

See section 6.1.

6.8 State the estimated annual budget impact on the NHS in England.

The introduction of pembrolizumab to the market in England is expected to displace the use of docetaxel and paclitaxel in second line for treatment of patients with stage IV urothelial cancer. This is presented with the PAS for pembrolizumab. MSD has not attempted to estimate the share of pembrolizumab in second line but rather has presented the potential maximum budget impact, assuming that all eligible patients would receive treatment with pembrolizumab.

Table 97: Estimated budget impact of pembrolizumab over 5 years (with PAS for pembrolizumab)

	Year 1	Year 2	Year 3	Year 4	Year 5
	2017	2018	2019	2020	2021
Total stage IV patients eligible for treatment with pembrolizumab in 2L	502	510	517	524	532
World without pembrolizumab					
Total treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total world without	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with pembrolizumab					
Total treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total world with	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference between the world with and the world without pembrolizumab					
Total treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

See section 6.1.

6.10 Highlight the main limitations within the budget impact analysis.

A number of assumptions were made in terms of proportion of patients treated in second line, which introduced uncertainty into the estimates here presented. Additionally, the model is based on a closed cohort of patients based on the eligible population presented in Table 93. Furthermore the model assumes displacement of only paclitaxel and docetaxel at the second line; the most up to date market shares available show some use of the combination carboplatin and paclitaxel for the second line treatment of stage IV urothelial cancer however due to the lack of available comparative data, this combination could not be included as a comparator in this submission. As a limitation to this approach, there may be a small proportion of patients who are eligible for therapy and has not been considered in these projections. Furthermore, consideration of the maximum amount of number of patients potentially treated with pembrolizumab in second line does not allow for an accurate estimation of the budget impact specifically related to pembrolizumab, since some patients may still get treated with some of the docetaxel or paclitaxel once pembrolizumab becomes available.

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vbn

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07th April 2017

Dear Helen,

Re. Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Further to the request for additional evidence and revisions to confidentiality marking for the above appraisal, please find enclosed MSD's responses to each point, as detailed below:

1. Could the company please provide the clinical results and figures for progression-free survival of pembrolizumab versus UK standard of care for the following groups:

    - Intention-to-treat
    - PD-L1 positive (CPS=1%)
    - PD-L1 strongly positive (CPS=10%)
    - PD-L1 negative (CPS<1%)

The requested analyses are provided within this document.

2. Confidentiality marking of the economic model: Please consider unredacting the document and clearly highlighting using the established highlighting format the specific commercial in confidence data which is required to be redacted. To allow consultees and commentators to comment on the model please also supply a redacted version of model substituting commercial in confidential data with clinically plausible dummy data, clearly marking where data has been substituted.

A redacted version of the model has been uploaded on NICE Docs. Please note that, consistent with our previous redacted models, CiC information has been removed and marked in turquoise, while AiC data have been substituted with dummy data in order to ensure that the CiC information cannot be estimated. In addition a revised version of the model with highlighted ACiC information has been uploaded.

3. Clinical results for adjustment to treatment switching for pembrolizumab versus UK standard of care (i.e. comparator excludes vinflunine)

Given that the committee is to consider costs from a current NHS and personal social services perspective, it is highly likely that the results of the above subgroup will be a key component of committee discussion and decision-making. As NICE considers it essential that evidence on which the Appraisal Committee's decisions are based is publicly available, please consider underacting at a minimum the following 'academic in confidence' information:

- Summary statistics for overall survival (i.e. hazard ratios and p-values);

  - company submission page 135 and 179
  - company appendices page 162-184

As per our email commuinication dated 06 April 2017, these post-hoc subgroup analyses comparing against UK SOC (based on pre-specified populations in terms of CPS level [i.e. =1% and >=10%]) were conducted to ensure we were providing data against only those comparators of relevance to the UK, and to be consistent with the subgroups identified as relevant in the final scope issued by NICE. Therefore the current AiC marking will be retained.

4. Clinical and cost-effectiveness results for PD-L1 expression subgroups (with and without treatment switching adjustments) for pembrolizumab versus UK standard of care (i.e. comparator excludes vinflunine)

Given that PD-L1 expression has been incorporated into the marketing authorisation for other indications of pembrolizumab, it is highly likely that the results of the above subgroups will be discussed by committee. Please consider underacting the following information at a minimum for subgroups concerning PD-L1 expression of CPS<1%, CPS=1%, and CPS=10%:

- All ICERs of the above subgroups;
  - company appendices (appendix 22) pages 267-270
  - company response to clarification Section B Pages 17-18; 20-21; 23; 33-34
  - company response to clarification appendices pages 38-41 and 54-57

- Summary statistics for overall survival (i.e. hazard ratios and p-values);
  - company appendices page 189-204
  - company response to clarification appendices pages 7-10

To ensure that committee are able to discuss results with clinical experts, and to be consistent with your other marking, please also consider remarking from 'commercial in confidence' to 'academic in confidence' the following:

- All clinical and cost-effectiveness results (excluding those discussed above) from the CPS<1% PD-L1 expression subgroup;

  - company response to clarification Section B Pages 33-34
  - company response to clarification appendices pages 7-10

As per our email commuinication dated 06 April 2017, the post-hoc subgroup analyses comparing against UK SOC (based on pre-specified populations in terms of CPS level [i.e. =1% and >=10%] were conducted to ensure we were providing data against only those comparators of relevance to the UK, and to be consistent with the subgroups identified as relevant in the final scope issued by NICE. Therefore the current AiC marking will be retained.

With regards to the post-hoc subgroup analyses comparing against UK SOC in the CPS<1% sub-population provided in response to clarification questions: it is important to note that unlike CPS>=1% and CPS>=10%, the CPS<1% subgroup was never a pre-specified subgroup in the overall ITT population of KEYNOTE-045, and therefore no analyses in the ITT population had been planned. Following the request received during clarification questions, we provided the analyses for this subgroup, specifically versus UK SOC. However when considering the distinction compared with the above mentioned subgroup analyses, we consider this information to be CiC and therefore the current confidentiality marking will be retained.

5. Justification for the cut-offs used (CPS =1% and CPS =10%) in KEYNOTE-045

In order for this information to be discussed at the Committee meeting, this text has been remarked as AiC, and a revised version of the Appendices to the clarification questions (ACIC) has been submitted via NICE Docs accordingly.

We believe that we have addressed all of the questions, but should you or the ERG require any further clarification, please do not hesitate to contact us.

Best regards,

[redacted]

Additional evidence and confidentiality marking: pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Question: Could the company please provide the clinical results and figures for progression-free survival of pembrolizumab versus UK standard of care for the following groups:

- **Intention-to-treat**
- **PD-L1 positive (CPS=1%)**
- **PD-L1 strongly positive (CPS=10%)**
- **PD-L1 negative (CPS<1%)**

MSD Response:

Please find below the requested data and figures:

A sub-population of the intention-to-treat (ITT) population is used for the analysis of progression-free survival (PFS). Subjects pre-assigned by investigator, prior to randomisation, to receive either paclitaxel or docetaxel should they have subsequently been randomised to the Standard of Care (SOC) arm, are included in the analyses according to the treatment group to which they were randomised. Subgroup analyses in patients with CPS>=1%, CPS>=10% and CPS<1% were carried out if the number of subjects within the subgroup allowed it.

Table 1 and Figure 1 give the results of the main sub-population analysis and Kaplan-Meier (KM) curve for PFS for subjects pre-assigned to taxanes.

Table 2 and Figure 2 give the results of the subgroup analyses and KM curves for PFS in patients with CPS>=1%, in the sub-population of patients pre-assigned to taxanes.

Table 3 and Figure 3 give the results of the subgroup analyses and KM curves for PFS in patients with CPS>=10%, in the sub-population of patients pre-assigned to taxanes.

Table 4 and Figure 4 give the results of the subgroup analyses and KM curves for PFS in patients with CPS<1%, in the sub-population of patients pre-assigned to taxanes.

Discussion

Subgroup analyses are exploratory and therefore have to be interpreted with caution given the small sample size. The results are associated with large uncertainties and should be interpreted with caution. The focus is on estimation with uncertainty quantified by the 95% confidence interval.

Table 1: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>= 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).

‡‡ Two-sided p-value based on stratified log-rank test.

(Database Cutoff Date: 07SEP2016)

Figure 1: Kaplan-Meier of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

[redacted]

(Database Cutoff Date: 07SEP2016)

Table 2: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) CPS >= 1% ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>= 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).

‡‡ Two-sided p-value based on stratified log-rank test.

(Database Cutoff Date: 07SEP2016)

Figure 2: Kaplan-Meier of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) CPS >= 1% ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

[redacted]

(Database Cutoff Date: 07SEP2016)

Table 3: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) CPS >= 10% ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>= 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).

‡‡ Two-sided p-value based on stratified log-rank test.

(Database Cutoff Date: 07SEP2016)

Figure 3: Kaplan-Meier of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) CPS >= 10%ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

[redacted]

(Database Cutoff Date: 07SEP2016)

Table 4: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) CPS < 1% ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>= 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).

‡‡ Two-sided p-value based on stratified log-rank test.

(Database Cutoff Date: 07SEP2016)

Figure 4: Kaplan-Meier of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) CPS < 1% ITT Population - Pembrolizumab vs. Taxanes (Paclitaxel, Docetaxel)

(Database Cutoff Date: 07SEP2016)

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Single technology appraisal

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Dear [redacted],

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 16 February 2017 from Merck Sharp & Dohme. 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 **27 March 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 Thomas Strong, Technical Lead (Thomas.Strong@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Background

A1. Please provide a source for the number of expected cases data (company submission page 39, table 5).

A2. In the discussion of the end of life criteria (company submission page 168, table 61) the company submission refers to references 77 and 78. These were not included in the background section, please provide details of the estimates of life expectancy in these two studies.

Clinical effectiveness

A3. **Priority question:** The original search was conducted on 8th June 2016. Please update the systematic review, providing references for any new included and excluded studies identified.

A4. Please clarify the correct numbers for figure 5 as the numbers do not match the text on company submission page 45 (text states 31 full texts, figure states 32), and figure shows 25 studies were excluded but only 24 are listed in table 4 of Appendix 3 (page 76 of the company appendices).

A5. **Priority question:** The KEYNOTE-045 trial is pivotal and of the 29 countries involved only 4 patients from the UK. Can you please clarify how representative the trial is to the UK population?

A6. **Priority question:** Please provide the following additional information on number of patients for each group and subgroup in the table below:

	Control	Pembrolizumab
Total number CPS ≥ 1% CPS ≥ 10% Non-PDL1 positive		
CPS ≥ 1% Paclitaxel Docetaxel Vinflunine Pembrolizumab Switched treatments* Missing		
CPS ≥ 10% Paclitaxel		

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Docetaxel Vinflunine Pembrolizumab Switched treatments* Missing		
Non PD-L1 positive (PD-L1 negative) Paclitaxel Docetaxel Vinflunine Pembrolizumab Switched treatments* Missing		

***** If patients switched treatments, please can you clarify what treatments the patients switched too (see also question A15)
Abbreviations: CPS, combined positive score

A7. Please clarify why non-RCTs of pembrolizumab were excluded (company submission page 44)?

A8. Please provide further details of the allocation method used within the randomisation process e.g. blocking, block size?

A9. KEYNOTE-045: what was the basis for the investigators choice of comparator should a participant be randomised to control? Were there decision rules other than those below figure 6? Also, in countries where vinflunine is approved, were the other 2 treatments also an option?

A10. Page 90 of the company submission refers to emerging evidence that PD-L1 expression level and clinical outcomes may be correlated. Please provide evidence for the link between PD-L1 expression and clinical outcomes. Please also provide further justification for the cut-offs used (combined positive score ≥1% for PD-L1 positive and combined positive score ≥10% for PD-L1 strongly positive)?

A11. Figure 7 suggests that the 1.5% of people in the pembrolizumab arm (n=4) and 6.25% in the control arm (n=17) who did not start their respective treatments were included in the ITT analysis. Is this correct, and if so what data were used? Furthermore, the ERG are concerned about the exclusion of pembrolizumab patients who were pre-randomisation allocated to vinflunine – how did the company reduce any potential bias that this may create?

A12. Please confirm if treatment switching was allowed in the study protocol; there are some contradictions in the company submission (e.g. pages 15, 118, 134). At what point did the patients switch, i.e. how long did they receive control treatment for and which control treatments did they switch from?

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A13. What is the definition for drug-related adverse events: “possibly”, “probably”, and “definitely”? (company submission page 152)

A14. Please provide details of any longer-term adverse event data for pembrolizumab (in any indication), in particular adverse events of special interest?

A15. Please provide subgroup clinical effectiveness data for the PD-L1 negative (non PD-L1 positive) subgroup for completeness.

A16. Please can the company explain why nearly 20% of control group had no post-baseline imaging?

A17. The company submission (page 90) states that “PD-L1 strongly positive subjects and all subjects were included in the multiplicity controlled statistical testing” but on page 106 of the submission it states that the p-value for objective response rate for those with PD-L1 combined positive score ≥10% compared with control states was not multiplicity adjusted. Is this an error?

A18. The company submission (page 44 and elsewhere) says studies of potential relevance for the indirect comparisons were RCTs with comparisons between any interventions of interest. However, the list of included studies of potential relevance (company submission table 49) include those with comparisons with other interventions (e.g. best supportive care). Please clarify the inclusion criteria for the indirect comparison.

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. **Priority question:** Table 66 in the company submission (page 181). Please can you clarify/elaborate why some analyses have not been undertaken? Please also provide Kaplan-Meier curves for overall survival adjusting for treatment switching using the RPSFT and IPCW methods.

B2. Please explain why in Table 67 (page 182 of the company submission) 2-sided p-values are provided, whereas in the clinical effectiveness sections p-values are one-sided? Also, please clarify why the p-values have been retained from the intention-to-treat for the two (simplified two-stage and RPSFT) adjustments for treatment switching? The hazard ratio reported for the simplified two-stage adjustment is [redacted]. The ERG would expect there to be a p-value that is <0.05.

B3. With respect to table 67 (page 182 of the company submission), please provide further information on the models used to generate hazard ratios? Was a cox proportional-hazard model used?

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B4. The company submission used a two-phase piecewise approach to derive overall survival. First phase used data directly from the Kaplan-Meier plots and in the second phase used data from the 40-week cut-off point and fitted with a log-normal curve to these data. Please justify why the log-normal fit was used for this extrapolation? The ERG understands that Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were derived for the fully fitted parametric models to the UK standard of care and the pembrolizumab arms. Additionally, please clarify if other curves have been fitted to the cumulative hazard for overall survival (Figure 36, page 187).

B5. **Priority question:** Please can you provide the following individual patient data from KEYNOTE-045, by each sub-group and excluding people who received vinflunine treatment? (see the table below)

Table 1: Individual patient-level data requested by the Evidence review group

Patient ID number	Comparator	Time of event or censoring	Event or censoring
Intention-to-treat			
1	• UK SOC (docetaxel and paclitaxel) • Docetaxel • Paclitaxel		
2			
3			
4			
Etc.			
PD-L1 positive (CPS≥1%)			
1	UK SOC (docetaxel and paclitaxel)		
2			
3			
Etc.			
PD-L1 strongly positive (CPS≥10%)			
1	UK SOC (docetaxel and paclitaxel)		
2			
3			
Etc.			
PD-L1 negative			
1	UK SOC (docetaxel and paclitaxel)		
2			
3			
Etc.			
Event = 1 Censoring = 0			

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Cost-effectiveness analysis

B6. **Priority question**: Can you confirm whether the Patient Access Scheme (PAS) referred to throughout the company submission is conditional on positive guidance for another indication. If so, please use the currently operational PAS in all further base-case analyses. Furthermore please submit an addendum of all previously supplied cost-effectiveness analyses using the currently operational PAS.

B7. **Priority question**: In the economic model the EQ-5D data also includes vinflunine. Please can the company provide the utility values (based on time to death, progression status and adverse events), an economic model and the corresponding results without vinflunine (only include paclitaxel and docetaxel) as this is not UK standard of care.

B8. **Priority question**: The cost-effectiveness results for the PD-L1 subgroups as reported in the company submission (appendix pages 268-270) are key and the results could not be exactly replicated by the ERG. Please can the company either explain the methodology used to produce these results or provide the correct corresponding economic models including tornado diagrams, probabilistic results (expected ICERs and cost-effectiveness acceptability curve) and survival modelling methods.

B9. **Priority question**: For all cost-effectiveness analyses as reported in the appendix please can the company provide cost-effectiveness acceptability curves.

B10. **Priority question**: Can the company provide scenario analyses for the following:

a. Varying the number of progression-free people who would continue treatment after 2 years
b. Varying the expected continued treatment effect for people who have stopped treatment

Provide probabilistic sensitivity analysis results for the different scenarios outlined in the format of table 2 on the final page of this letter. Please also provide separately the corresponding costs and QALY results for these scenarios.

B11. Please can the company provide cost-effectiveness results in the subgroup of patients negative for PD-L1 along with the corresponding probabilistic results (expected ICER and cost-effectiveness acceptability curves)?

B12. In Figures 32, 42 and 43, 126 papers were evaluated in full. Please can the company provide more information about these papers, including references and why these studies were excluded for each of the 3 research questions?

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Section C: Textual clarifications and additional points

C1. Page 103 of the company submission – please can you confirm whether this should be "at least 1 post-baseline imaging" rather than "at least 1 baseline imaging"? Also, please explain what happened to the other patients who did not have post-baseline imaging, as the sample size for both arms is lower than the total for each arm? Please also confirm that using people with imaging as the denominator gives a non-significant difference between the groups?

C2. On page 106 of the company submission it states "ORR per confirmed RECIST 1.1 by central radiology assessment among subjects with PD-L1 CPS ≥10%" - can you confirm that the difference between the groups is not significant if using the denominator of people with at least 1 (presumably post-) baseline imaging assessment.

C3. With regard to tables 54-59 and table 61 of the company submission - please provide revised tables indicating when there is a statistically significant difference ($p < 0.05$) between groups for each event?

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Table 2 Cost-effectiveness results for pembrolizumab compared with UK standard of care (docetaxel and paclitaxel) for previously treated advanced or metastatic urothelial cancer

	Lifetime treatment effect	Continued treatment effect over 10 years; no treatment effect thereafter	Continued treatment effect over 5 years; no treatment effect thereafter	Continued treatment effect over 3 years; no treatment effect thereafter
100% of progression-free people continue treatment after 2 years (no stopping rule)				
25% progression-free people continue treatment after 2 years				
0% continue treatment after 2 years (full implementation of the stopping rule)				

Section A: Clarification on effectiveness data

Background

A1. Please provide a source for the number of expected cases data (company submission page 39, table 5).

In the last paragraph of Section 3.4 of our submission dossier, we had cross referenced the relevant section (Section 6.2) where the list of assumptions made to estimate the expected number of cases may be found.

A2. In the discussion of the end of life criteria (company submission page 168, table 61) the company submission refers to references 77 and 78. These were not included in the background section, please provide details of the estimates of life expectancy in these two studies.

We apologise for not including the details of these references within the background section. The estimated life expectancy of patients with advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy is estimated to be between 6.5 and 9 months based on the following trials sourced from references 77 and 78.

- Paclitaxel was investigated in 2 phase II trials, where patients achieved a median overall survival of 6.5 and 7.2 months.[1, 2]
- Docetaxel was investigated in 2 phase II trials, where patients achieved a median overall survival of 7.3 and 9 months.[3, 4]

Clinical effectiveness

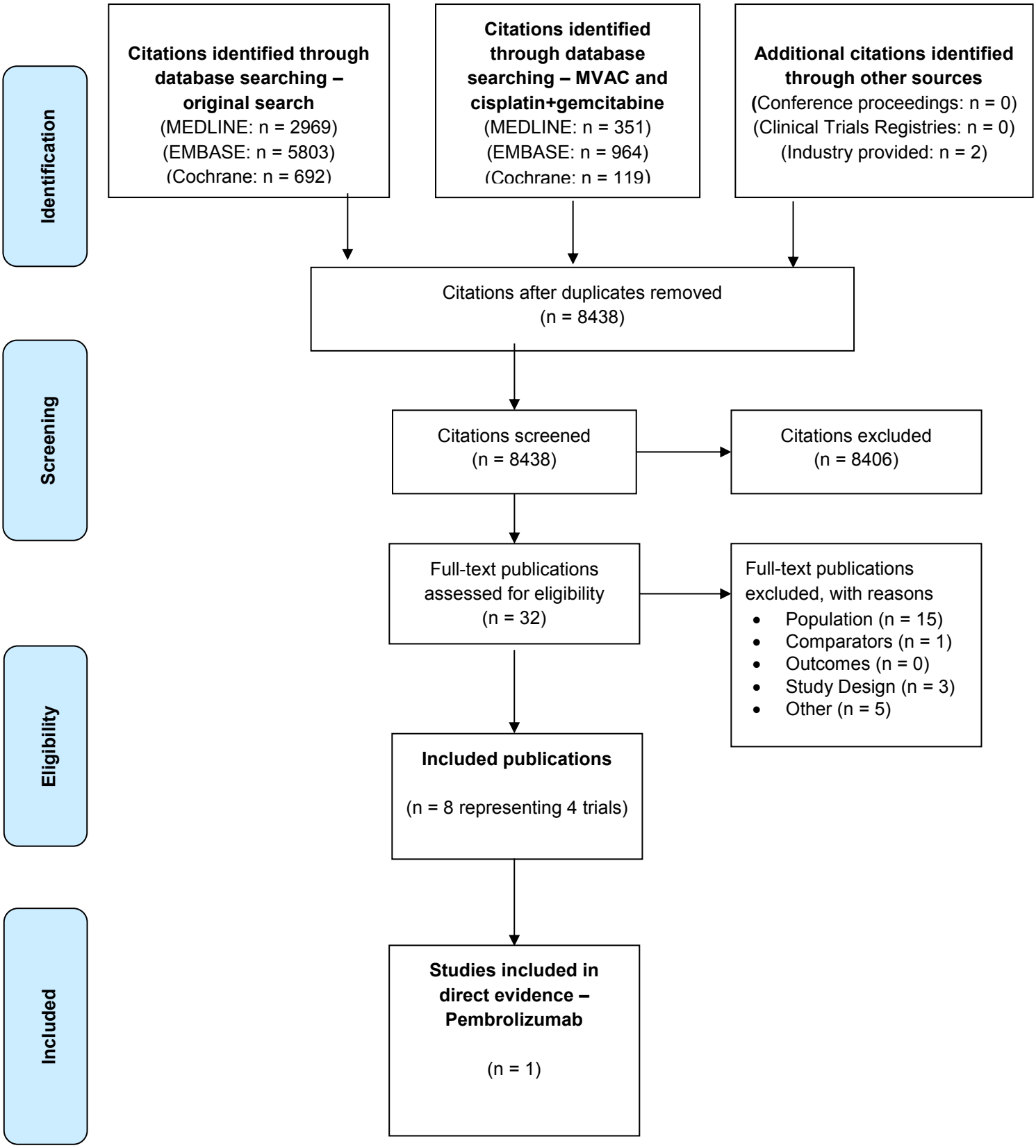
A3. **Priority question:** The original search was conducted on 8th June 2016. Please update the systematic review, providing references for any new included and excluded studies identified.

It was not possible to run the updated search in the short timeline provided. However, we do not anticipate any new studies, given the limited clinical advancements in this area.

A4. Please clarify the correct numbers for figure 5 as the numbers do not match the text on company submission page 45 (text states 31 full texts, figure states 32), and figure shows 25 studies were excluded but only 24 are listed in table 4 of Appendix 3 (page 76 of the company appendices).

Please accept our apologies for the typo in Figure 5 of the company submission. We can confirm that 32 full texts were reviewed, with 24 studies subsequently excluded (as per the list provided in Appendix 3). An updated version of Figure 5 from the submission document is provided below (named as Figure 1 below).

Figure 1: PRISMA flow diagram of the systematic review process



A5. **Priority question:** The KEYNOTE-045 trial is pivotal and of the 29 countries involved only 4 patients from the UK. Can you please clarify how representative the trial is to the UK population?

Although only four UK patients were enrolled in KEYNOTE-045, MSD UK believes this trial is representative of the UK population when considering following:

- 75 patients (13.8%) enrolled in KEYNOTE-045 were from Western European countries (Belgium, France, Ireland, Netherlands, United Kingdom)
- 223 patients (41.1%) enrolled in KEYNOTE-045 were from European countries (Italy, Spain, France, Hungary, Austria, Denmark, Germany, Netherlands, Belgium, Norway, Portugal, Romania, United Kingdom, Ireland, Poland and Sweden).
- 338 patients (62.3%) enrolled in KEYNOTE-045 were from either European countries or the USA

The numbers of enrolled patients participating from each country are provided below in Table 1, for information.

Please note that in order to ensure the data included in our submission was reflective of UK clinical practice, subgroup analyses were presented which excluded patients who were pre-randomisation allocated to vinflunine (regardless of whether they were eventually randomised to the pembrolizumab arm or SOC arm). As a result, only UK-relevant SOC regimens (docetaxel and paclitaxel) were included as comparators in the data feeding the cost-effectiveness analyses.

Additionally, the incidence of urothelial cancer worldwide appears to reflect the prevalence of tobacco smoking.[5] Tobacco smoking is recognised as the most important risk factor for urothelial cancer. The UK shares similar prevalence of tobacco smoking as the rest of Europe so it is likely that the non-UK patients enrolled in KEYNOTE-045 have been exposed to similar risk factors as UK patients.[6]

Table 1: KEYNOTE-045: Number of patients enrolled from each participating country

Country	Number of patients enrolled	Proportion of total number of patients enrolled
Australia	13	2.4%
Austria	11	2.0%
Belgium	13	2.4%
Canada	20	3.7%
Chile	8	1.5%
Denmark	19	3.5%
France	25	4.6%
Germany	11	2.0%
Hungary	15	2.8%

Ireland	4	0.7%
Israel	40	7.4%
Italy	36	6.6%
Japan	52	9.6%
Netherlands	29	5.4%
New Zealand	4	0.7%
Norway	6	1.1%
Peru	2	0.4%
Poland	3	0.6%
Portugal	4	0.7%
Puerto Rico	1	0.2%
Romania	5	0.9%
Singapore	7	1.3%
South Korea	31	5.7%
Spain	35	6.5%
Sweden	3	0.6%
Taiwan	23	4.3%
Turkey	13	2.4%
UK	4	0.7%
USA	105	19.3%
TOTAL	**542**	

A6. **Priority question:** Please provide the following additional information on number of patients for each group and subgroup in the table below:

	Control	**Pembrolizumab**
Total number CPS ≥ 1% CPS ≥ 10% Non-PDL1 positive		
CPS ≥ 1% Paclitaxel Docetaxel Vinflunine Pembrolizumab Switched treatments* Missing		
CPS ≥ 10% Paclitaxel Docetaxel Vinflunine Pembrolizumab Switched treatments* Missing		
Non PD-L1 positive (PD-L1 negative) Paclitaxel Docetaxel Vinflunine Pembrolizumab Switched treatments* Missing		

***** If patients switched treatments, please can you clarify what treatments the patients switched too (see also question A15)

Abbreviations: CPS, combined positive score

A summary of the actual treatment received is provided in Table 2, and Table 3 summarises the treatments which patients subsequently received.

Counts by type of therapy are provided for the overall population and the requested CPS sub-populations (i.e. CPS >=1%, CPS>=10%, CPS<1%). As documented in Table 17 (Subject Characteristics) in our submission document, a total of 14 patients were neither classified as CPS>=1% nor CPS<1% (and a total of 16 patients were classified as neither CPS >=10% nor CPS<10%). The screening samples of these patients were considered "non-evaluable".

It should be noted there was no cross-over allowed in the KEYNOTE-045 study protocol. Subjects were allowed, however, to receive subsequent therapies as their treating physicians deemed appropriate and this information was collected in the electronic database. In the submission document, we used wordings such as "treatment switching" to describe patients that received subsequent therapy. To avoid confusion, this will be described as "subsequent therapy" in Table 3 below and throughout this response.

Table 2: Actual Study Treatment Received

KEYNOTE- 045[a]	Control	Pembrolizumab
Main Population	272	270
Docetaxel	84	
Paclitaxel	84	
Vinflunine	87	
Pembrolizumab		266
Missing	17	4
CPS>=1%	120	110
Docetaxel	41	
Paclitaxel	36	
Vinflunine	31	
Pembrolizumab		107
Missing	12	3
CPS>=10%	90	74
Docetaxel	37	
Paclitaxel	26	
Vinflunine	20	
Pembrolizumab		71
Missing	7	3
CPS<1%	147	151
Docetaxel	41	
Paclitaxel	46	
Vinflunine	55	
Pembrolizumab		150
Missing	5	1
a: Database Cutoff Date: 07SEP2016		

Table 3: Subjects who subsequently received Anti PD-L1 / Anti PD-1 Thearapies

KEYNOTE-045[a]	Control[b]	Pembrolizumab[b]
Main Population		
Subsequent anti PD-L1/anti PD-1 therapies received	33 (22)	2 (2)
anti-PDL1 monoclonal antibody (unspecified)	1 (1)	
atezolizumab	7 (4)	2 (2)
avelumab	2 (2)	
durvalumab	3 (2)	
nivolumab	4 (3)	
pembrolizumab	16 (10)	
CPS>=1%		
Subsequent anti PD-L1/anti PD-1 therapies received	15 (10)	2 (2)
anti-PDL1 monoclonal antibody (unspecified)	1 (1)	
atezolizumab	4 (4)	2 (2)
avelumab	1 (1)	
durvalumab	2 (1)	
nivolumab	1 (0)	
pembrolizumab	6 (3)	
CPS>=10%		
Subsequent anti PD-L1/anti PD-1 therapies received	10 (7)	1 (1)
anti-PDL1 monoclonal antibody (unspecified)	1 (1)	
atezolizumab	3 (3)	1 (1)
avelumab	1 (1)	
nivolumab	1 (0)	
pembrolizumab	4 (2)	
CPS<1%		
Subsequent anti PD-L1/anti PD-1 therapies received	18 (12)	
atezolizumab	3 (0)	
avelumab	1 (1)	
durvalumab	1 (1)	
nivolumab	3 (3)	
pembrolizumab	10 (7)	

a: Database Cutoff Date: 07SEP2016

b: Results in table: Number of patients who subsequently received Anti PD-L1 / Anti PD-1 Treatments (Number of patients who subsequently received Anti PD-L1 / Anti PD-1 Treatments who had disease progression prior to receiving these subsequent therapies)

A7. Please clarify why non-RCTs of pembrolizumab were excluded (company submission page 44)?

As stated in the 2013 NICE methods guide, RCTs are considered to be most appropriate for measures of relative treatment effect. Therefore the systematic search was focused on RCTs to identify the best available evidence concerning pembrolizumab in the population of interest. This is the same approach as applied in previous MSD UK NICE submissions.

A8. Please provide further details of the allocation method used within the randomisation process e.g. blocking, block size?

Central randomisation with blocking size 2 was implemented as the allocation method for this study.

A9. KEYNOTE-045: what was the basis for the investigators choice of comparator should a participant be randomised to control? Were there decision rules other than those below figure 6? Also, in countries where vinflunine is approved, were the other 2 treatments also an option?

Investigators were allowed to choose between paclitaxel, docetaxel and vinflunine, according to their clinical practice, and provided vinflunine was approved in their countries. There were no additional decision rules to determine the choice of comparator other than those detailed below Figure 6 in our submission (study design of KEYNOTE-045), noting that the protocol also stated that preparation and administration of comparators would follow local product labels. Paclitaxel and docetaxel were also available to investigators in countries that vinflunine is approved. Given the high unmet need in this population and the fact that the phase III trial of vinflunine versus best supportive care[7] showed no benefit in the ITT population (albeit a small benefit was shown in a subset analysis), the study sponsor felt it was appropriate not to limit paclitaxel and docetaxel only to countries where vinflunine was not approved. Of note, the proportion of subjects receiving vinflunine in the control arm was planned to be capped at approximately 35% (according to FDA and EMA discussions); however the threshold of 35% was not reached and therefore the cap was notimplemented. Approximately one third of the patients in the control arm received each of the chemotherapy drugs available.

A10. Page 90 of the company submission refers to emerging evidence that PD-L1 expression level and clinical outcomes may be correlated. Please provide evidence for the link between PD-L1 expression and clinical outcomes. Please also provide further justification for the cut-offs used (combined positive score ≥1% for PD-L1 positive and combined positive score ≥10% for PD-L1 strongly positive)?

Data external to KEYNOTE-045 informed the decision on the PD-L1 IHC scoring method and cut-offs.

Analyses of tumour specimens from the KEYNOTE-012 clinical trial[8] using the PD-L1 IHC 22C3 pharmDx assay led to the selection of the combined positive score (CPS) as the scoring method for urothelial and other cancers, with a >1% cut-off for positivity. In addition, based on review of data from the first 100 subjects enrolled in KEYNOTE-052,[9] an additional strongly positive cut-off (i.e., a CPS score higher than the CPS ≥ 1% cut-off) was identified for urothelial

carcinoma. Data from these 100 subjects were considered the training set for the purposes of establishing the CPS ≥ 10% (strongly positive) cut-off.

KEYNOTE-045 was amended to include the analysis of efficacy outcomes, based on data from KEYNOTE-012 and KEYNOTE-052. Notably, the overall survival benefit of pembrolizumab versus chemotherapy was observed across all PD-L1 CPS expression levels.

Further details are provided in Appendix 1.

A11. Figure 7 suggests that the 1.5% of people in the pembrolizumab arm (n=4) and 6.25% in the control arm (n=17) who did not start their respective treatments were included in the ITT analysis. Is this correct, and if so what data were used? Furthermore, the ERG are concerned about the exclusion of pembrolizumab patients who were pre-randomisation allocated to vinflunine – how did the company reduce any potential bias that this may create?

A total of 542 patients were randomised into KEYNOTE-045, and therefore comprise the ITT population (control: 272; pembrolizumab: 270).

Among the 17 subjects in the control arm who were randomised and did not receive study drug, 16 withdrew consent, and one experienced an AE. Among the subjects in the pembrolizumab arm (n=4) who were randomised and did not receive study drug, two were randomised in error and two died prior to cycle 1 day 1.

Overall survival data was collected in the subjects who were randomised and not treated, provided that despite withdrawing consent for therapy, they continued to consent to survival follow up.

The KEYNOTE-045 results presented in section 4.7 reflect the ITT population. Pembrolizumab patients who were pre-randomisation allocated to vinflunine were not excluded from the KEYNOTE-045 efficacy analyses presented in section 4.7 of the submission.

In the subgroup analyses (i.e. results presented in section 4.8 of the submission document, under the subheadings “Analysis of overall survival adjusting for treatment switch - subgroup analysis” and “Subgroup analyses based on PD-L1 status for paclitaxel or docetaxe pre-assigned subjects”), subgroups are presented based on SOC treatment as assigned by investigator pre-randomisation (pembrolizumab vs. docetaxel, pembrolizumab vs. paclitaxel, pembrolizumab vs. (docetaxel or paclitaxel)). With regards to the pembrolizumab patients included in these subgroups, the numbers of patients reflect those patients who had been pre-assigned to receive a specific SOC regimen, in the event that they were randomised to the SOC arm, but were instead eventually randomised to the pembrolizumab arm. Therefore the number of pembrolizumab patients is a subset of the overall KEYNOTE-045 ITT population randomised to the pembrolizumab arm. Using this approach, the intention-to-treat principle was maintained in the subgroup analyses, allowing treatment arms to be more comparable. Therefore, no subjects pre-randomisation allocated to vinflunine were included in the above-mentioned subgroup analyses (i.e. in either arm).

A12. Please confirm if treatment switching was allowed in the study protocol; there are some contradictions in the company submission (e.g. pages 15, 118, 134). At what point did the patients switch, i.e. how long did they receive control treatment for and which control treatments did they switch from?

Subjects were randomised to receive either pembrolizumab or the investigator's choice of paclitaxel, docetaxel or vinflunine according to the design of KEYNOTE-045 at the time of the second interim analysis (IA2). There was no cross-over allowed in the study protocol. Subjects were allowed, however, to receive subsequent therapies after progression of disease if their treating physicians deemed appropriate and this information was collected in the electronic database. In the submission document, we used wordings such as "treatment switching" to describe subsequent therapy. To avoid confusion, this will be described as "subsequent therapy" in Table 4 below and throughout this response.

Several subjects in the control arm received subsequent therapy with anti-PD-1/PD-L1 agents, as noted in Table 4 below:

Table 4: Subsequent therapies received by subjects in KEYNOTE-045

KEYNOTE-045[a]	Control[b]	Pembrolizumab[b]
Main Population		
Subsequent anti PD-L1/anti PD-1 therapies received	33 (22)	2 (2)
anti-PDL1 monoclonal antibody (unspecified)	1 (1)	
atezolizumab	7 (4)	2 (2)
avelumab	2 (2)	
durvalumab	3 (2)	
nivolumab	4 (3)	
pembrolizumab	16 (10)	

a: Database Cutoff Date: 07SEP2016

b: Results in table: Number of patients who subsequently received Anti PD-L1 / Anti PD-1 Treatments (Number of patients who subsequently received Anti PD-L1 / Anti PD-1 Treatments who had disease progression prior to receiving these subsequent therapies)

Following the Data Monitoring Committee (DMC) review of IA2 results, and given the overall survival benefit of pembrolizumab over chemotherapy in all subjects, the protocol was amended, and subjects in the control arm were given the opportunity to cross-over and receive pembrolizumab upon disease progression. Please note that efficacy results post IA2 are not currently available.

A13. What is the definition for drug-related adverse events: "possibly", "probably", and "definitely"? (company submission page 152)

In KEYNOTE-045, investigators were asked to assess the following components, when assessing for relationship between the adverse events (AEs) and the study drug, as had been detailed in the study protocol:

Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: if a rechallenge is planned for an adverse event which was serious and which may have been caused by the sponsor's product, or if reexposure to the sponsor's product poses additional potential significant risk to the subject, then the rechallenge must be approved in advance by the sponsor clinical director as per dose modification guidelines in the protocol.
Consistency with the Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

Upon this analysis, the investigator would record in case report forms the relationship of the AE as:

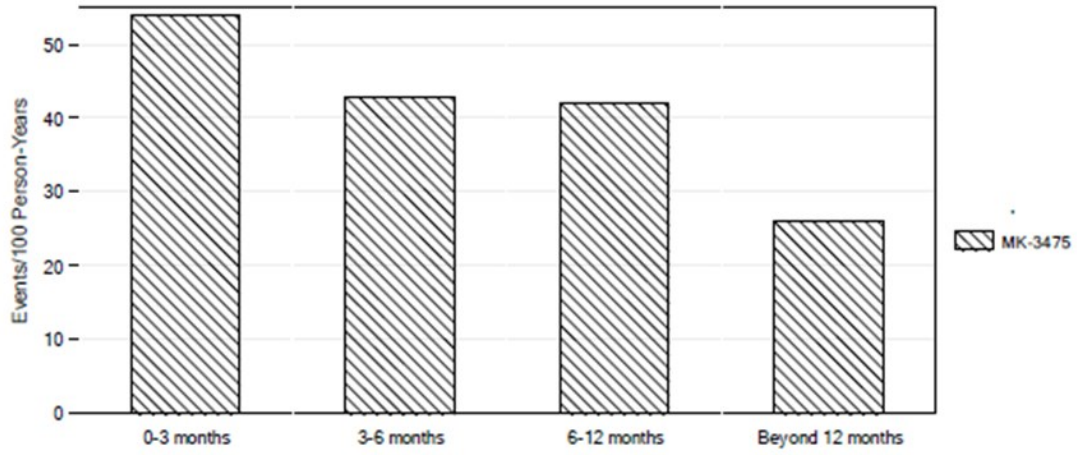
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)

The text alluding to "possibly", "probably" and "definitely" as assessment of relationship of AE to study treatment reflects how the assessment was done in studies prior to KEYNOTE-045. Please accept our apologies for any confusion caused.

A14. Please provide details of any longer-term adverse event data for pembrolizumab (in any indication), in particular adverse events of special interest?

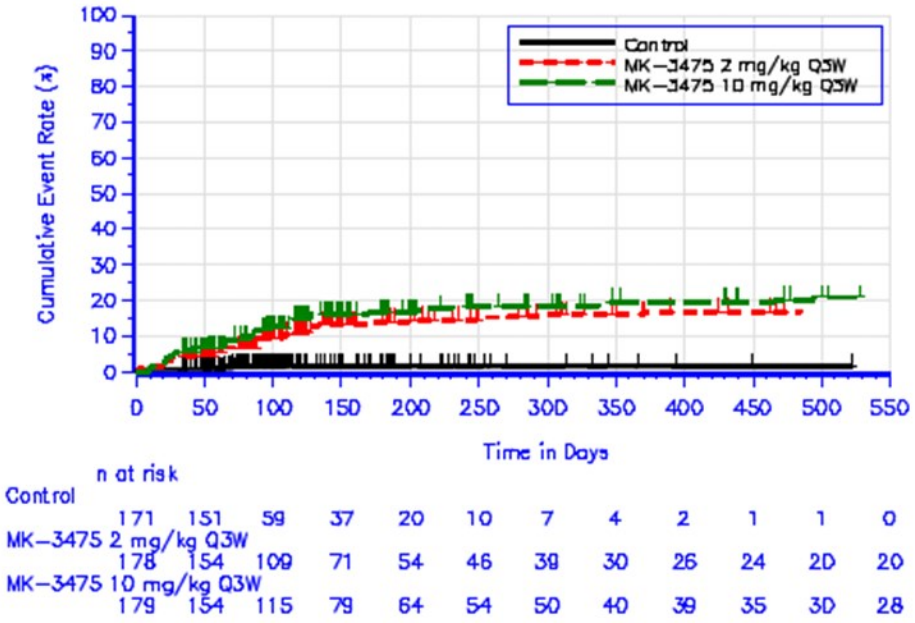
Long term safety data is available from KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006. The mean exposure from each study was 347.4 days (all doses); 232.3 days on 2 mg/kg Q3W, 276.2 days on 10 mg/kg Q3W; and 312 days (10 mg/kg Q2W) and 292 days (10mg/kg Q3W), respectively. Data from those studied did not reveal an increase in the incidence of adverse events of special interest (AEOSIs) over time, In fact, the highest incidences of AEOSIs occurred during the first 3 to 6 months on therapy and declined afterwards. No new safety signal was identified in association with longer exposure. Three figures from KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006 are included immediately below (see Appendix 2 for more details).

Figure 2: KEYNOTE-001 – Exposure adjusted AEOSI by observation period (including multiple occurrences of events (APaT population)



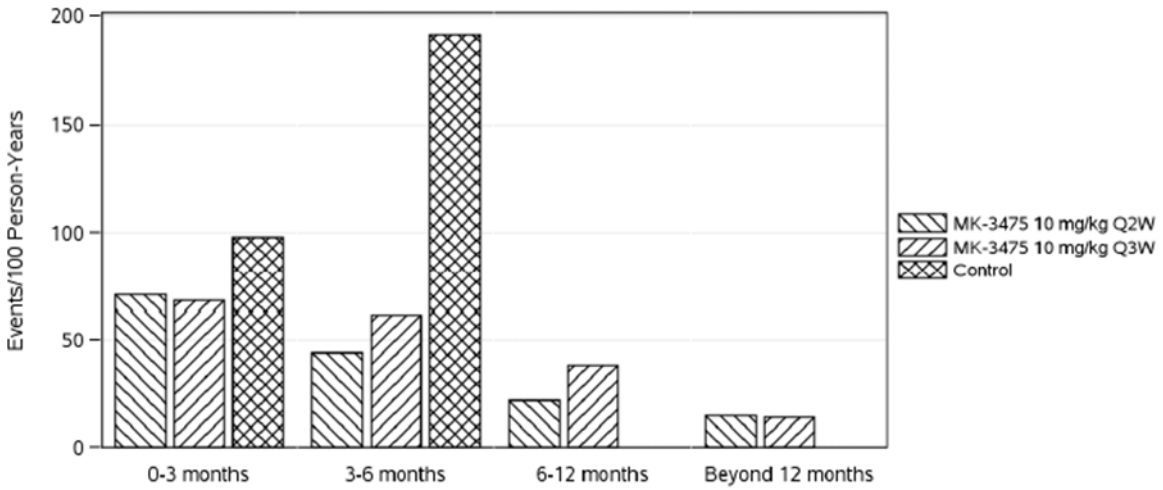
(Database Cutoff Date: 18SEP2015).

Figure 3: KEYNOTE-002 – Kaplan-Meier estimates of time to first AEOSI based on cumulative incidence analysis AEOSI – v10 (APaT population)



(Database Cutoff Date: 16NOV2015).

Figure 4: KEYNOTE-006 – Exposure-adjusted AEs by observation period (including multiple occurrences of events) – AEOSI (APaT population)

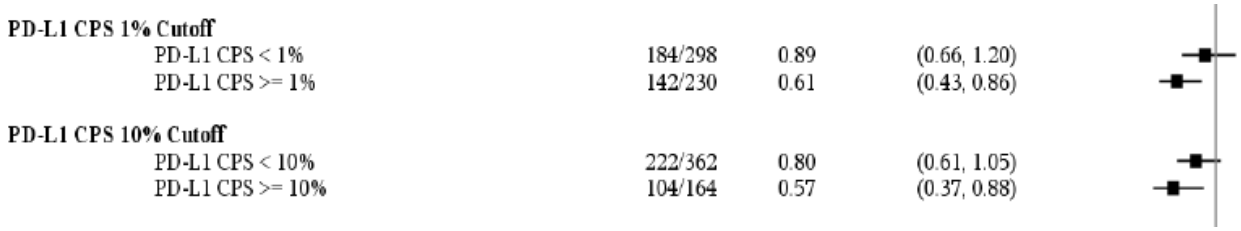


(Database Cutoff Date: 03DEC2015).

A15. Please provide subgroup clinical effectiveness data for the PD-L1 negative (non PD-L1 positive) subgroup for completeness.

The All subjects (ITT population) subgroup analysis demonstrates consistent overall survival benefit of pembrolizumab versus chemotherapy across all levels of PD-L1 expression, as highlighted in Figure 5 below which depicts a section of the Forest plot (originally presented as part of Figure 28 in our submission document)

Figure 5: KEYNOTE-45 Overall survival by PD-L1CPS level subgroup factor - Point estimate and nominal 95% confidence interval – All subjects (ITT population)



The Overall Survival Hazard Ratio (95% CI) for pembrolizumab vs. control in subjects with PD-L1 CPS <1% was 0.89 (0.66, 1.20) and for subjects with PD-L1 CPS <10% was 0.8 (0.61, 1.05). The Progression Free Survival Hazard Ratio (95% CI) for pembrolizumab vs. control in subjects with PD-L1 CPS <1% was 1.07 (0.82,1.39) and for subjects with PD-L1 CPS <10% was 1.04 (0.82, 1.33) (as depicted in Figure 29 in our submission document).Results of OS and PFS analysis in these subgroups were consistent with the results observed in the overall population.

The results of the analyses of overall survival adjusting for subsequent treatments received, in the sub-population of subjects defined by CPS <1%, specifically within the subgroup of subjects pre-assigned by investigator to docetaxel or paclitaxel pre-randomisation, is presented in Appendix 3.

A16. Please can the company explain why nearly 20% of control group had no post-baseline imaging?

Patients who did not have any post-baseline imaging assessments are reported as missing responses in the response summary and treated as non-responders in ORR analysis per ITT principle. A summary table with the reasons why patients did not have post-baseline imaging assessments for ORR analysis is provided in the Table 5 below:

Table 5: KEYNOTE-045 Reasons for missing responses in ORR analysis

Reason for Missing Response in ORR Analysis	Control	Pembrolizumab	Total
Discontinued from study prior to Week 9 scheduled scan	22	27	49
Randomized but never treated	17	4	21
Discontinued treatment due to a reason other than progressive disease, remained in follow-up, but received new anti-cancer treatment prior to Week 9 scheduled scan	3	0	3
Discontinued treatment, remained in follow-up, but did not have post randomization image due to patient's clinical deterioration	3	0	3
Discontinued treatment prior to Week 9 scheduled scan and withdrew consent from study procedures	2	0	2
Discontinued treatment prior to Week 9 scheduled scan due to clinical progression or adverse event and did not continue into first course follow-up with imaging. Subjects died within 11 weeks of randomization.	4	0	4
Total	51	31	82

Reasons for discontinuing from the study prior to the first scheduled post-baseline scan at Week 9 (N=49) include: death (control: 9, pembrolizumab: 17); adverse event (control: 7, pembrolizumab: 8) and consent withdrawal (control: 6, pembrolizumab: 2).

A17. The company submission (page 90) states that "PD-L1 strongly positive subjects and all subjects were included in the multiplicity controlled statistical testing" but on page 106 of the submission it states that the p-value for objective response rate for those with PD-L1 combined positive score ≥10% compared with control states was not multiplicity adjusted. Is this an error?

No, this not an error. Primary efficacy outcomes (OS and PFS) for all subjects and PD-L1 CPS>10% subjects were included in the multiplicity controlled statistical testing (as stated on page 88 of the submission document). Once testing of all primary efficacy outcomes was performed, residual alpha was rolled to the secondary endpoint of ORR in all subjects. This is the only secondary endpoint included in the multiplicity analysis. The secondary endpoint of ORR in PD-L1 CPS>10% subjects was not multiplicity controlled. Nonetheless, the objective response rate was greater in the pembrolizumab arm (21.6% versus 6.7%) in the PD-L1 CPS>10% subjects and the non-multiplicity controlled p value was 0.00020.

Further details concerning multiplicity adjustments were provided in Appendix 6 (Multiplicity) of the submission.

A18. The company submission (page 44 and elsewhere) says studies of potential relevance for the indirect comparisons were RCTs with comparisons between any interventions of interest. However, the list of included studies of potential relevance (company submission table 49) include those with comparisons with other interventions (e.g. best supportive care). Please clarify the inclusion criteria for the indirect comparison.

As mentioned in section 4.1.2 of the submission document, to meet the requirements of different regulatory authorities, all the comparators recommended for treatment of advanced/unresectable or metastatic urothelial carcinoma with progression after treatment with a platinum-based chemotherapy were included in the search strategy (Appendix 2 of the submission document). However, to address the decision problem set by NICE, only studies with comparators relevant to the UK setting were included (see PICOS eligibility criteria in Table 5 of submission document).

The comparators of interest when attempting to identify any studies of relevance to the UK clinical practice for an indirect comparison were as follows (as detailed in section 4.10.2 of the submission):

- Platinum-based chemotherapy
  - Paclitaxel/Gemcitabine
  - Carboplatin/Paclitaxel
  - Cisplatin+gemcitabine
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
- Docetaxel
- Paclitaxel

Trial NCT00315237, although identified in the overall search to satisfy worldwide regulatory authorities, should have been excluded from Table 49 of the submission document and further discussion in section 4.10 of the submission, given this study included only interventions which are not of interest to the UK setting (i.e. BSC and vinflunine). Please accept our apologies for this oversight and any confusion caused.

Section C: Textual clarifications and additional points

C1. Page 103 of the company submission – please can you confirm whether this should be “at least 1 post-baseline imaging” rather than “at least 1 baseline imaging”? Also, please explain what happened to the other patients who did not have post-baseline imaging, as the sample size for both arms is lower than the total for each arm? Please also confirm that using people with imaging as the denominator gives a non-significant difference between the groups?

We can confirm that this was a typo, and it indeed should read “at least 1 post-baseline imaging” rather than “at least 1 baseline imaging”. Detailed information on the subjects who did not have post-baseline imaging is provided in A16.

The ORR analyses provided in the submission were based on the ITT population. All subjects, regardless of the status of post-baseline imaging, were included in the analysis. The ITT population consists of 542 (270 in the pembrolizumab arm and 272 in the control arm)

subjects. Among them, 82 subjects (31 in the pembrolizumab arm and 51 in the control arm) had no post-baseline imaging. Per the agency's request, a sensitivity analysis of ORR was conducted on subjects with post-baseline imaging. The 9.8% (95% CI: 2.7% - 17.0%) absolute improvement on ORR with a p-value of 0.0038 still demonstrates the statistically significant treatment effect (see Table 6 below).

Table 6: Analysis of Confirmed Objective Response Based on RECIST 1.1 per Central Radiology Assessment All Subjects with Post-Baseline Imaging (ITT Population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate(95 % CI)†	p-Value††
Control	221	31	14 (9.7,19.3)		
Pembrolizumab	239	57	23.8 (18.6,29.8)	9.8 (2.7,17.0)	0.00376

† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cutoff Date: 07SEP2016

C2. On page 106 of the company submission it states "ORR per confirmed RECIST 1.1 by central radiology assessment among subjects with PD-L1 CPS ≥10%" - can you confirm that the difference between the groups is not significant if using the denominator of people with at least 1 (presumably post-) baseline imaging assessment.

The ORR analyses provided in the submission were based on the ITT population. All subjects, regardless of the status of post-baseline imaging, were included in the analysis. The ITT population for subjects with CPS >=10% consists of 164 (74 in the pembrolizumab arm and 90 in the control arm) subjects. Among them, 32 subjects (12 in the pembrolizumab arm and 20 in the control arm) had no post-baseline imaging. As per the above request from the ERG, a sensitivity analysis of ORR was conducted on subjects with post-baseline imaging in the CPS>=10% group. Results are presented below in Table 7. The 21% (95% CI: 8.2% - 35.0%) absolute improvement on ORR with a p-value < 0.001 still demonstrate the remarkably strong treatment effect.

Table 7: Analysis of Confirmed Objective Response Based on RECIST 1.1 per Central Radiology Assessment - Subjects with PD-L1 CPS >= 10% and Post-Baseline Imaging (ITT Population)

Treatment	N	Number of Objective Response	Objective Response Rate(%)(95% CI)	Pembrolizumab vs Control	
				Estimate (95% CI)†	p-Value††
Control	70	6	8.6 (3.2,17.7)		
Pembrolizumab	62	16	25.8 (15.5,38.5)	21 (8.2,35.0)	0.00074

† Based on Miettinen & Nurminen method stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months); if no Subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % =0 versus H1: difference in % > 0.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cutoff Date: 07SEP2016

C3. With regard to tables 54-59 and table 61 of the company submission - please provide revised tables indicating when there is a statistically significant difference ($p < 0.05$) between groups for each event?

P-values were not reported for the by-group comparisons of adverse events (AEs) in this study. The rationale of this is based on the considerations that p-values are difficult to interpret for this type of safety analyses. Across the extremely large number of AE terms, the lack of multiplicity control on type 1 error would very likely result with false positive findings. The unlimited number of permutations and combinations in AE aggregations make it even harder to have a meaningful control of errors. In addition, many of such analyses are often underpowered due to the low incidences that may result in non-interpretable p-values regardless of the relative comparisons with the cutoff (e.g, > 0.05 or < 0.05).

For events with high incidence rate, the estimate of risk difference along with its 95% confidence interval can provide reasonable evidence of the by-treatment comparison. In this case the confidence interval can demonstrate the strength of treatment effect similarlyas p-value. For example, in the rainfall plot (Figure 31 of company submission document; presented below as Figure 6 for ease of reference) of high incidence events (incidence >=15% in one or more treatment groups), a confidence interval that excludes 0 is equivalent to a two-sided p-value < 0.05. In this plot, the by-treatment risk differences that are clearly in favour of pembrolizumab versus control are on AEs of Alopecia, Anaenimia, Neutropenia, Constipation, Asthenia, Nausea, Fatigue, Oedema peripheral. On the other hand, the risk difference that is clearly in favour of the control arm is on the AE of Pruritus.

Similarly, the rainfall plot on Grade 3-5 AEs provided below (Figure 7) demonstrates similar trends. The majority of the by-treatment risk differences are strongly in favour of pembrolizumab.

Figure 6: (originally presented as Figure 31 in submission document): KEYNOTE-045 Between-treatment comparisons in AEs: Selected AEs (incidence >=15% in one or more treatment groups) and sorted by risk difference of pembrolizumab (266) vs. control (255) - All subjects (APaT population)

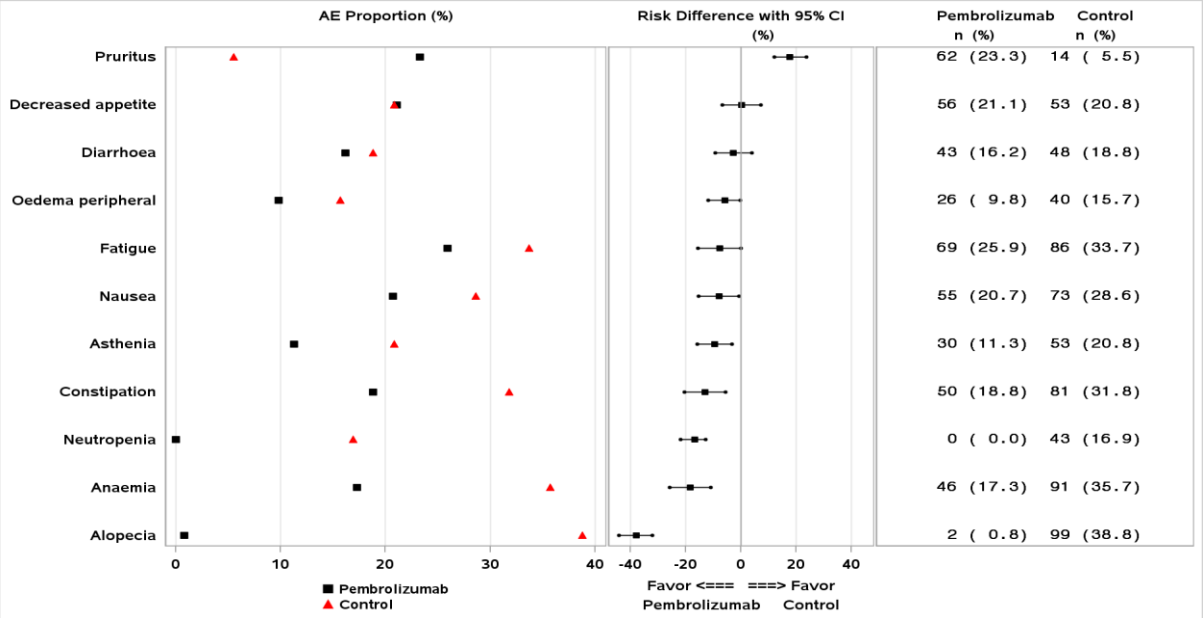
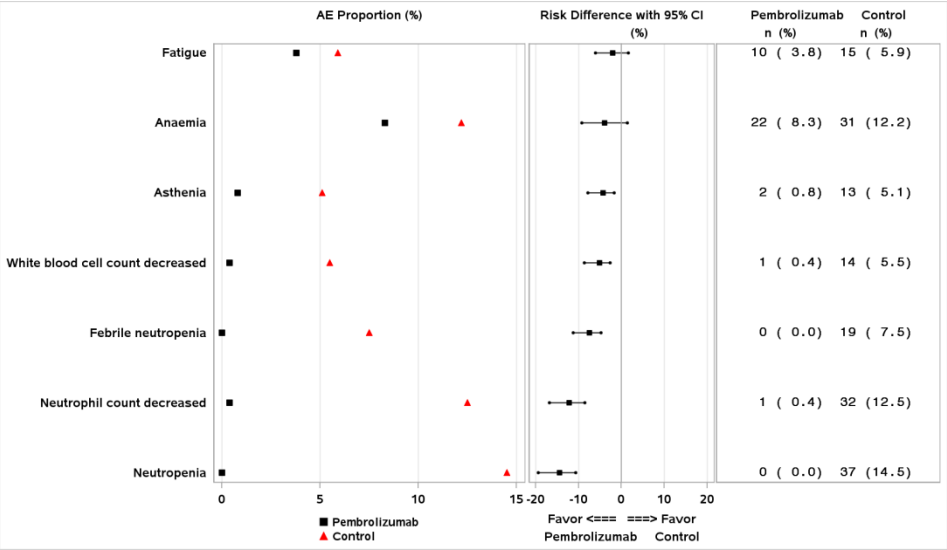


Figure 7: KEYNOTE-045 Between-treatment comparisons in Grade 3-5 Adverse Events Selected Adverse Events (Incidence >=5% in One or More Treatment Groups) and Sorted by Risk Difference of Pembrolizumab (266) vs. Control (255) - All Subjects (APaT population)



References:

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9. Clinicaltrials.gov. Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (MK-3475-052/KEYNOTE-52) 2017 [Available from: https://clinicaltrials.gov/ct2/show/NCT02335424?term=KEYNOTE-52&rank=1. [Accessed 15 March 2017]

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. **Priority question:** Table 66 in the company submission (page 181). Please can you clarify/elaborate why some analyses have not been undertaken? Please also provide Kaplan-Meier curves for overall survival adjusting for treatment switching using the RPSFT and IPCW methods.

MSD would like to clarify that for certain sub-populations, it was not possible to carry out the adjustment for switching using the simplified 2- stage model or IPCW model due to small sample sizes in the sub-population of interest. Where there were 10 or fewer switchers it was considered that models would not be sufficiently robust and provide highly sensitive adjusted estimates. Please find in the figures below the requested Kaplan-Meier curves.

Figure 1. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using RPSFT method for pembrolizumab vs UK SOC

Figure 2. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using IPCW method for pembrolizumab vs UK SOC

Figure 3. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using RPSFT method for pembrolizumab vs paclitaxel

Figure 4. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using RPSFT method for pembrolizumab vs docetaxel

Figure 5. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using IPCW method for pembrolizumab vs docetaxel

[redacted]

Figure 6. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using RPSFT method for pembrolizumab vs UK SOC for patients with CPS≥1%

[redacted]

Figure 7. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using IPCW method for pembrolizumab vs UK SOC for patients with CPS≥1%

[redacted]

Figure 8. Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using RPSFT method for pembrolizumab vs UK SOC for patients with CPS>10%

[redacted]

B2. Please explain why in Table 67 (page 182 of the company submission) 2-sided p-values are provided, whereas in the clinical effectiveness sections p-values are one-sided? Also, please clarify why the p-values have been retained from the intention-to-treat for the two (simplified two-stage and RPSFT) adjustments for treatment switching? The hazard ratio reported for the simplified two-stage adjustment is [redacted]. The ERG would expect there to be a p-value that is <0.05.

Two-sided p-values are typically used in HTA driven analyses whereas in the CSR one-sided p-values are given. It should be noted though that the decision rule for superiority of pembrolizumab 200 mg Q3W is maintained as the two-sided p-value is being compared with double the alpha level used in the CSR.

The p-value for the adjusted OS analysis using the RPSFT or the simplified 2-stage method is retained from the ITT analysis, provided that the same statistical test is used in the ITT analysis than in the adjusted analysis. The reason is that, under the null hypothesis of no treatment effect, there is no switchover effect and thus the test statistics of the RPSFT and the simplified 2-stage methods follow the same statistical distribution as the ITT test statistic.

As the p-value is the probability to obtain a more extreme value than the observed one under the null hypothesis, the p-value from the ITT analysis is preserved in the 2-stage model approach and the RPSFT approach.[1-3]

In Table 67, the ITT retained p-value is presented with the 95% CI calculated by bootstrap. When results are close to the limit of significance, apparent inconsistencies are possible as testing and estimation are using two different approaches.

It should be noted that for both the simplified 2-stage model and RPSFT approach, one needs to take into account the uncertainty in the estimate of the acceleration factor when estimating the standard error and hence confidence interval of the adjusted hazard ratio. This can be done in two different ways: a) by deriving the adjusted confidence interval from the ITT confidence interval and the retained p-value or b) by using a bootstrap methodology[2]. In table 67, the bootstrap methodology was utilized for the calculation of the 95% CI around the adjusted hazard ratio.

B3. With respect to table 67 (page 182 of the company submission), please provide further information on the models used to generate hazard ratios? Was a cox proportional-hazard model used?

For the OS analyses adjusted for treatment switchover, a stratified Cox proportional hazard model with Efron's method of handling of ties was used to estimate the magnitude of the treatment difference (i.e. hazard ratio). The stratification factors were Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months). In fact, in the switchover analyses, the same model than used to estimate the ITT hazard ratio was applied to the survival times adjusted for switchover. Adjustment of the survival times was done using the simplified 2-stage approach, the RPSFT approach or the IPCW approach.

B4. The company submission used a two-phase piecewise approach to derive overall survival. First phase used data directly from the Kaplan-Meier plots and in the second phase used data from the 40-week cut-off point and fitted with a log-normal curve to these data. Please justify why the log-normal fit was used for this extrapolation? The ERG understands that Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were derived for the fully fitted parametric models to the UK standard of care and the pembrolizumab arms. Additionally, please clarify if other

curves have been fitted to the cumulative hazard for overall survival (Figure 36, page 187).

MSD Question: We would like to better understand what the ERG mean when they say "Additionally, please clarify if other curves have been fitted to the cumulative hazard for overall survival (Figure 36, page 187).". Please could the ERG clarify if they want confirmation that other curves have been fitted to the OS KM curves?

ERG response: Sorry for not explaining the second part of this question clearly. There are two parts to this question:

1) The company have supplied cumulative hazard plots for the Kaplan-Meier data of overall survival (figure 36, page 183 of the company submission) and progression-free survival (figure 38, page 186 of the company submission). To the best of our knowledge, log-cumulative hazard plots are used to examine the change in hazards over time. Please can the company provide log-cumulative hazard plots for the for the Kaplan-Meier data of overall survival and progression-free survival.

   Please find below in Figure 9 and Figure 10 the log-cumulative hazard plot of OS and PFS, respectively.

Figure 9. Log-cumulative hazard plot of OS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and UK SOC based on KEYNOTE-045

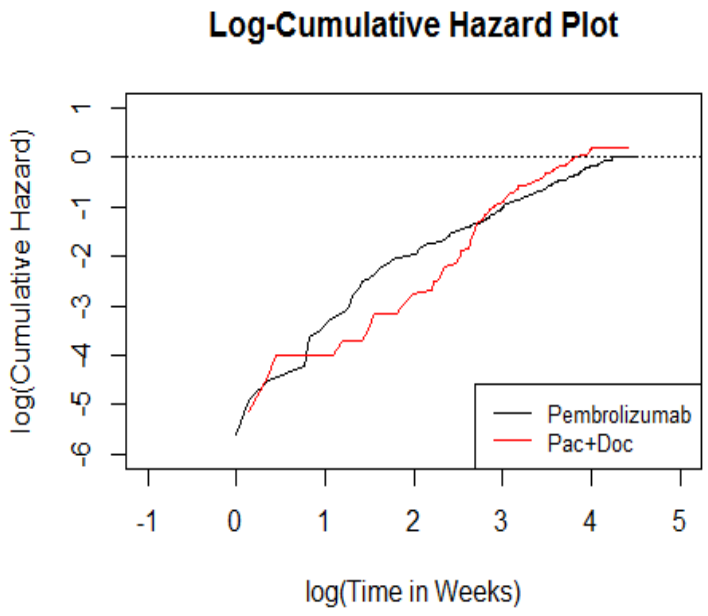
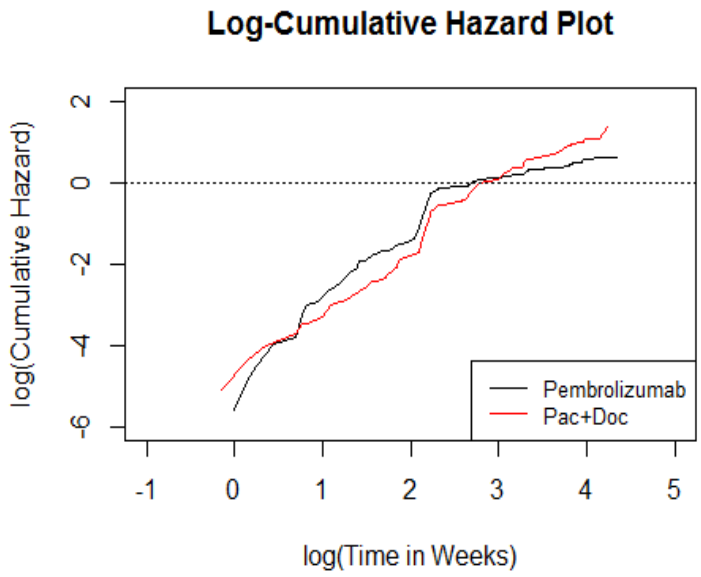


Figure 10. Log-cumulative hazard plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and UK SOC based on KEYNOTE-045



2) The company have supplied information on fitting several curves for the fully fitted parametric approach (table 69, page 184 of the company submission). Figure 37 (page 184 of the company submission) shows the company's preferred 2-phase piecewise model with a fitted log-normal curve after week 40. Can the company confirm whether curves other than log-normal were investigated for fitting to the 2-phase piecewise model and provide any information similar to table 69 for curves fitted for the 2-phase approach.

Table 69 in our submission refers to goodness-of-fit measures for OS with cut-off at 40 weeks. We would like to apologise for the incorrect label of the table and would like to clarify that we have explored alternative parametric curves for extrapolation at 40 weeks. Justification for selecting the log-normal distribution as the most appropriate parametric curve is provided in our submission. For completeness, please find in the Table 1 below the goodness-of-fit measures for the fully fitted parametric approach.

Table 1. Fitted exponential curves for the fully fitted parametric approach for OS

Fitted Function	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC
Exponential	1612.4	1616	1092.5	1095.7
Weibull	1612.9	1620.1	1085.7	1092.2
Gompertz	1608.1	1615.3	1093.5	1099.9
Llogistic	1606.3	1613.5	1075.1	1081.5
Lnormal	1601.5	1608.7	1078.2	1084.6
GenGamma	1602.8	1613.6	1079.5	1089.1

B5. **Priority question:** Please can you provide the following individual patient data from KEYNOTE-045, by each sub-group and excluding people who received vinflunine treatment? (see the table below)

Table 1: Individual patient-level data requested by the Evidence review group

Patient ID number	Comparator	Time of event or censoring	Event or censoring
Intention-to-treat			
1	• UK SOC (docetaxel and paclitaxel) • Docetaxel • Paclitaxel		
2			
3			
4			
Etc.			
PD-L1 positive (CPS≥1%)			
1	UK SOC (docetaxel and paclitaxel)		
2			
3			
Etc.			
PD-L1 strongly positive (CPS≥10%)			
1	UK SOC (docetaxel and paclitaxel)		
2			
3			
Etc.			
PD-L1 negative			
1	UK SOC (docetaxel and paclitaxel)		
2			
3			
Etc.			
Event = 1 Censoring = 0			

Please find the individual patient level data in Appendix 4.

Cost-effectiveness analyses

While updating the cost-effectiveness model for the clarification questions, some errors have been identified and corrected in the model. These include the following:

- *Estimation Sheet:*
  - Removed linkage of macro to the columns having KMs (Column K, S, AA, AI, AQ, AY; Row 10 onwards) in order to ensure that KM data are updated properly.
  - Updated the formula in PSA column BO(9:16) and BX(9:16)
- *Markov Sheet:*
  - Removed (-AT8) from the formulae in AV5 and (-DH8) from the formulae in DJ5, since it is already subtracted from Column AU and DI5.
  - Added maximum treatment duration for comparator arm in column BS (BS8 onwards)
- *KN045_1 and KN045_2 sheets:* Efficacy data changed for Scenario 17(Paclitaxel only) and Scenario 19(Docetaxel only). This is because a patient was wrongly pre-assigned to docetaxel arm instead of paclitaxel.

MSD would like to apologise for any inconvenience caused. Please find an addendum in Appendix 5 including updated cost-effectiveness results.

B6. **Priority question**: Can you confirm whether the Patient Access Scheme (PAS) referred to throughout the company submission is conditional on positive guidance for another indication. If so, please use the currently operational PAS in all further base-case analyses. Furthermore please submit an addendum of all previously supplied cost-effectiveness analyses using the currently operational PAS.

MSD confirms that the Patient Access Scheme (PAS) referred to throughout our submission document is conditional on positive guidance for another indication. An addendum of all cost-effectiveness analyses using the current PAS, can be found in Appendix 6

B7. **Priority question**: In the economic model the EQ-5D data also includes vinflunine. Please can the company provide the utility values (based on time to death, progression status and adverse events), an economic model and the corresponding results without vinflunine (only include paclitaxel and docetaxel) as this is not UK standard of care.

Please find below the EQ-5D health utility scores excluding utility values from patients receiving vinflunine in KEYNOTE-045 by time-to-death and progression status in Table 2 and Table 3, respectively. The utility values for individuals with and without Grade 3+ AEs are provided in Table 4. Please find in Table 5 below the base-case cost-effectiveness analyses results for the requested scenario.

Table 2: EQ-5D health utility scores by time-to-death

Time to Overall Survival (days)	Pembrolizumab					UK SOC (Paclitaxel and Docetaxel)					Pembrolizumab and UK SOC Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥360*	77	259	0.765	0.017	(0.731, 0.799)	28	93	0.823	0.021	(0.782, 0.864)	105	352	0.78	0.014	(0.753, 0.808)
[180, 360)	51	158	0.686	0.022	(0.643, 0.728)	34	111	0.673	0.019	(0.635, 0.710)	85	269	0.68	0.015	(0.651, 0.710)
[90, 180)	75	158	0.566	0.025	(0.517, 0.615)	52	106	0.595	0.028	(0.539, 0.650)	127	264	0.578	0.019	(0.541, 0.614)
[30, 90)	63	106	0.457	0.037	(0.384, 0.529)	55	107	0.414	0.04	(0.335, 0.494)	118	213	0.435	0.027	(0.382, 0.489)
<30	29	35	0.336	0.077	(0.180, 0.493)	13	14	0.337	0.127	(0.062, 0.612)	42	49	0.337	0.065	(0.206, 0.467)

† n=Number of patient with non-missing EQ-5D score
‡ n=Number of records with non-missing EQ-5D score
*This time-to-death category includes the records of the patients whose death dates were observed or censored ≥ 360 days after the report of EQ-5D scores. Other categories only include the records of patients with an observed death date.

Table 3: EQ-5D health utility scores by progression status

	Pembrolizumab					UK SOC (Paclitaxel and Docetaxel)					Pembrolizumab and UK SOC Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	234	907	0.757	0.009	(0.740, 0.775)	150	464	0.709	0.013	(0.685, 0.734)	384	1371	0.741	0.007	(0.727, 0.755)
Progressive	178	488	0.680	0.015	(0.650, 0.709)	100	172	0.554	0.03	(0.495, 0.613)	278	660	0.647	0.014	(0.620, 0.674)

† n=Number of patients with non-missing EQ-5D score
‡ n=Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included

Table 4: Utility values for individuals with and without Grade 3+ AEs in the KN045 clinical trial

	Pembrolizumab					UK SOC (Paclitaxel and Docetaxel)					Pembrolizumab and UK SOC Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression -Free with Grade3+ AE	51	110	0.586	0.032	(0.523, 0.649)	59	115	0.666	0.028	(0.611, 0.721)	110	225	0.627	0.021	(0.585, 0.668)
Progression -Free w/o Grade3+ AE	209	797	0.781	0.009	(0.764, 0.798)	124	349	0.724	0.014	(0.696, 0.751)	333	1146	0.764	0.007	(0.749, 0.778)

Table 5: Base-case results (discounted, with PAS) using EQ-5D values excluding vinflunine

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£20,938	1.59	1.09	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,115	0.86	£45,712
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B8. **Priority question**: The cost-effectiveness results for the PD-L1 subgroups as reported in the company submission (appendix pages 268-270) are key and the results could not be exactly replicated by the ERG. Please can the company either explain the methodology used to produce these results or provide the correct corresponding economic models including tornado diagrams, probabilistic results (expected ICERs and cost-effectiveness acceptability curve) and survival modelling methods.

Patients with CPS≥1%

For the subgroup of patients with PD-L1 status, a 32-week cut-off was selected as a point for extrapolation. Unlike our base-case, the 40-week cut-off point for the UK SOC with RPSFT adjustment had a small number of patients left at risk. Therefore, the extrapolation from this point would have been uncertain.

The exponential curve presented the closest statistical fit to the data for both pembrolizumab and the UK SOC. However, please note that the exponential curve might underestimate the UK SOC with only 0.4% OS rates at 5 years. Alternative scenario analysis is presented below applying a log-normal distribution, in line with our base-case, with 7.5% OS rate in UK SOC at 5 years which is closer to the estimates observed by Cancer research UK.

Separate parametric curves were fitted to the treatment duration data from KEYNOTE-045 based on the AIC/BIC measures for this subgroup of patients. The function with the lowest AIC/BIC is Weibull for pembrolizumab and exponential for the UK SOC.

Table 6. Goodness-of-fit measures for OS with cut-off at 32 weeks

Fitted Function	Pembrolizumab		UK SOC, ITT		UK SOC, RPSFT adjustment		UK SOC, IPCW adjustment	
	AIC	AIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	**207**	**209.2**	**148**	**149.5**	**40.6**	**41.9**	**119.5**	**120.9**
Weibull	208.8	213.1	149.8	152.9	42.6	45.1	121.5	124.2
Gompertz	209	213.3	148.7	151.9	42.6	45.1	121.3	124

Llogistic	209.1	213.4	149	152.1	42.6	45.1	121.1	123.8
Lnormal	210.9	215.2	149.6	152.8	43	45.5	122.3	125
GenGamma	210.7	217.2	151.3	156.1	44.5	48.3	123.4	127.5

Table 7. Goodness-of-fit measures for ToT

Fitted Function	Pembrolizumab		UK SOC	
	AIC	AIC	AIC	BIC
Exponential	768.4	771.1	**514.1**	**516.4**
Weibull	**748.4**	**753.8**	515.3	519.9
Gompertz	759.8	765.1	516.1	520.8
Llogistic	756	761.4	534.3	539
Lnormal	761.7	767	542.6	547.3
GenGamma	749.5	757.6	514.2	521.2

Please find below the deterministic and probabilistic results for pembrolizumab vs UK SOC for patients with CPS≥1%. For completeness, alternative scenario is presented with log-normal parametric distribution for OS extrapolation.

Table 8. Deterministic incremental cost-effectiveness results for the comparison of pembrolizumab vs. UK SOC (discounted, with PAS)* - 32-week cut-off point

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**The two-stage adjustment could not be implemented in this population*

Table 9. Scenario analyses results for the comparison of pembrolizumab vs. UK SOC (discounted, with PAS)* - 32-week cut-off point using log-normal parametric curve for OS extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**The two-stage adjustment could not be implemented in this population*

Figure 11. Tornado diagram presenting the results of the deterministic sensitivity analysis for pembrolizumab vs UK SOC for patients with CPS≥1% (ITT population).

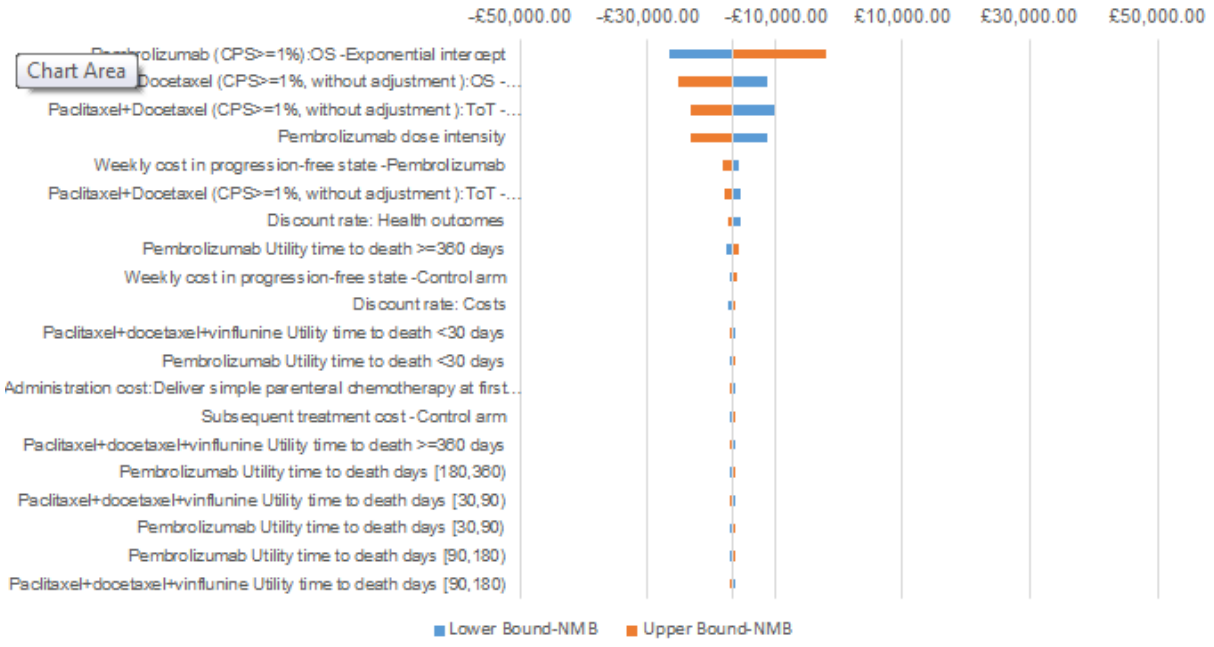


Figure 12. Tornado diagram presenting the results of the deterministic sensitivity analysis for pembrolizumab vs UK SOC for patients with CPS≥1% (with RPSFT adjustment).

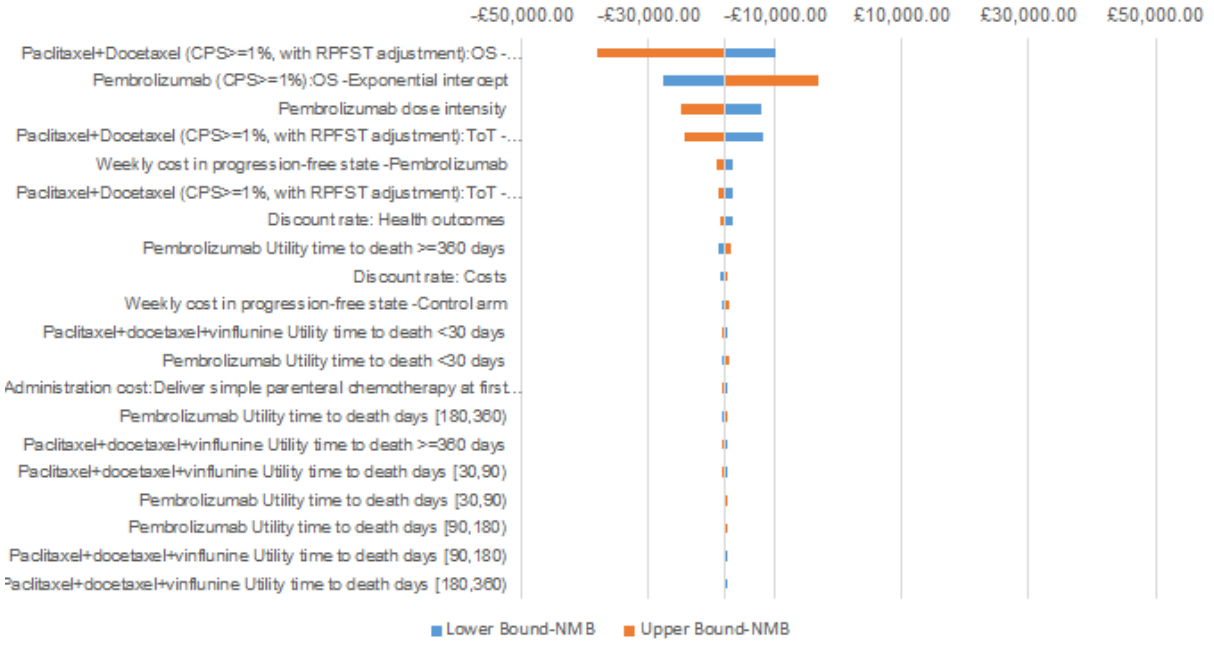


Figure 13. Tornado diagram presenting the results of the deterministic sensitivity analysis for pembrolizumab vs UK SOC for patients with CPS≥1% (with IPCW adjustment).

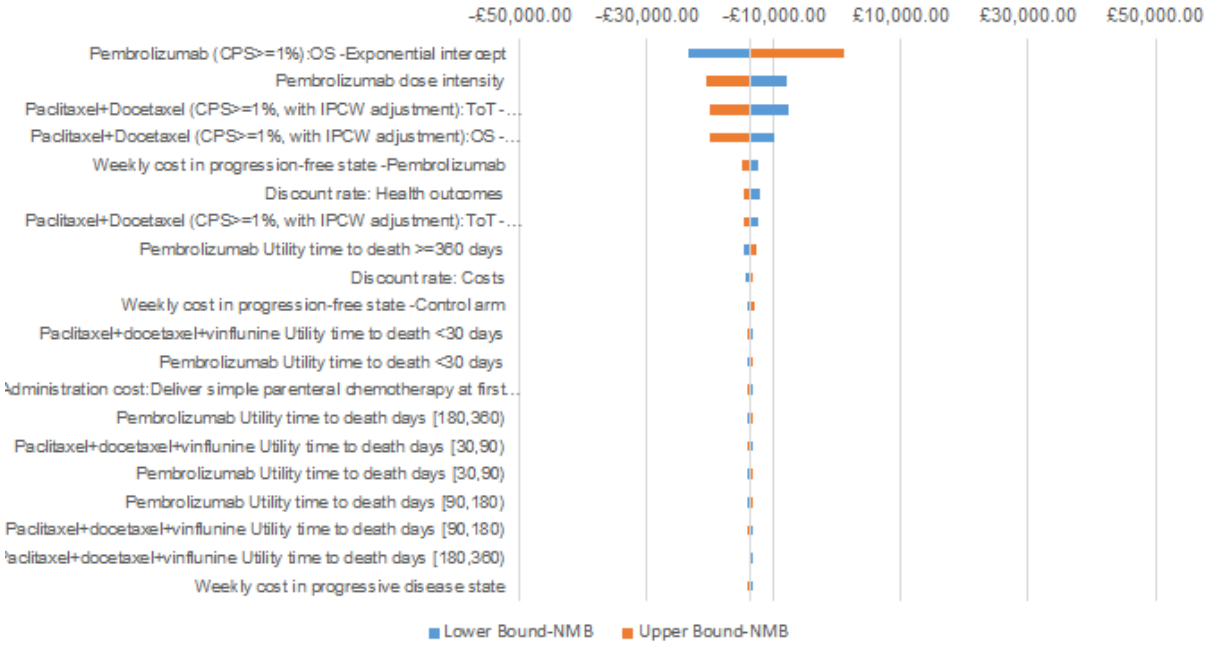


Table 10. Probabilistic incremental cost-effectiveness results for the comparison of pembrolizumab vs. UK SOC (discounted, with PAS)* - 32-week cut-off point – exponential distribution

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						
**The two-stage adjustment could not be implemented in this population*						

Table 11. Probabilistic incremental cost-effectiveness results for the comparison of pembrolizumab vs. UK SOC (discounted, with PAS)* - 32-week cut-off point – log-normal distribution

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						
**The two-stage adjustment could not be implemented in this population*						

Patients with CPS≥10%

Similar to the CPS≥1% subgroup, for patients with CPS≥10%, a 24-week cut-off was selected as a point for extrapolation. This is because at the 40-week and 32-week cut-off points for the UK SOC with RPSFT adjustment, either no or a small number of patients were at risk. Therefore, a 24-week cut-off point was deemed more appropriate. Although, the exponential distribution was a better fit based on AIC/BIC, the log-normal distribution was selected for consistency between ITT and RPSFT adjusted UK SOC population and because, as mentioned above, it did not underestimate the OS rates for the UK SOC arm at 5 years.

Table 12. Goodness-of-fit measures for OS with cut-off at 24 weeks

Fitted Function	Pembrolizumab		UK SOC, ITT		UK SOC, RPSFT adjustment	
	AIC	AIC	AIC	BIC	AIC	BIC
Exponential	163.3	165.1	125.1	126.4	22.5	23.5
Weibull	164.8	168.3	127.1	129.7	21.5	23.6
Gompertz	164.5	168	126.7	129.3	22.4	24.5
Llogistic	164.7	168.2	126.1	128.7	21.3	23.4
Lnormal	**166**	**169.6**	**125.3**	**127.9**	**20.9**	**22.9**
GenGamma	166.8	172	126.5	130.4	20.2	23.3

Table 13. Deterministic incremental cost-effectiveness results for the comparison of pembrolizumab vs. SOC for patients with CPS≥10% (discounted, with PAS)* - 24 weeks extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**The two-stage and IPCW adjustments could not be implemented in this population*

Figure 14. Tornado diagram presenting the results of the deterministic sensitivity analysis for pembrolizumab vs UK SOC for patients with CPS≥10% (ITT population).

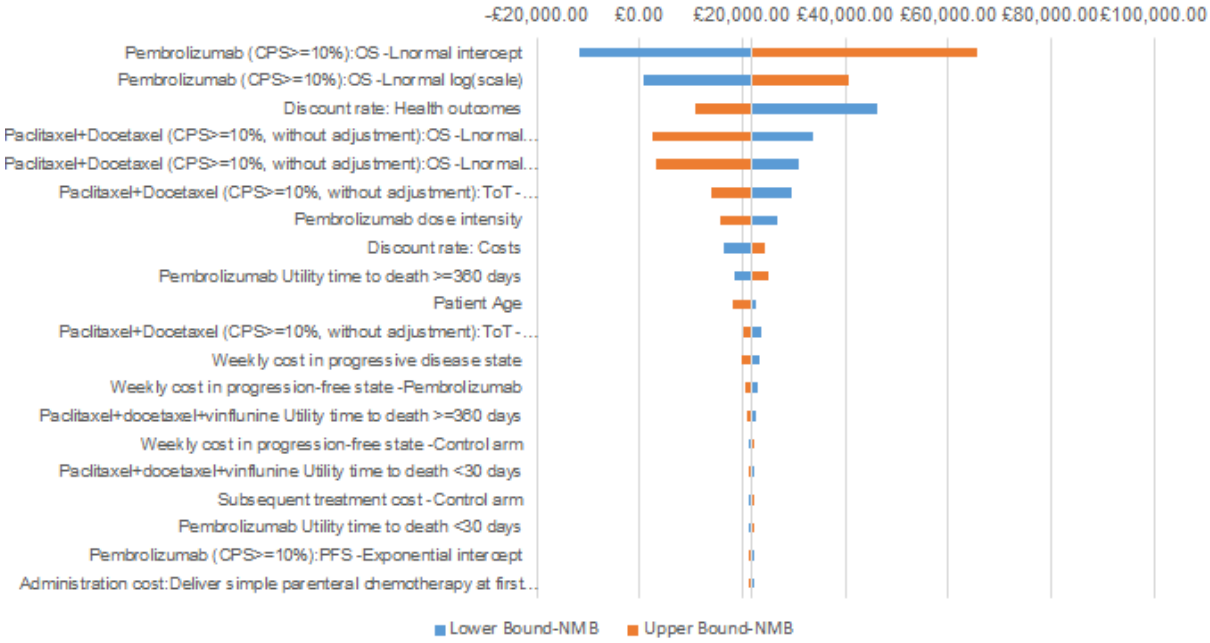


Figure 15. Tornado diagram presenting the results of the deterministic sensitivity analysis for pembrolizumab vs UK SOC for patients with CPS≥10% (with RPSFT adjustment).

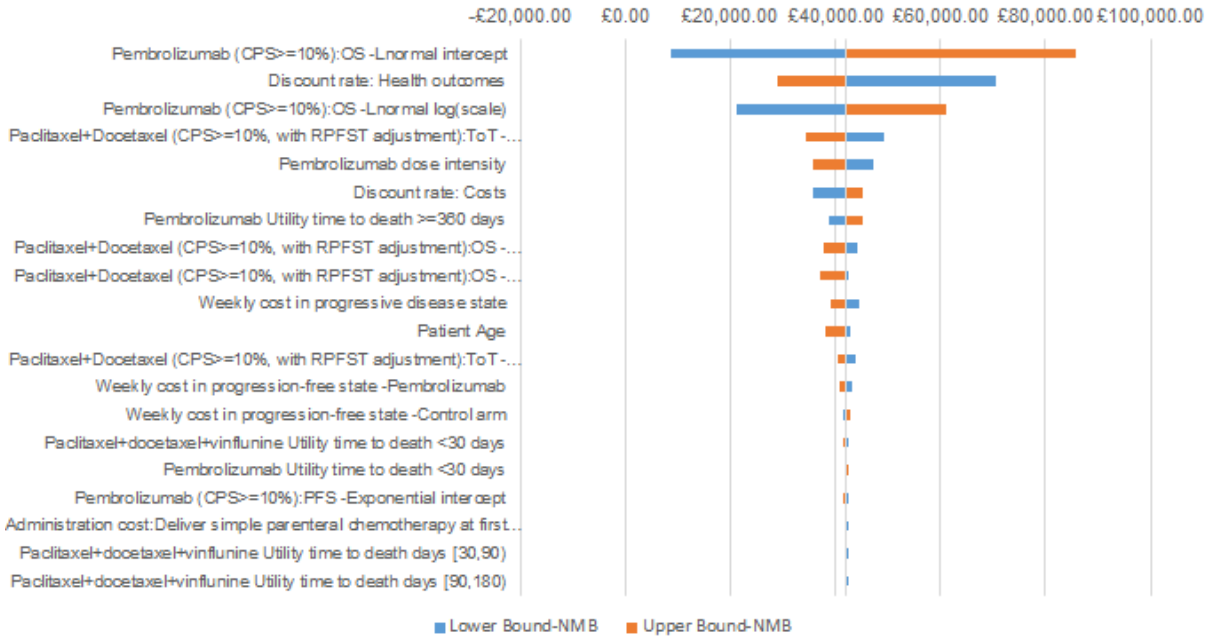


Table 14. Probabilistic incremental cost-effectiveness results for the comparison of pembrolizumab vs. SOC for patients with CPS≥10% (discounted, with PAS)* - 24 weeks extrapolation

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**The two-stage and IPCW adjustments could not be implemented in this population*

Cost-effectiveness acceptability curves for the PD-L1 subgroups are presented in MSD's response to question B9 below.

B9. **Priority question**: For all cost-effectiveness analyses as reported in the appendix please can the company provide cost-effectiveness acceptability curves.

Please find below the cost-effectiveness acceptability curves for the cost-effectiveness analyses of pembrolizumab compared to paclitaxel, docetaxel, and UK SOC based on histology and PD-L1 subgroups. Please note that all subgroup analyses are exploratory and should be interpreted with caution, especially due to the small sample size.

Figure 16. Cost-effectiveness acceptability curves for pembrolizumab vs paclitaxel (ITT population)

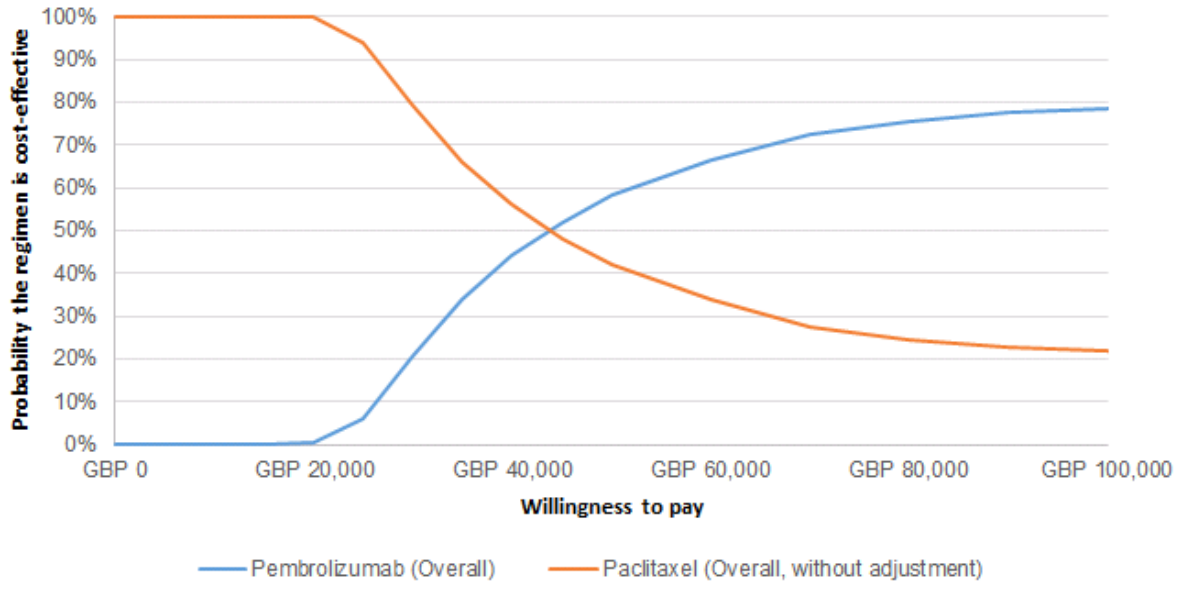


Figure 17. Cost-effectiveness acceptability curves for pembrolizumab vs paclitaxel for patients with RPSFT adjustment

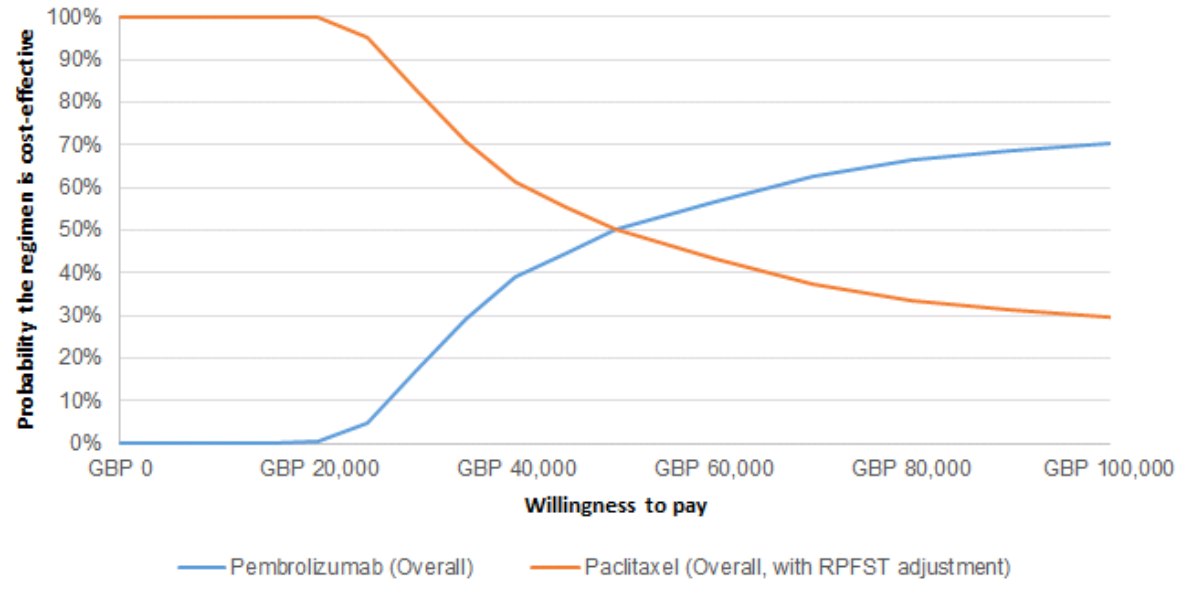


Figure 18. Cost-effectiveness acceptability curves for pembrolizumab vs docetaxel (ITT population)

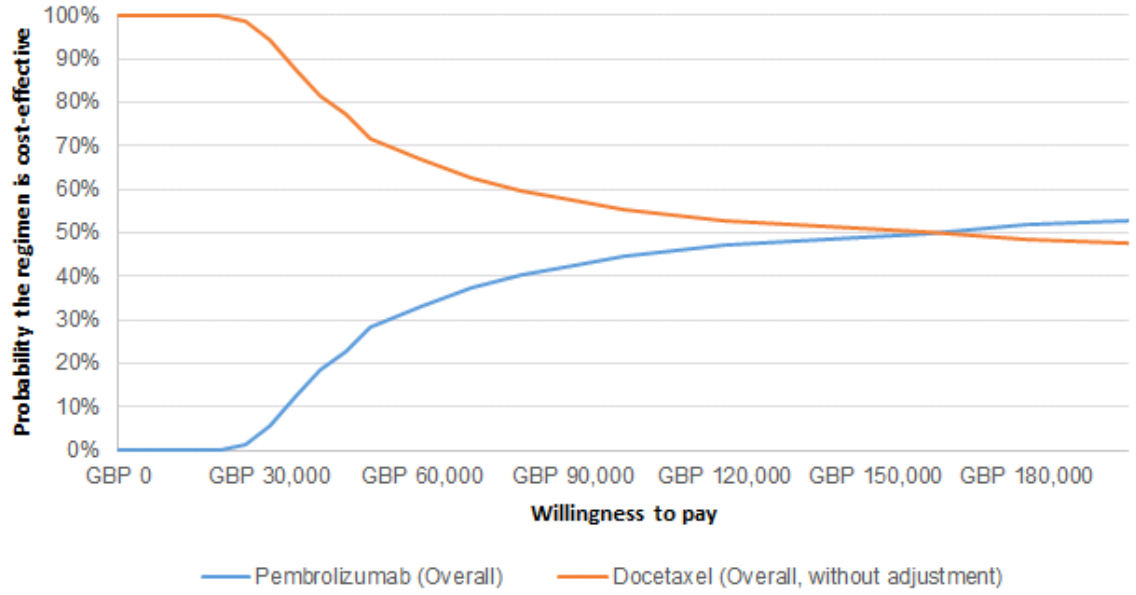


Figure 19. Cost-effectiveness acceptability curves for pembrolizumab vs docetaxel (with RPSFT adjustment

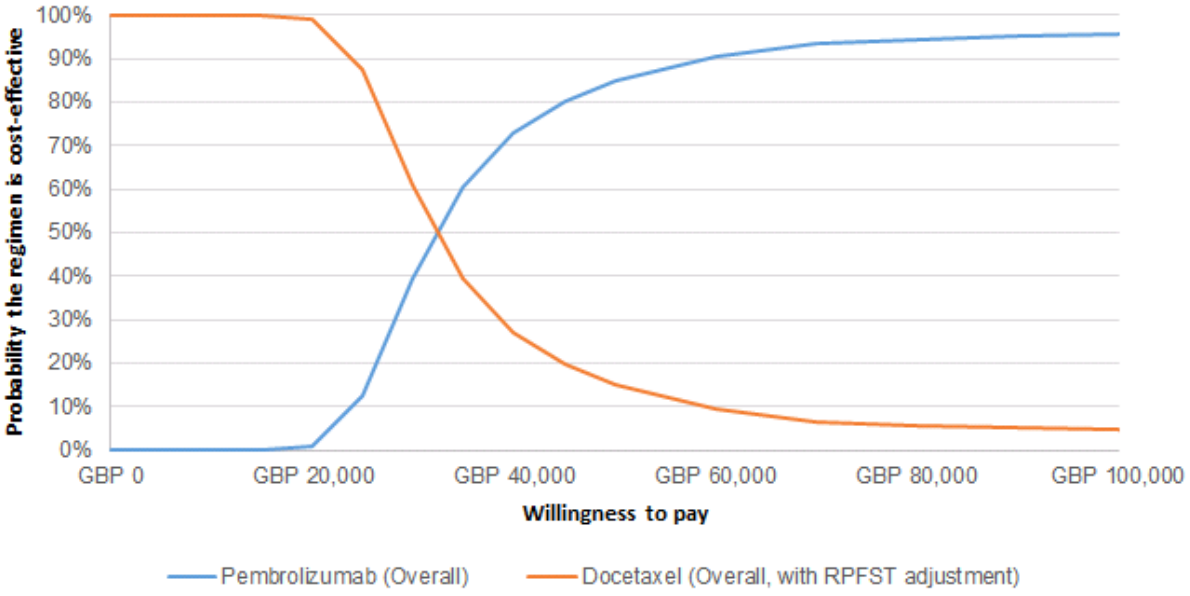


Figure 20. Cost-effectiveness acceptability curves for pembrolizumab vs docetaxel (with IPCW adjustment

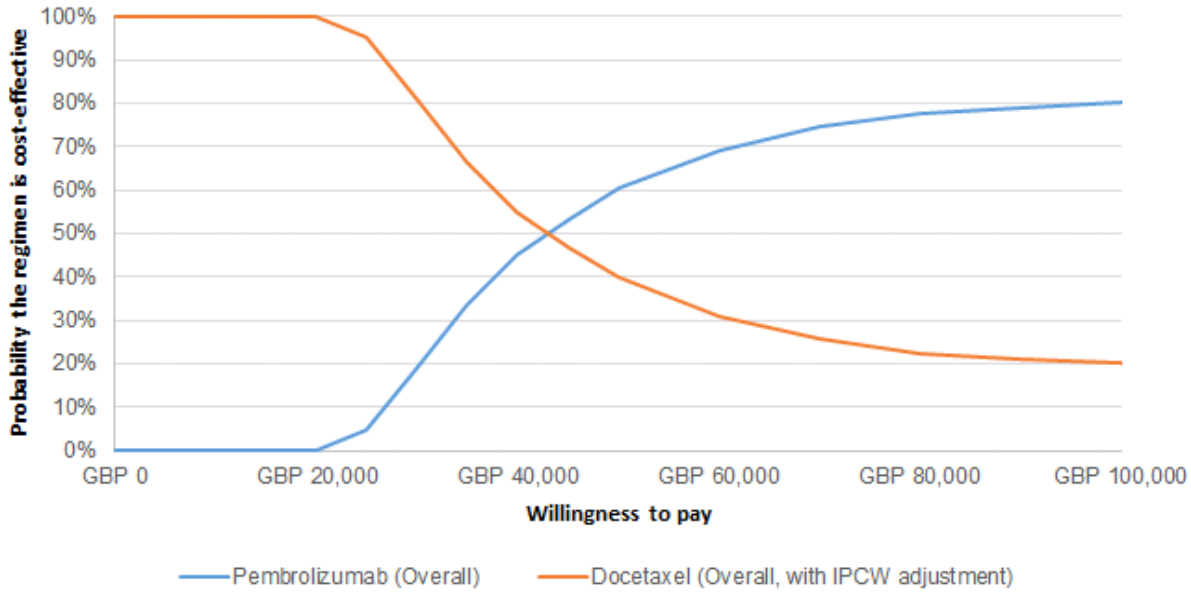


Figure 21. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with predominantly transitional cell urothelial carcinoma

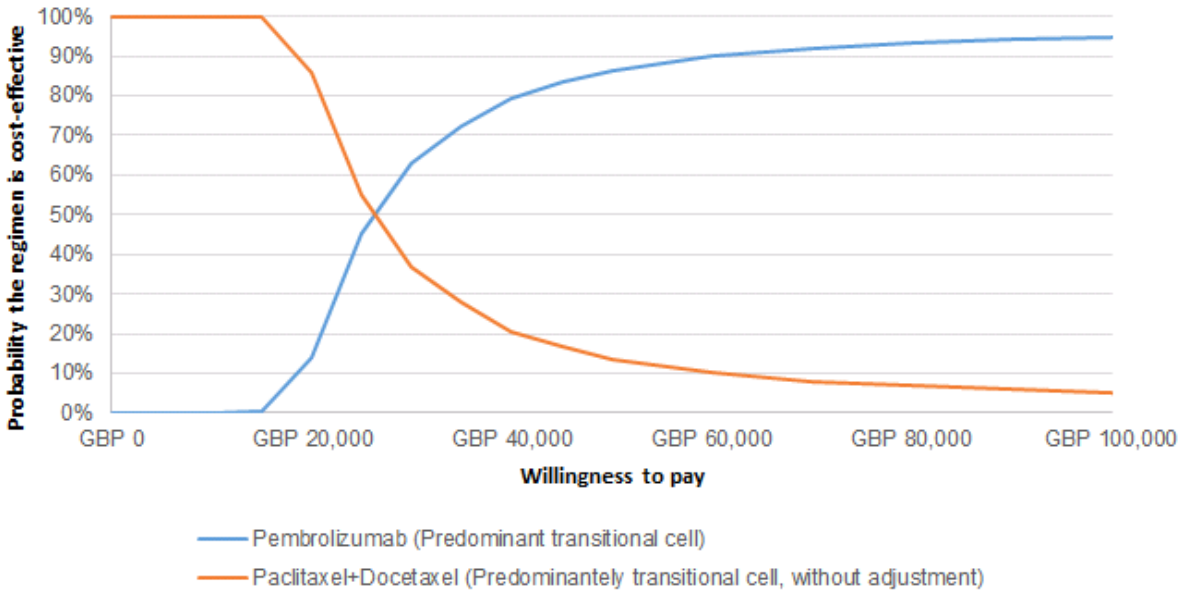


Figure 22. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with pure transitional cell urothelial carcinoma

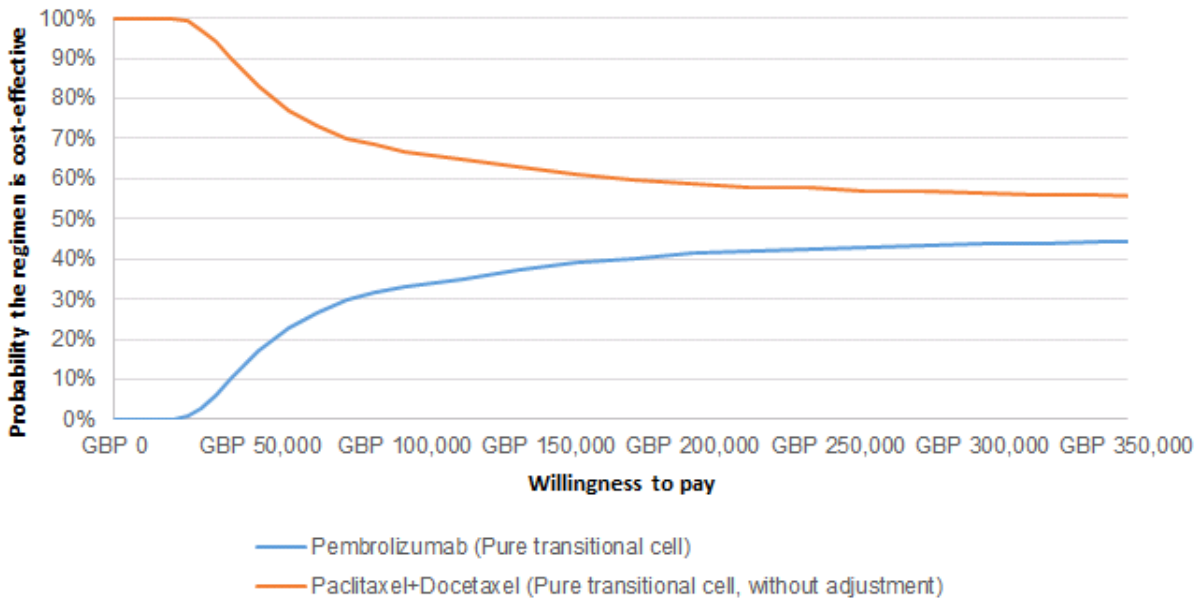


Figure 23. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with CPS≥1% (ITT population)

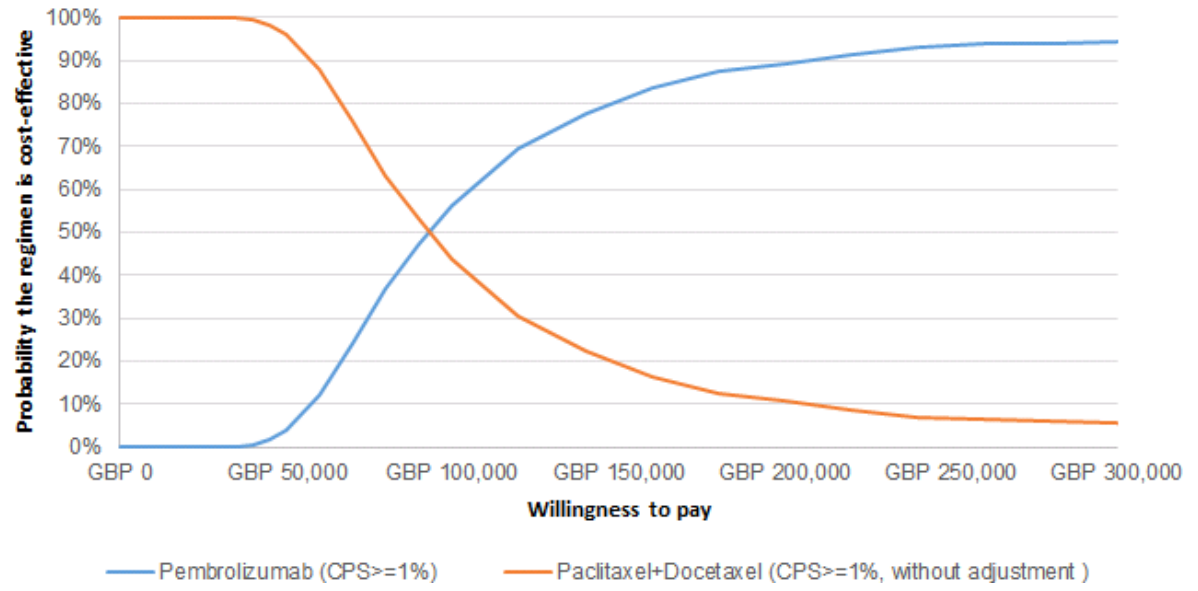


Figure 24. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with CPS≥1% (with RPSFT adjustment)

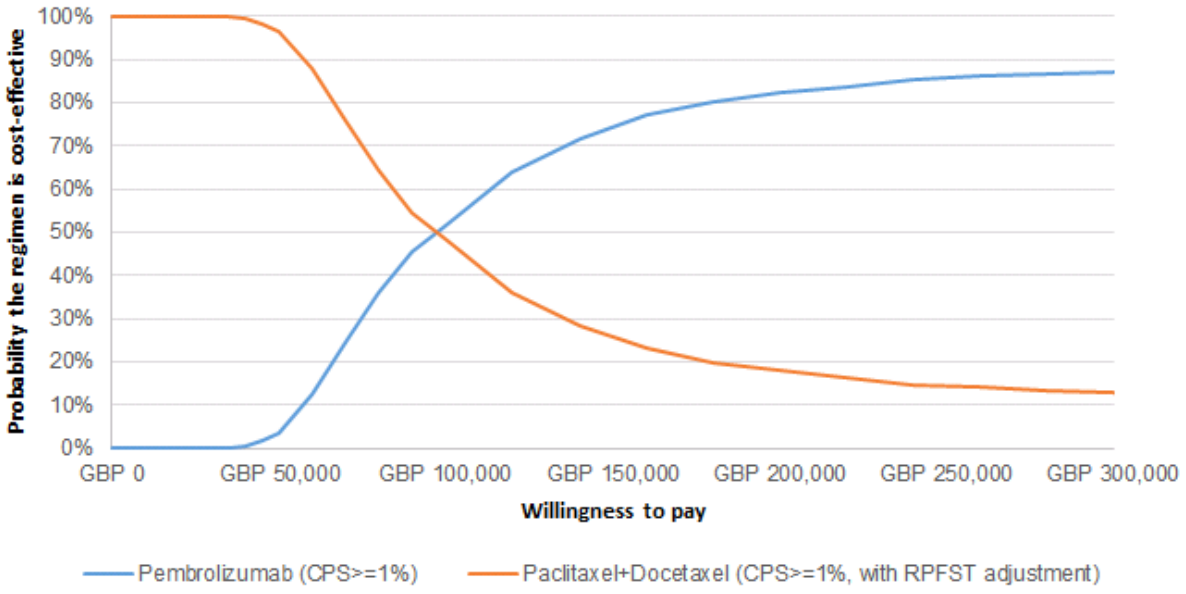


Figure 25. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with CPS≥1% (with IPCW adjustment)

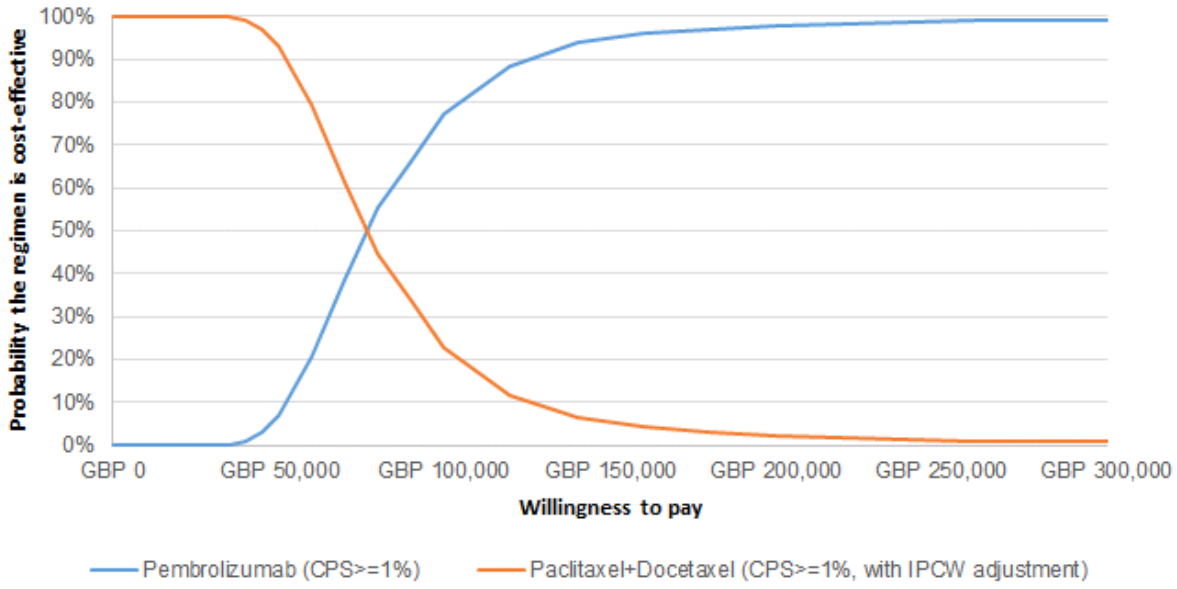


Figure 26. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with CPS≥10% (ITT population)

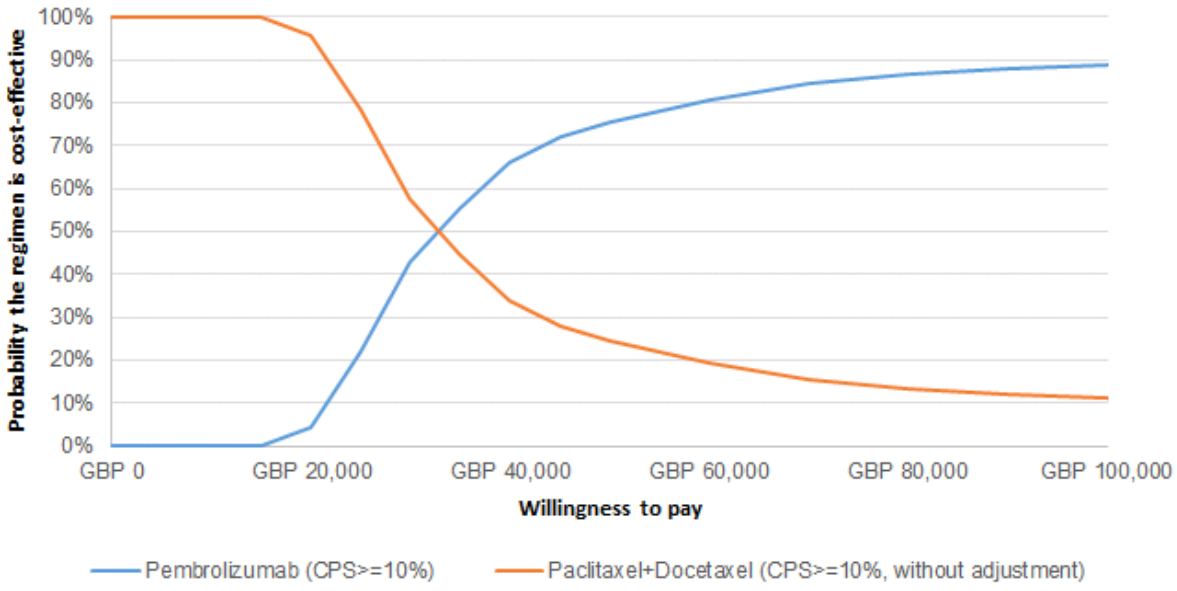
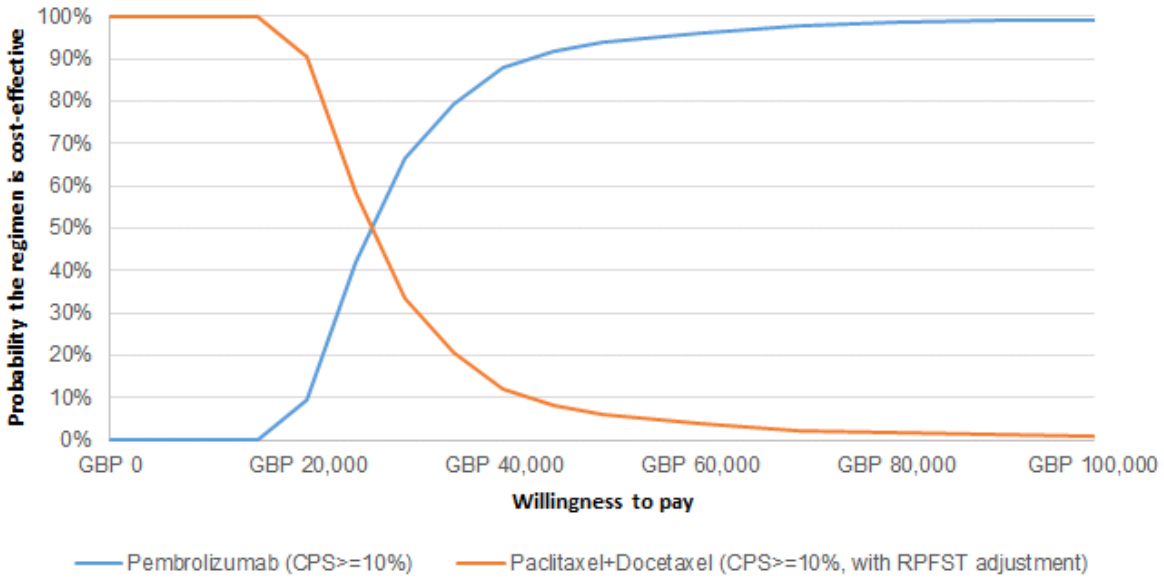


Figure 27. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with CPS≥10% (with RPSFT adjustment)



B10. **Priority question**: Can the company provide scenario analyses for the following:

a. Varying the number of progression-free people who would continue treatment after 2 years
b. Varying the expected continued treatment effect for people who have stopped treatment

Provide probabilistic sensitivity analysis results for the different scenarios outlined in the format of table 2 on the final page of this letter. Please also provide separately the corresponding costs and QALY results for these scenarios.

Please find in Table 15 the probabilistic sensitivity analyses results for the different scenarios of varying the proportion of patients on pembrolizumab therapy after 2 years and the continued treatment effect for patients who have stopped treatment.**Table 15: Probabilistic sensitivity analysis results for Base-case results (discounted, with PAS)**

Table 15: Probabilistic sensitivity analysis results for Base-case results (discounted, with PAS)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
0% continue treatment after 2 years and lifetime treatment effect						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£60,634	1.98	2.76	£39,267	0.85	£46,194
0% continue treatment after 2 years and continued treatment effect over 10 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£60,241	1.94	2.70	£38,875	0.81	£48,129
0% continue treatment after 2 years and continued treatment effect over 5 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£59,542	1.87	2.60	£38,175	0.73	£52,130
0% continue treatment after 2 years and continued treatment effect over 3 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£58,938	1.80	2.52	£37,571	0.67	£56,360
25% continue treatment after 2 years and lifetime treatment effect						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£62,371	1.98	2.76	£41,005	0.85	£48,238
25% continue treatment after 2 years and continued treatment effect over 10 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£61,979	1.94	2.70	£40,612	0.81	£50,280
25% continue treatment after 2 years and continued treatment effect over 5 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£61,280	1.87	2.60	£39,913	0.73	£54,502
25% continue treatment after 2 years and continued treatment effect over 3 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£60,676	1.80	2.52	£39,309	0.67	£58,967
100% continue treatment after 2 years and lifetime treatment effect						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£66,830	1.98	2.76	£45,464	0.85	£53,484
100% continue treatment after 2 years and continued treatment effect over 10 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£66,438	1.94	2.70	£45,072	0.81	£55,801
100% continue treatment after 2 years and continued treatment effect over 5 years						
UK SOC	£21,367	1.13	1.64	-	-	-
Pembrolizumab	£65,739	1.87	2.60	£44,372	0.73	£60,592
100% continue treatment after 2 years and continued treatment effect over 3 years						
UK SOC	£21,367	1.13	1.64	-	-	-

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab	£65,135	1.80	2.52	£43,768	0.67	£65,656

B11. Please can the company provide cost-effectiveness results in the subgroup of patients negative for PD-L1 along with the corresponding probabilistic results (expected ICER and cost-effectiveness acceptability curves)?

Please find in Table 16 and

Table 17 below the deterministic and probabilistic results of patients with CPS<1% respectively. Cost-effectiveness acceptability curves can be found in

Figure **28** and

Figure 29 for the unadjusted and the RPSFT adjusted analyses, respectively. Details of adjusting for treatment switching can be found in Appendix 3. Please note that the study was neither designed nor powered to examine treatment effects for this subgroup-within-a-subpopulation. Exploratory overall survival analyses were conducted post hoc and results should be interpreted with extreme caution, especially as a number of subgroups were examined.

Table 16: Deterministic incremental cost-effectiveness results for the comparison of pembrolizumab vs. UK SOC for patients with CPS<1% (discounted, with PAS)* - 40 weeks extrapolation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**The two-stage and IPCW adjustments could not be implemented in this population*

Table 17: Probabilistic incremental cost-effectiveness results for the comparison of pembrolizumab vs. UK SOC for patients with CPS<1% (discounted, with PAS)* - 40 weeks extrapolation

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**The two-stage and IPCW adjustments could not be implemented in this population*

Figure 28. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with CPS<1% (ITT population)

[redacted]

Figure 29. Cost-effectiveness acceptability curves for pembrolizumab vs UK SOC for patients with CPS<1% (with RPSFT adjustment)

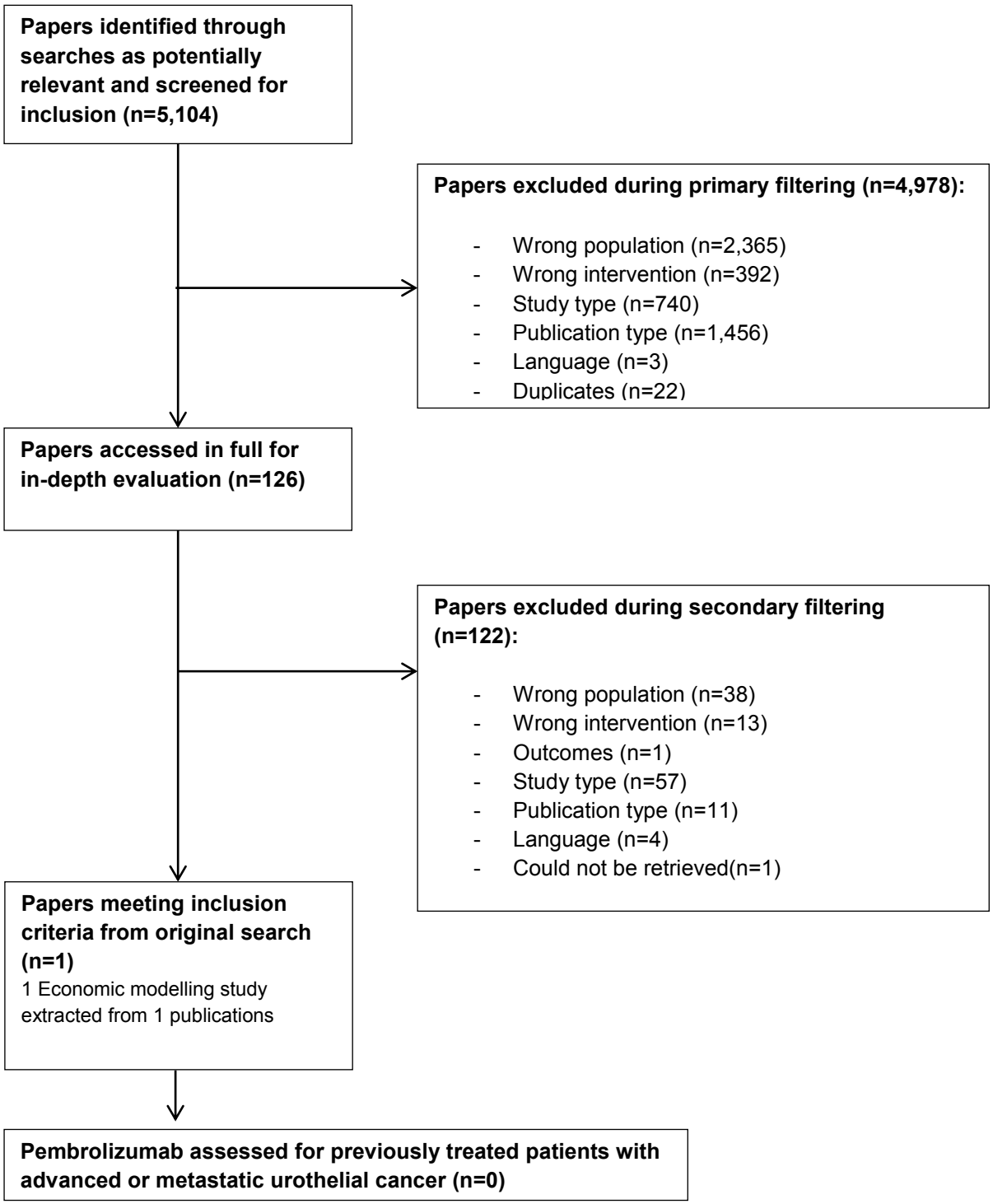
[redacted]

B12. In Figures 32, 42 and 43, 126 papers were evaluated in full. Please can the company provide more information about these papers, including references and why these studies were excluded for each of the 3 research questions?

References and exclusion codes for the 126 papers included in the systematic literature review (SLR) following the primary screening are available in the attached excel document 'ID1019 Economic SLR'.

MSD has also provided an updated PRISMA diagram in Figure 30 below for the SLR of cost-effectiveness studies. The original PRISMA provided in the submission included 3 publications which should have been excluded during the secondary screening as although they provide relevant information in regards to the economic modeling, they were published prior to 2005 and therefore fall outside of the search strategy. For the purpose of transparency, the 3 publications are highlighted in red within the attached excel document.

Figure 30. Updated PRISMA diagram – Economic evaluation review*



Key: n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

*From the updated search conducted in December 2016, 342 additional hits were identified, none of them was included.

Table 2 Cost-effectiveness results for pembrolizumab compared with UK standard of care (docetaxel and paclitaxel) for previously treated advanced or metastatic urothelial cancer

	Lifetime treatment effect	Continued treatment effect over 10 years; no treatment effect thereafter	Continued treatment effect over 5 years; no treatment effect thereafter	Continued treatment effect over 3 years; no treatment effect thereafter
100% of progression-free people continue treatment after 2 years (no stopping rule)	£53,484	£55,801	£60,592	£65,656
25% progression-free people continue treatment after 2 years	£48,238	£50,280	£54,502	£58,967
0% continue treatment after 2 years (full implementation of the stopping rule)	£46,194	£48,129	£52,130	£56,360

References:

1. White IR, Babiker AG, Walker S, Darbyshire JH. Randomization-based methods for correcting for treatment changes: examples from the Concorde trial. Stat Med. 1999;18(19):2617-34.

2. Watkins C HX, Latimer N, Tang Y, Wright EJ.,. Adjusting overall survival for treatment switches: commonly used methods and practical application. Pharmaceutical Statistics 2013;12:348–57.

3. Latimer N BH, Abrams K, Amonkar M, Casey M.,. Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer Medicine 2016;5(5):806–15.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Pembrolizumab for previously treated urothelial cancer

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 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?

☒ 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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for previously treated urothelial cancer [ID1019]

Thank you for agreeing to make a submission on your organisation's 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 submission, 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: NCRI-RCP-RCR-ACP-BUG

Comments coordinated by: [redacted]

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for previously treated urothelial cancer [ID1019]

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?

There are no NICE approved agents for the treatment of urothelial cancer (UC) that relapses or progresses after platinum based chemotherapy. Re-induction of platinum based chemotherapy is used in case of a relapse or progression after more than 12 months. Otherwise, current practice includes the use of single agent taxanes like paclitaxel or docetaxel and rarely the combination of gemcitabine and paclitaxel. With single agent chemotherapy response rates in the second or third line setting are usually low and rarely exceeding 12%, progression free survival PFS) around 2-4 months and overall survival (OS) around 5-7 months. Combination chemotherapy can provide higher response rates (about 40%) but the PFS and OS are similar to the taxanes.

There are geographical differences in treatment of UC in the second line setting. In the United States, until recently, besides Paclitaxel also Pemetrexed was used. The treatment landscape has changed with the FDA approval of Atezolizumab, a PD-L1 inhibitor, which in the meantime has become part of the treatment armamentarium in the US and worldwide based on a large single arm trial.

In Europe and other parts of the world Vinflunine has been approved and regarded as the standard of care since 2008, based on the only randomised phase III trial and so far the highest level of evidence ever provided for a second line UC treatment.
This was true until recently when the data of KEYNOTE 045 trial was presented. This is the first presented randomised phase III trial with immunotherapy in this setting. It showed a significant OS benefit of Pembrolizumab compared to any chemotherapy. Because of the disparity of care internationally, the comparator arms of this trial and basically all others in this setting were either Vinflunine or paclitaxel or docetaxel, according to investigator's choice.
A phase III trial compared long-term OS of patients with advanced UC treated with vinflunine plus BSC (best supportive care) or BSC alone, after failure of platinum-based chemotherapy. The study showed a 2.6 month survival difference in favour of the vinflunine arm, which was maintained after >3.5 years' follow-up. Moreover, risk of death was reduced by 22% in the vinflunine arm; there were some long-term survivors in the vinflunine arm at 40 months (vs. none in BSC arm).

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 are well established adverse prognosis factors for pretreated patients that were developed in the data set set of the pivotal vinflunine study and externally validated. These adverse prognostic factors include liver metastases, Hb <10 g/dL, and ECOG PS. Four subgroups were defined based on the presence of null, one, two, or three of these prognostic factors; the median OS times for these groups were 14.2, 7.3, 3.8, and 1.7 months ($P < .001$), respectively. So far, these subgroups have not been validated in patients treated with immunotherapy.

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)?

Similar to the use of chemotherapy and other anticancer treatments, pembrolizumab should be given in centres with trained staff (including physicians and nurses) that have made themselves familiar with the new technology and in particular the side effect profile. It should not be used in primary care and preferably the first prescription should be in a specialist clinic.

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?

Pembrolizumab was first granted EU Marketing authorisation in July 2015 for the treatment of advanced (unresectable or metastatic) melanoma in adults. In October 2015 NICE issued a final recommendation for pembrolizumab as a first-line treatment option for adults with advanced (unresectable and metastatic) melanoma.

Pembrolizumab was subsequently granted EU Marketing authorisation in August 2016 for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥1% TPS (tumour proportion score) and who have received at least one prior chemotherapy regimen. In December 2016 NICE has published a Final Appraisal Determination (FAD) that recommends the use of pembrolizumab as an option for treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen.

In December 2016 the EU Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending pembrolizumab for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% TPS with no EGFR or ALK positive tumour mutations.

Pembrolizumab will also get EMA approval for the cisplatin unfit patient population in the first line setting.

In the Phase 2 KEYNOTE-052 trial significant efficacy and a favourable safety profile was shown. KEYNOTE-052 is an open-label, phase 2 study evaluating pembrolizumab (200 mg every three weeks) monotherapy as a first-line treatment in an estimated 350 patients with unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy. The primary endpoints include ORR in all patients enrolled in the study (total study population) and in patients with PD-L1 positive tumours (expression of one percent or more). Secondary endpoints include duration of response, progression-free survival (PFS), and overall survival (OS). Tumour response was measured according to RECIST (Response Evaluation Criteria in Solid Tumours) v1.1 as assessed by blinded independent central review.

A planned interim analysis of the first 100 patients was presented at the ESMO 2016 Congress, which was intended to evaluate ORR and determine the PD-L1-high expression cut-point as examined by expression in tumour and immune cells. Forty-five percent of patients (n=45/100) had an ECOG (Eastern Cooperative Oncology Group) Performance Status (PS) score of two, 30 percent (n=30/100) had a PS score of one, and 24 percent (n=24/100) had a PS score of zero.

In the total study population, ORR was 24 percent (n=24/100) (95% CI, 16-34) with a complete response rate of six percent (n=6/100) (95% CI, 2-13). Review of the outcomes based on PD-L1 expression showed that in patients with PD-L1 expression of less than one percent, ORR was 18 percent (n=6/33) (95% CI, 7-36) with a complete response rate of three percent (n=1/33) (95% CI, 0.1-16); in patients with PD-L1 expression greater than or equal to one percent and less than 10 percent, ORR was 15 percent (n=5/33) (95% CI, 5-32) with no complete responses; and, in patients expressing PD-L1 at levels equal to or greater than 10 percent, ORR was 37 percent (n=11/30) (95% CI, 20-56) with a complete response rate of 13 percent (n=4/30) (95% CI, 4-31). Among the 24 percent of patients in the total study population who were responding to treatment, the median duration of response had not been reached (range 1.4+ to 9.8+ months), with 83 percent of patients (n=20/24) having responses of six months or longer.

The safety profile of pembrolizumab was consistent with that observed in previously reported pembrolizumab studies. The treatment-related adverse events observed in this trial (any grade occurring in five percent or more of patients) were fatigue (n=14), pruritus (n=12), pyrexia (n=8), decreased appetite (n=7), diarrhea (n=7), rash (n=7), chills (n=6), hypothyroidism (n=6), and nausea (n=6). Grade 3-4 treatment-related adverse events observed (occurring in 2 or more patients) were fatigue (n=4), muscle spasms (n=2), decreased appetite (n=1), and diarrhea (n=1). Immune-mediated adverse events of Grade 3-4 were nephritis (n=1) and pneumonitis (n=2). Five patients discontinued due to a treatment-related adverse event; there were no treatment-related deaths.

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.
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?

The use of pembrolizumab will be similar to the use of standard chemotherapy with i.v. infusion every 3 weeks. In those centres where weekly instead of 3-weekly taxanes are standard of care, pembrolizumab use will be easier with less seating time. Concomitant treatment will be less with pembrolizumab (less with regards to antiemetics and corticosteroid pretreatment).
In responding and stable patients treatment with pembrolizumab will be until unequivocal progression.

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.

Response assessment for pembrolizumab is similar to chemotherapy. Rarely pseudo-progression has occurred with immune-oncology (IO) treatments and should be taken into consideration when assessing tumour response or progression by CT.
The median time to response with IOs was around 6-7 weeks which means that tumour evaluation by CT every 8-10 weeks, so after 2-3 cycles is adequate.

Contrary to NSCLC and based on the currently available data and knowledge in urothelial cancer, additional testing for biomarkers like PD-L1 is not recommended for routine use in urothelial cancer because responses were reported in all biomarker subgroups based on the currently available testing. Even a more sophisticated biomarker cut point determined to be 10% or greater total PD-L1 expression in immune cells or tumour cells could not adequately separate responders and non-responders as shown in KENOTE-052.

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?

Pembrolizumab has been studied in KEYNOTE-045, a randomised, pivotal, phase 3 study in patients with advanced urothelial cancer previously treated with platinum-containing chemotherapy.
The trial outline and control arm reflected current clinical practice in the UK. As mentioned above, the control arm was at investigators' choice including taxanes that are commonly used in the UK for the treatment of urothelial cancer progressing after first line platinum base chemotherapy.
Pembrolizumab was superior to investigator-choice chemotherapy for the primary endpoint of overall survival. There were two co-primary endpoints included in the protocol which was OS and progression free survival. Therefore, the primary trial outcome measure reflects long-term outcome and provides level one evidence. In addition to a significant improvement in OS, response rate and in particular the duration of response is an important outcome measure for urothelial cancer and with immunotherapy. These endpoints were adequately tested in the pivotal trial.

The details of KEYNOTE-045 are as follows:

Patients with metastatic or locally advanced, unresectable (inoperable) urothelial cancer (urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra) that has recurred or progressed following platinum-based chemotherapy were enrolled in this study. The co-primary endpoints are OS and progression-free survival (PFS); secondary endpoints are overall response rate (ORR), duration of response, and safety. The study randomized 542 patients to receive pembrolizumab (200 mg every three weeks) (n=270) or investigator-choice chemotherapy (n=272) – either paclitaxel (175 mg/m every three weeks), docetaxel (75 mg/m every three weeks), or vinflunine (320 mg/m every three weeks). The study was designed to assess key endpoints in patients with or without PD-L1 (programmed death-ligand 1 expression) (the total study population, n=542), as well as in patients with PD-L1 expressing tumours (expression of 10% or more) (n=74/270 in the pembrolizumab arm; n=90/272 in the chemotherapy arm).
A significant improvement has been shown in the total study population in OS with pembrolizumab compared to chemotherapy, with a 27 percent reduction in the risk of death (HR: 0.73 [95% CI, 0.59 - 0.91], p-value: 0.0022). Median OS was 10.3 months (95% CI, 8.0 - 11.8) with pembrolizumab, compared to 7.4 months (95% CI, 6.1 - 8.3) in the chemotherapy arm.
The estimated one-year OS rate was 43.9 percent with pembrolizumab, compared to 30.7 percent in the chemotherapy arm.

In the OS analysis of patients with PD-L1 expression, there was a 43 percent reduction in the risk of death with pembrolizumab, compared to chemotherapy (HR: 0.57 [95% CI, 0.37 - 0.88], p-value: 0.0048). Median OS was 8.0 months (95% CI, 5.0 - 12.3) with pembrolizumab, compared to 5.2 months (95% CI, 4.0 - 7.4) in the chemotherapy arm. The estimated one-year OS rate was 39.8 percent with pembrolizumab, compared to 26.9 percent in the chemotherapy arm.
An analysis of the study's second primary endpoint, PFS, in the total study population showed a median PFS of 2.1 months (95% CI, 2.0 - 2.2) with pembrolizumab, compared to 3.3 months (95% CI, 2.3 - 3.5) in the chemotherapy arm (HR: 0.98 [95% CI, 0.81 - 1.19], p-value: 0.42). The six month PFS rate was 28.8 percent with pembrolizumab, compared to 26.8 in the chemotherapy arm; the one-year PFS rate was 16.8 percent with pembrolizumab, compared to 6.2 percent in the chemotherapy arm.
The difference in response rates between the two arms was 9.6 percentage points (p-value: .0011), which was statistically significant and in favour of pembrolizumab. The ORR was 21.1 percent with pembrolizumab (7.0% were complete responses), compared to 11.4 percent in the chemotherapy arm (3.3% were complete responses). In patients with PD-L1 expression, ORR was 21.6 percent with pembrolizumab (6.8% were complete responses), compared to 6.7 percent in the chemotherapy arm (2.2% were complete responses).
The median duration of response for patients treated with pembrolizumab had not yet been reached at the time of analysis (range: 1.6+ to 15.6+ months) – with 68 percent of responses estimated to last for 12 months or more. In the chemotherapy arm, the median duration of response was 4.3 months (range: 1.4+ to 15.4+ months) – with 35 percent of responses estimated to last for 12 months or more.

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 safety profile of pembrolizumab in the pivotel trial KEYNOTE-045 was consistent with that observed in previously reported studies involving patients with advanced urothelial cancer.
The treatment-related adverse events observed in this trial (any grade occurring in 10 percent or more) were pruritus (19.5% with pembrolizumab; 2.7% with chemotherapy), fatigue (13.9% with pembrolizumab; 27.8% with chemotherapy), nausea (10.9% with pembrolizumab; 24.3% with chemotherapy), diarrhea (9.0% with pembrolizumab; 12.9% with chemotherapy), decreased appetite (8.6% with pembrolizumab; 16.1% with chemotherapy), asthenia (5.6% with pembrolizumab; 14.1% with chemotherapy), anemia (3.4% with pembrolizumab; 24.7% with chemotherapy), constipation (2.3% with pembrolizumab; 20.4% with chemotherapy), peripheral sensory neuropathy (0.8% with pembrolizumab; 11.0% with chemotherapy), peripheral neuropathy (0.4% with pembrolizumab; 10.6% with chemotherapy), neutrophil count decreased (0.4% with pembrolizumab (pembrolizumab); 14.1% with chemotherapy), alopecia (37.6% with chemotherapy) and neutropenia (15.3% with chemotherapy). Immune-mediated adverse events were thyroid abnormalities (9.4% with pembrolizumab (pembrolizumab); 1.6% with chemotherapy), pneumonitis (4.1% with pembrolizumab; 0.4% with chemotherapy), colitis (2.3% with pembrolizumab; 0.4% with chemotherapy), infusion reactions (0.8% with pembrolizumab; 3.9% with chemotherapy), severe skin toxicity (0.8% with pembrolizumab; 1.2% with chemotherapy), nephritis (0.8% with pembrolizumab), adrenal insufficiency (0.4% with pembrolizumab) and myositis (0.4% with chemotherapy). Fifteen patients in the pembrolizumab arm and 28 patients in the chemotherapy arm discontinued treatment due to a treatment-related adverse event; there were four treatment-related deaths in each arm.

The main experience with pembrolizumab in urothelial cancer stems from clinical trials and from the routine use in other tumour entities like NSCLC or melanoma as pointed out above. So far, reported and published quality of life (QoL) data with pembrolizumab mainly come from its use in other tumour entities like NSCLC. QoL data from the urothelial cancer trials still await reporting.

The lung cancer patient population and comparator arms with taxane based single agent chemotherapy is similar to the urothelial cancer population.
The HRQoL (health related QoL) data presented for NSCLC were based on change from baseline to week 15 as assessed by two European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaires measuring global health status (such as physical, emotional, cognitive, and social functioning as well as fatigue and pain) (QLQ-C30) and time to deterioration (measuring symptoms such as cough, chest pain, alopecia, and dyspnea) (QLQ-LC13). The findings showed that HRQoL and symptoms were improved or maintained to a greater degree with pembrolizumab compared to chemotherapy (based on 299 patients who completed at least one questionnaire). Specifically, the improvement in global health status from baseline to week 15 (difference in least squares) for pembrolizumab was 6.9 (95% CI, 3.3-10.6) compared to -0.9 (95% CI, -4.8-3.0) in the chemotherapy arm. Analysis based on specific functioning and symptoms showed more patients treated with pembrolizumab reporting an improvement in global health status and/or quality of life, fatigue, and pain compared to patients treated with chemotherapy. Fewer patients in the pembrolizumab arm experienced deterioration compared to chemotherapy (30.5% and 39.2%, respectively), with a prolonged time to deterioration also observed in the pembrolizumab arm (hazard ratio: 0.66 [95% CI, 0.44-0.97; p=0.029]).

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.

None

Implementation issues
The NHS is required by the Department of Health 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 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)?

Pembrolizumab is generally well tolerated and caused less adverse events and serious adverse events than chemotherapy. The most common side effects of pembrolizumab

included decreased appetite, fatigue, nausea, dyspnea, cough, and constipation. Rare but serious adverse events included immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.

As with every novel technology and treatment with new mode of action, physicians and staff need adequate training. Treatment application is straight forward with a short i.v. infusion every 3 weeks. The teams need to make themselves familiar with immune mediated side effects and their treatment. Side effect evaluation is based on clinical judgement and published guidelines. In case of clinical suspicion, additional tests might be needed to secure the diagnosis of a side effect with e.g. an establish blood test for thyroid function. Most side effects are reversible and management is based on temporary or permanent treatment discontinuation. Side effect treatment is mainly with corticosteroids that are inexpensive and readily available. No new equipment or facilities are needed.

Equality
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.

Submission by NHS England on pembrolizumab in the systemic therapy of locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy

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. If patients are unfit for carboplatin plus gemcitabine, it is unlikely that they will be fit for any chemotherapy or checkpoint inhibitor.
8. The administration of any chemotherapy to patients with urothelial cancer and of performance status 3 is inappropriate. Only selected patients with a performance status of 2 are treated with palliative 1st line chemotherapy.
9. 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 pembrolizumab in this appraisal. The use of single agent treatment with paclitaxel and docetaxel is sometimes used in highly selected patients in NHS England practice ie in those that are fit (performance status 0 or 1) and also 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.

10. 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. As well as recruiting patients treated with palliative 1st line platinum-based chemotherapy, the pembrolizumab KEYNOTE 045 study also allowed patients to enter the study if they had previously received adjuvant treatment post-cystectomy or neoadjuvant chemotherapy prior to cystectomy as long as these latter two groups of patients had relapsed 12 months or less following completion of chemotherapy.
11. Checkpoint inhibitors represent the first significant new drug advance in the systemic therapy of locally advanced/metastatic disease urothelial cancer for 15+ years.
12. In addition to pembrolizumab, other checkpoint inhibitors have emerging evidence bases in urothelial cancer: atezolizumab, nivolumab, durvalumab and avelumab. Pembrolizumab is the only checkpoint inhibitor which so far as evidence of survival benefit in a phase III trial of patients previously treated with platinum-based chemotherapy. Atezolizumab is currently being appraised by NICE in urothelial cancer.

<u>Pembrolizumab in the treatment of advanced/metastatic urothelial cancer</u>

13. The wording of the marketing authorisation has not yet been set by the EMA although it is likely to reflect the key features of the design of the KEYNOTE 045 study ie pembrolizumab will be indicated in adults with locally advanced or metastatic urothelial cancer after prior platinum-based chemotherapy.
14. Fixed doses of pembrolizumab were used in the 045 study and were given every 3 weeks to disease progression or for a maximum of 2 years, whichever was the earlier event. NHS England is confident about being able to commission such the maximum duration of treatment being 2 years.

15. NHS England regards the duration of follow-up (median of 10.3 months) to be very short and thus there is a large degree of uncertainty as to the longer term impact of pembrolizumab on survival.
16. Although there were fewer treatment-related serious adverse events with pembrolizumab vs chemotherapy, there are still very important toxicities with checkpoint inhibitors such as pembrolizumab. This is a very important issue given 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.
17. NHS England notes that patients in the 045 study were excluded from entry if they had received 2 or more prior chemotherapy treatments for metastatic disease and NHS England also notes that nearly all patients treated in the 045 study were of good performance status (0 or 1).
18. NHS England notes that the 045 study was a RCT of pembrolizumab vs active treatment of physicians' choice (a taxane or vinflunine). However, this study will not offer direct evidence of the benefit of pembrolizumab over best supportive care.
19. NHS England wishes to state that it is very important that the economic model reflects the actual duration of drug treatment and does not use the duration of progression free survival as a surrogate for treatment duration. This is because clinicians sometimes continue the use of pembrolizumab beyond formal documentation of progressive disease especially in the context of continued symptomatic benefit and the evidence of disease progression being witnessed in only one of the sites of metastatic spread.
20. If NICE recommends pembrolizumab for use, 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 AND who have relapsed 12 or less months since completing platinum-based chemotherapy are eligible but must satisfy all other criteria
- ECOG performance status score of 0 or 1 or 2 but treatment of patients with performance status 2 should only proceed with caution
- To be treated until disease progression or excessive toxicity or for a maximum of 2 years, 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)
- Pembrolizumab to be otherwise used as set out in its Summary of Product Characteristics

[redacted]

[redacted]

19 May 2017

NICE National Institute for Health and Care Excellence

Patient expert statement

Pembrolizumab for previously treated urothelial cancer [ID1019]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Andrew Winterbottom**
2. Are you (please tick all that apply):	☑ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Fight Bladder Cancer
4. Did your nominating organisation submit a submission?	☐ yes, they did ☑ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☑ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☑ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Being diagnosed with urothelial cancer is a rollercoaster of tests, treatments and check-ups, often for the rest of your life. As a patient we know that this cancer has a very high recurrence rate and that progression is always a possibility. At most points in the pathway there is currently very limited choice on treatments and that many of these treatments are not very effective which accounts for the high recurrence rate and possibility of progression. Most current treatments are also very invasive, have significant side effects and substantially affect the patient emotionally as well. For advanced/metastatic urothelial cancer there is currently no effective second line treatment and prognosis is currently extremely poor for patients with this diagnosis.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Current treatments for urothelial cancer limited at every part of the pathway. This is mostly due to a significant lack of research into this cancer for the last 35 years, which is when the last new treatment (BCG) was introduced for high-risk non-invasive bladder cancer. The treatments across the whole pathway are invasive and have many serious and problematic side effects that there is little support for. There are currently limited second line treatments across the whole pathway, which leads to patient anxiety on recurrence and progression. In advanced/metastatic urothelial cancer, prognosis is very poor with very limited treatments being available.
10. Is there an unmet need for patients with this condition?	Many of the existing treatments for urothelial cancer have limited effectiveness which results in the poor overall prognosis for this cancer and specifically very poor for those with advanced/metastatic cancer. There is a significant unmet need for new treatments for this condition.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The new technology for the treatment of urothelial cancer offers hope for patients and carers for this much ignored cancer. The hope is that these possible new treatments will improve prognosis, reduce recurrence and reduce side effects. Ideally we hope to see improvements against all of these factors but understand that not every patient will see benefits across them all.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Currently we do not know enough details about the effectiveness or the quality of life issues surrounding the new technology to pass judgement at this stage. Patients would always want to balance effectiveness on recurrence and progression against the quality of life during and after treatment.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is possible that the use of this technology might benefit specific sections of the patient population according to how their immune system reacts to the treatment and it might be possible to identify these patients with the use of biomarkers or the like. The patients who would benefit most would likely be those who's current first line treatment has failed but it is possible that this technology could become an effective first line treatments across the pathway.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None known
Other issues	
15. Are there any other issues that you would like the committee to consider?	Urothelial cancer has come at the bottom of the annual NHS cancer patient experience survey since its launch. The new technology offers a ray of hope for a step change in treatment for this much ignored cancer. The high risk of recurrence and progression has led to this cancer seeing one of the highest associated suicide rates for cancer patients due to the emotional strains of the treatment and quality of life issues.

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • No new treatments for urothelial cancer for over 35 years • Urothelial cancer has the highest recurrence rate of any cancer due to existing treatments being relatively ineffective • Existing treatments are invasive and have significant side effects and resultant Quality of Life issues • The new immunotherapy treatments could see a step change in treating this much ignored cancer where we have not seen any real improvements in decades. • They will possible offer hope to many, extra time to many and possibly be curative for some.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Pembrolizumab for previously treated urothelial cancer [ID1019]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Melanie Costin**
2. Are you (please tick all that apply):	☑ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Fight Bladder Cancer
4. Did your nominating organisation submit a submission?	☐ yes, they did ☑ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☑ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☑ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with this condition is very difficult due to the constant treatments, check-ups and appointments that are needed due to its high recurrence rate, particularly at high grades. The options are very few and due to the harsh side effects there is often the question of whether it is worth continuing with treatments that may not work and may result in bladder removal anyway and at a time when the cancer has become more advanced. It is certainly mentally draining for those of us who cannot tolerate current treatments and we would love to have more hope.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	They are very concerned that there are so few options and that the side effects are too severe, therefore many are opting for bladder removal in the hope that this is the best chance for survival long term. They find it hard to understand why bladder cancer is bottom of the list in areas such as care, knowledge and research and would hope that there is something else on the horizon, as BCG, which can often have severe and intolerable side effects, was the last new treatment and this was an astonishing 35 years ago.
10. Is there an unmet need for patients with this condition?	There is definitely an unmet need for patients with this condition.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	They would hope that the advantages of the technology will bring not only more much needed options but also the chance to have a better situation as regards their future with more tolerable side effects and definitely a way to delay recurrences. Ultimately they would hope for a better quality of life during treatment and a better long term prognosis.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit	Obviously until we know more about this new technology it is hard to say but the hope is that it could benefit those who are unable to have current treatments or that have failed to respond to them. I would also hope for a new option to the current ones to suit particular patients' circumstances better.

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Urothelial cancer has the highest rate of recurrence of any other and yet there has been no new treatments for 35 years • People are opting for bladder removal due to experiencing or worrying about intolerable side effects	

- The high chance of treatment failing is making many decide upon bladder removal to give them a better chance of long term survival and hopefully a cure
- People are extremely keen to have the hope of a new treatment as the options are so few and are looking for something that can treat or even cure.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Produced by: Warwick Evidence

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Date completed: 27th April 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/108/19.

Declared competing interests of the authors
Dr Maria De Santis received consultancy fees within the last 5 years from MSD, Merck, Pfizer, Roche, AstraZeneca, Pierre Fabre, Sanofi, BMS**,** Amgen, Astellas, Bayer, Celgene, Eisai, ESSA,

Ferring, GSK, Ipsen, Janssen, Novartis, Dendreon, Seattle Genetics, Shionogi, Synthon, Teva and OncoGenex. She also received reimbursement for attending a symposium and/or speaker fees from Bayer, MSD, Janssen, Astellas, Sanofi, Pierre Fabre, GSK and funds for research from Pierre Fabre.

Dr Jo Cresswell is employed by South Tees NHS Trust Hospital. South Tees is part of the Imvigor clinical trial which is a commercially funded RCT. The research costs are met by Roche. Dr Cresswell has not received any personal funding from Roche.

Acknowledgements

We would like to thank Dr Emma Loveman for providing advice and comments during the two week clarification period and Dr Martin Connock for providing advice and comments on the survival analysis. Professor Aileen Clarke read the report and provided advice.

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.

This report should be referenced as follows

Pembrolizumab for previously treated advanced or metastatic urothelial cancer: A Single Technology Appraisal. Warwick Evidence, 2017.

Contributions of authors

Xavier Armoiry (Senior Research Fellow) helped co-ordinate the project and the report, and conducted, reviewed and critiqued the clinical effectiveness evidence; Theodoros Mantopoulos (Research Associate) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Daniel Gallacher (Research Associate) conducted, reviewed and critiqued the survival analysis and cost-effectiveness evidence; Peter Auguste (Research Fellow) conducted, reviewed and critiqued the survival analysis and undertook additional analyses; Jacoby Patterson (Independent Research Consultant) conducted, reviewed and critiqued the clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional analyses; Karoline Munro (Research Project Administrator) conducted, reviewed and critiqued the background section; Maria De Santis (Associate Clinical Professor) provided expert clinical advice; Joanne Cresswell (Consultant Urological Surgeon) provided expert clinical advice; Hema Mistry (Assistant Professor) co-ordinated the project and

the report, and reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses.

Word count: 41,506

Please note that: Sections highlighted [redacted] are redacted.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AE	Adverse Event
AEOSI	AEs of Special Interest
AIC	Akaike Information Criterion
ALK	Anaplastic Lymphoma Kinase
APaT	All Patients as Treated
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BOR	Best Overall Response
BSA	Body Surface Area
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIS	Carcinoma In Situ
CPS	Combined Positive Score
CRD	Centre for Review and Dissemination
CR	Complete Response
CS	Company Submission
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DoR	Duration of Response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMit	Electronic Market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology

EU	European Union
FDA	Food and Drug Administration
FAS	Full Analysis Set
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IPCW	Inverse Probability of Censoring Weighting
ITT	Intention-To-Treat
IVRS/IWRS	Interactive Voice Response System/ Interactive Voice and Web Response System
KM	Kaplan Meier
LS	Least Squares
LTUC	Lower Tract Urinary Cancers
LYG	Life Year Gained
MIBC	Muscle Invasive Bladder Cancer
MHRA	Medicines & Healthcare Products Regulatory Agency
mRECIST	Modified RECIST
MSD	Merck Sharp and Dohme
MVAC	Methotrexate, Vinblastine, Doxorubicin and Cisplatin
NMA	Network Meta-Analysis
NCCN	National Comprehensive Cancer Network
NMB	Net Monetary Benefit
NMIBC	Non-Muscle Invasive Bladder Cancer
NSCLC	Non-Small Cell Lung Cancer
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive Disease

PD-1	Programmed Death 1 protein
PD-L1	Programmed cell Death 1 ligand 1
PD-L2	Programmed cell Death 1 ligand 2
PFS	Progression-Free Survival
PH	Proportional Hazards
PICOS	Population Intervention Comparator Outcome Study design
PIM	Promising Innovative Medicines
PR	Partial Response
PS	Performance Score
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality Assessment
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
RoB	Risk of Bias
RPSFT	Rank Preserving Structural Failure Time
RR	Response Rate
SD	Standard Deviation
SOC	Standard of Care
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
StD	Stable Disease
TA	Technology Appraisal
ToT	Time on Treatment
TPS	Tumour Proportion Score
TTP	Time To Progression
TTR	Time To Response
TNM	Tumour, Node and Metastases
UK	United Kingdom
US	United States

UTUC	Upper Tract Urinary Cancers
VAS	Visual Analogue Score
WTP	Willingness To Pay

1 SUMMARY

1.1 Critique of the decision problem in the company submission

The company submission (CS) decision problem matches the population, the intervention and outcomes described in the final National Institute of Health Care and Excellence (NICE) scope, as seen in Box 1. The CS decision problem differs from the NICE scope on the comparators, with retreatment with 1st line platinum-based chemotherapy, and best supportive care (BSC) being excluded from the decision problem.

As of April 2017, pembrolizumab is not licensed for the treatment of the scoped population since the submission is being appraised by the Committee for Medicinal Products for Human Use (CHMP).

The proposed indications submitted to the European Medicines Agency (EMA) by the company are:

- treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy.
- treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

	Final scope issued by NICE
Population	Adults with locally advanced and unresectable or metastatic urothelial cancer that have progressed on or after platinum-containing chemotherapy.
Intervention	Pembrolizumab
Comparator (s)	• Retreatment with 1st line platinum-based chemotherapy (only for people whose disease has had an adequate response) • Docetaxel • Paclitaxel • Best supportive care (BSC)
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates (RRs) • Adverse effects (AEs) of treatment

	• Health-related quality of life (HRQoL)

Box 1: NICE Final Scope

1.2 Summary of submitted clinical effectiveness evidence

The CS undertook a systematic review for evidence of clinical effectiveness of relevance to the decision problem. The review included searches for studies on the intervention and comparators for a potential network meta-analysis (NMA).

The CS includes direct evidence of pembrolizumab compared with standard of care (SOC) which comprised of docetaxel, paclitaxel or vinflunine from one phase 3 randomised controlled trial (RCT) - KEYNOTE-045. The CS presents outcomes of survival (progression-free survival, overall survival), response rates, health-related quality of life and adverse events.

The main results according to the population stated in the primary objectives are summarised below. For assessment of response, only results per response evaluation criteria in solid tumours (RECIST) 1.1 criteria by blinded independent committee review (BICR) are presented:

Entire population:

- For PFS, the hazard ratio (HR) suggested no reduction in risk of progression or death (HR 0.98, 95% CI: 0.81, 1.19) with pembrolizumab although the PFS at 12 months was higher in the pembrolizumab group (16.8% vs. 6.2%).
- For OS, the HR indicated better outcome in those treated with pembrolizumab compared with SOC (HR for death 0.73, 95% CI: 0.59, 0.91).
- The rate of objective response (complete or partial response) was higher with pembrolizumab compared to SOC (21.1% vs. 11.4%; p=0.00106).
- Using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, the score was stable from baseline to week 15 with pembrolizumab, while the score decreased with SOC; the difference in least squares (LS) means between both arms was 9.05 (95% CI: 4.61, 13.48) favouring pembrolizumab. Time to traditional deterioration (a 10-point or greater score decrease from baseline) was prolonged with pembrolizumab (HR 0.70, 95% CI: 0.55, 0.90).

- The scores using EuroQol 5 Dimensions (EQ-5D) instruments (visual analogue score (VAS) and utility) showed similar results (stable scores with pembrolizumab and worsened scores with SOC).
- The most common treatment-related adverse events of any grade were pruritus (19.5%), fatigue (13.9%), and nausea (10.9%) in the pembrolizumab group and alopecia (37.6%), fatigue (27.8%), and anaemia (24.7%) in the SOC arm. There were no treatment-related events of grade ≥ 3 severity that occurred with an incidence of ≥5% in the pembrolizumab group. In the SOC arm, treatment-related events of grade ≥ 3 severity with an incidence ≥5% were neutropenia (13.3%), decreased neutrophil count (12.2%), anaemia (7.8%), febrile neutropenia (7.1%), and decreased white-cell count (5.1%).

Patients positive for Programmed cell Death 1 ligand 1 (PD-L1) expression (combined positive score (CPS) ≥1%):

- For PFS, the HR suggested no reduction in risk of progression or death (HR 0.91, 95% CI: 0.68, 1.24) with pembrolizumab although the PFS at 12 months was higher (20.9% vs. 4.4%).
- For OS, the hazard ratio indicated better outcome in those treated with pembrolizumab compared with SOC (HR for death 0.61, 95% CI: 0.43, 0.86).
- The rate of objective response (complete or partial response) was higher with pembrolizumab compared to SOC (23.6% vs. 8.3%; p=0.00022)

Patients strongly positive for PD-L1 expression (CPS≥10%):

- For PFS, the HR suggested no reduction in risk of progression or death (HR 0.89, 95% CI: 0.61, 1.28) with pembrolizumab although the PFS at 12 months was higher (17.7% vs. 3.7%).
- For OS, the hazard ratio indicated better outcome in those treated with pembrolizumab compared with SOC (HR for death 0.57, 95% CI: 0.37, 0.88).
- The rate of objective response (complete or partial response) was higher with pembrolizumab compared to SOC (21.6% vs. 6.7%; p=0.00020)

Subgroup analyses:

- Most of the analyses of OS by subgroup showed consistency of survival benefit favouring pembrolizumab with consistent point estimates for the HR in important subgroups such as Eastern Cooperative Oncology Group (ECOG) Performance Score (PS), liver metastasis, haemoglobin, time from prior chemotherapy, prior platinum (cisplatin versus carboplatin), investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine), and Bellmunt risk scores.
- The ERG believes that the results in people with negative PD-L1 expression are inconclusive.

The CS attempted to present indirect and mixed treatment comparisons but no network meta-analysis was undertaken owing to a disconnected network. The ERG believes that an exploratory NMA could have been undertaken to compare pembrolizumab indirectly to BSC. However, given that this comparison would have used data from people with ECOG PS 0-2 and that BSC is only a relevant comparator in people with ECOG PS>2, the relevance of these estimates would have been questionable.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considered the systematic review to be of reasonable quality and substantially agreed with the CS appraisal of the pivotal phase 3 trial comparing pembrolizumab with standard of care (SOC). SOC included vinflunine (which is not a drug recommended within the NHS), and two of the scoped comparators, paclitaxel or docetaxel. The outcomes and analytical approach to the phase 3 trial were appropriate. The population in the trial appear to be relevant to those treated in the NHS. The KEYNOTE-045 trial was of good quality, with a low risk of bias in most domains except for the blinding of participants and personnel since the study was open-label (high-risk of bias). Given the presence of a key-domain rated as high-risk of bias, the ERG concludes that the KEYNOTE-045 as a whole is at high risk of bias.

However, even if the study had been double-blinded, the ERG believes that the KEYNOTE-045 study would still have been at high-risk of performance bias. That is because, given the very specific safety profile of the drugs evaluated in the KEYNOTE-045 trial, it would be very likely that both patients and clinicians might have identified which arms patients were in.

The ERG noted several issues with the submitted clinical evidence.

- The ERG has concerns regarding the exclusion of two scoped comparators, BSC and retreatment with a platinum-based regimen, from the decision problem.
- The company justified the exclusion of BSC stating that alternative treatments are available (e.g. docetaxel and paclitaxel). While the statement is true, these drugs are offered only in people with good performance status, which is the population included in KEYNOTE-045. In people with poorer PS (>2), BSC is a valid option within the NHS. Since KEYNOTE-045 only included patients with PS≤2, the CS includes no evidence on the clinical effectiveness of pembrolizumab in people who would otherwise be offered BSC.
- The company justified the exclusion of a retreatment with platinum-based chemotherapy since there is no evidence to compare with pembrolizumab. The ERG agrees there is no evidence but disagrees that this makes a treatment with platinum-based chemotherapy an irrelevant comparator.
- The anticipated label indication of pembrolizumab is broader than the population in KEYNOTE-045. If the label indication does not restrict the use of pembrolizumab to patients who previously received a platinum-based regimen, the label indication cannot be supported by clinical evidence since 100% of people in KEYNOTE-045 had a prior platinum-based regimen. Some evidence on the effectiveness of pembrolizumab in people ineligible for cisplatin will be provided by the full results of KEYNOTE-052 that is a single-arm study that enrolled 370 patients.
- Assuming pembrolizumab obtains a label indication in patients with urothelial cancers regardless of the PD-L1 expression, this means that patients who are negative for PD-L1 expression could also be offered pembrolizumab which is a drug that specifically acts on the PD-L1 pathway. As previously stated, the ERG believes that the results in people with negative PD-L1 expression are inconclusive.
- The evaluation of the quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a *de novo* partitioned survival model comparing pembrolizumab with UK SOC i.e. investigator's choice of paclitaxel or docetaxel. A weekly cycle length and a lifetime horizon were used. The model had three defined health states: progression-free, progressed disease and death. All patients in the pembrolizumab and UK SOC arms started in the progression-free health state.

The population modelled in this submission were patients with metastatic or locally advanced/unresectable urothelial cancer which has recurred or progressed following platinum containing chemotherapy.

The company also presented results for the following subgroups of patients in the Appendix:

- Patients with advanced or metastatic urothelial cancer of predominantly transitional cell histology.
- Patients with advanced or metastatic urothelial cancer of pure transitional cell histology.
- Patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥1%) urothelial cancer.
- Patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥10%) urothelial cancer.

Data for pembrolizumab and UK SOC arms came from the KEYNOTE-045 trial. For the UK SOC, overall survival was estimated by adjusting for treatment switching using a two-stage adjustment method. Overall survival and progression-free survival for pembrolizumab and UK SOC were both derived using a piecewise modelling approach:

- For overall survival, KEYNOTE-045 Kaplan-Meier data was used for the initial period of 40 weeks with a log-normal distribution fitted to data beyond 40 weeks.
- For progression-free survival, KEYNOTE-045 Kaplan-Meier data was used for the first 21 weeks, with an exponential distribution fitted to data beyond 21 weeks.

Quality of life values were obtained using EQ-5D-3L from the KEYNOTE-045 trial. For the base-case analysis, utility values were estimated based on time-to-death. Time-to-death was categorised in the following groups: 360 or more days to death, 180 to 360 days to death, 90 to 180 days to death, 30 to 90 days to death, and under 30 days to death. The company included

data for patients receiving vinflunine in the estimation of utility values, however, vinflunine is not currently recommended in England. Quality of life losses associated with adverse events and ageing were included in the base-case analysis.

The National Health Service (NHS) and Personal Social Services (PSS) perspective was adopted for the costs. An annual discount rate of 3.5% was used for both costs and outcomes. Costs of treatment with pembrolizumab were provided by the company. Pembrolizumab treatment was assumed to continue until disease progression, unacceptable toxicity or a maximum of 24 months of uninterrupted treatment (approximately 35 cycles). The treatment effect was assumed to persist for the lifetime of the model. For UK SOC, patients received treatment for a maximum of six cycles to reflect UK clinical practice. To estimate the duration of treatment in the pembrolizumab and UK SOC arms, time on treatment data from KEYNOTE-045 was used. UK SOC treatment costs were obtained from the latest electronic market information tool (eMit). The model also included costs for adverse events, routine care and terminal care.

The base-case analysis indicates that pembrolizumab provides additional quality-adjusted life years (QALYs) but at an additional cost. The deterministic incremental cost-effectiveness ratio (ICER) is £45,833 per QALY for pembrolizumab versus UK SOC with a patient access scheme (PAS). Probabilistic results were in close agreement with deterministic results. The parameters included in sensitivity analyses to which these estimates are most sensitive to are the parameters in the lognormal distributions used to model overall survival in the pembrolizumab and UK SOC arms. The ICER is also sensitive to the discount rate applied to health outcomes.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The model constructed by the company is logical and appears to capture two important features of the disease (progression-free survival and overall survival). The cycle length (7 days) is sufficiently short to allow accurate modelling of changes over short time periods. The perspective, time horizon and discount rates chosen by the company follow NICE recommendations, and are appropriate to the decision problem.

Other than two easily fixed errors (application of maximum time on treatment and estimation of QALYs), which the company corrected and provided an updated model, there were no

discrepancies found between the models reported in the company submission and the copy of the model given to the ERG.

The overall survival modelling methods used are not well justified. The ERG believes that a 24 week cut-off point in the piece-wise modelling approach and a log-logistic parametric survival model should be used in the economic model. Furthermore, the CS compared the extrapolated OS for people in the UK SOC with that reported by Cancer Research UK for patients with stage IV bladder cancer. The ERG however, has concerns regarding the comparability of people in the KEYNOTE-045 trial with those from Cancer Research UK.

The CS model incorporates utility scores based on time to death, which results in a relatively unusual method to estimate life years (based on death incidence) and subsequent QALYs. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC arms relative to life years based on progression status. The ERG believes that using utility scores based on progression status is a more appropriate method to estimate life years and subsequent QALYs.

The base-case analysis included data for patients receiving vinflunine in the estimation of utility values, which is currently not recommend in England. The ERG believes that such patients should have been excluded from the analysis.

The age-related utility decrements are estimated from an outdated study that does not allow incorporation of decrements for patients aged more than 75 years old. The ERG believes that this is a limitation that possibly overestimates QALYs in both treatment arms.

In the base-case analysis, pembrolizumab was compared to UK SOC based on the distribution of the regimens observed in KEYNOTE-045. The ERG believes that cost of UK SOC should be based on the UK market share of docetaxel and paclitaxel.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Overall, the quality of the systematic reviews of clinical effectiveness and of cost-effectiveness were reasonable and all relevant evidence have been identified.

The CS had several strengths:

- Overall, the quality of the systematic review was deemed to be reasonable, and assessment of risk of bias of the pivotal RCT was generally appropriate.
- The quality of the included trial was good, despite being an open-label trial, with a low risk of bias in most domains.
- The pivotal RCT had a comparator arm comprised of three possible drugs which is a good reflector of clinical practices since there is no internationally admitted comparator at this disease stage.
- The patient population recruited in the trial appears to be broadly similar to patients likely to receive pembrolizumab in England.
- Results for the trial were accurately presented and showed the risks and benefits of pembrolizumab compared to SOC.
- The company has undertaken an extensive survival analysis to model overall and progression-free survival.
- The economic model constructed by the company is logical and appears to capture two important features of the disease (progression-free survival and overall survival).

1.6.2 Weaknesses and areas of uncertainty

The CS had several weaknesses:

- Although the ERG believes that the inclusion of three possible drugs within the SOC arm is a good reflection of current practice, it would have been more methodologically acceptable to have only one single drug regimen in the SOC arm. Moreover, one of the three drugs available within SOC was vinflunine which is not recommended within the NHS.
- The ERG has concerns regarding the exclusion of two scoped comparators, BSC and retreatment with platinum-based regimen, from the decision problem.
- There is neither a head-to-head nor an indirect comparison of pembrolizumab with BSC which is a relevant comparator.

- Owing to open-label design of KEYNOTE-045, the results on quality of life should be treated with caution.
- There was uncertainty in the effectiveness of the methods used to adjust for treatment switching in the UK SOC.
- There was uncertainty in the extrapolation of overall survival estimates from the trial to the duration of the economic model, with cost-effectiveness results being sensitive to the methods used to extrapolate. The ERG has reservations regarding the choice of the cut-off point used for the piecewise modelling approach and the choice of parametric distribution used to model long-term overall survival.
- Health-related quality of life estimates included those for patients receiving vinflunine, which is not recommended in England. Using utilities by time to death is an unusual method of estimating life years and subsequent QALYs and resulted in slight overestimation of life years in both treatment arms compared to estimates based on progression status.
- Estimation of age-related utility decrements was based on an outdated study that did not incorporate a decrement for patients aged more than 75 years old, resulting in overestimation of QALYs.
- Counter-intuitive utility estimates were obtained when reported separately for each treatment arm. That is, when estimating utilities based on time to death patients receiving UK SOC reported higher estimates, whereas when estimating utilities based on progression status patients receiving pembrolizumab reported higher estimates.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of modifications to the model assumptions made by the company.

Overall changes:

- Excluding vinflunine patients from the estimation of utility values.
- Using utility values based on progression status rather than time to death.
- Using pooled utility and adverse event disutility values.
- Changing source of estimating age-related utility decrements.

- Setting adverse event prevalence and costs related to pneumonia, hypophosphatemia and fatigue to zero.
- Estimating the cost of UK SOC based on the UK market share of docetaxel and paclitaxel.
- Use a cut-off point of 24 weeks for the overall survival modelling approach.
- Use a log-logistic distribution for overall survival modelling for pembrolizumab and UK SOC.

The ERG have presented a scenario with a preferred base-case analysis for pembrolizumab versus UK SOC. The ICER has increased slightly compared with the CS submission, resulting in a deterministic ICER of £51,405 per QALY including a patient access scheme (PAS).

The ERG carried out some exploratory analyses using the ERG preferred base-case, and noted that the vast majority (84% to 97%) of benefits in terms of life years gained was from the extrapolated data rather than the observed data.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

Urothelial cancer arises from the transitional cells in the bladder. These are cells that stretch with the expansion of the organ and can occur in the bladder, renal pelvis, ureter, or urethra (Company Submission (CS), p33). The company states that urothelial cancer accounts for approx. 90% of bladder, renal pelvis, ureter and urethral cancers. Some locations of urothelial cancers are less common than others, e.g. upper tract urothelial cancer (UTUC) of the ureter is 4 times less likely than urothelial cancer in the renal pelvis (CS, p33).

The major distinction between different urothelial cancers is between non muscle-invasive and invasive carcinomas. According to Cancer Research UK, some non-muscle invasive carcinomas are papillary carcinomas, and others are flat carcinomas, e.g. carcinoma in situ (CIS) and high grade T1 tumours, which grow from the bladder lining into the layer below, the lamina propria.[1] Cancer Research UK also identify invasive cancers, which grow into the deeper layers and beyond into other organs.

The NICE guidelines suggest a similar distinction between non-muscle invasive (NMIBC) and muscle-invasive bladder cancers (MIBC). MIBC can, in later stages, be locally advanced or metastatic. The company suggests that muscle-invasive cancers that are locally advanced or metastatic could be treated with pembrolizumab in 2nd and 3rd line. Symptoms of the primary tumour in the bladder include blood in urine, burning when passing urine, increased urinary frequency or urgency, pain in the lower abdomen or back. Though these symptoms can lead to a misdiagnosis of urinary tract infection in women (CS, p35).

Survival rates are strongly correlated to disease stage (CS, p35). According to Cancer Research UK, around 90% of patients with stage 1 cancer survive beyond 5 years but the survival is no more than 10% at 5 years in stage 4 cancers.[2] This is in line with the company's description (CS, p39). The company states that 1-year and 5-year survival rates have not significantly improved in the past 10 years (CS, p31). This is supported by statistics on survival published by Cancer Research UK. They report that between 2005 and 2006, 73.9% of adults survive 1 year after diagnosis, and in 2010-2011 it was 72.4%. The 5-year survival rate was 55.5% in 2005-2006, and 53.7% in 2010-2011.[3] The company connects the lower survival rate of urothelial cancer compared to other GU cancers such as kidney cancer to the different biology of the carcinoma

and the low ability to detect the cancer at an early stage. The company also highlights that there is a lack of advances in the development of therapies (CS, p35).

The company indicates that staging of urothelial carcinoma is undertaken according to the Tumour, Node and Metastases (TNM) classification which provides staging information as 0, I, II, III or IV. The Evidence Review Group's (ERG) clinical advisors have confirmed the use of the TNM staging system.

On page 34, the company states that around 75% of newly diagnosed urothelial bladder cancers are non-muscle invasive (also called NMIBC), which have a high rate of recurrence (70%) and progression into muscle invasive disease (10-25%). The statement is misleading since it is high-risk NMIBC has a recurrence rate of 70% over 5 years and high-risk forms only represent 10% of all NMIBC. Low-risk NMIBC has low recurrence and progression is very rare.

The company states that patients with muscle invasive urothelial cancer will be offered radical surgical treatments, e.g. full cystectomy. The ERG's clinical experts commented that patients can also be treated with radical radiotherapy, ideally with chemo-radiotherapy. The ERG's clinical experts also commented that the correct terminology for the surgical procedure is radical cystectomy and overall that the phraseology used in the CS implies an unfamiliarity with United Kingdom (UK) bladder cancer practice.

The company states that surgery is followed by difficult lifestyle adjustments for patients and carers due to decreased urinary and sexual function. This reduces the quality of life "consistently and significantly" (CS, p36). This again can be supported by advice given by Cancer Research UK.

The ERG however found a discrepancy between the annual cost estimates that the company quoted. The company quotes estimates given by Leal et al.[4] for costs of bladder cancer in 2012 and Sangar et al.[5] for cost estimates in 2001-2. The company report that, according to Leal et al.,[4] informal care constitutes 18% of costs, productivity losses due to mortality and morbidity 23% (misquoted by company as 29%) and healthcare costs 59% (misquoted by company as 53%) of the total costs of bladder cancer in the European Union (EU) (CS, p36). According to Leal et al.,[4] the total healthcare costs were €286 million, the total costs including productivity loss and

informal care costs were €543 million in 2012 in the UK. Bladder cancer accounted for 5% of total healthcare costs and 3% of cancer costs in the EU.[4]

This is radically different to the total costs for bladder cancer quoted by the company from Sangar et al. of £55.39 million in 2001-2002. Sangar et al.[5] do not present the costs of an annual spend on bladder cancer, but direct and indirect costs over 5 years of cases. These costs include diagnosis, treatment and 5-year follow up of direct and indirect costs.[5] Direct costs include expenditure related to diagnosis, treatment and 5-year follow up.[5] Indirect costs include loss of earnings, which were taken as an average weekly wage in relation to age and sex.[5] They do not take relapses into account. If we assume that there is no relapse, and that patients are diagnosed every year, we can assume that the annual costs estimated by Sangar et al.[5] are £55.39 million, assuming that every year the same amount of patients are added to the group of cancer patients. This is much less than the annual costs suggested by Leal et al.[4] The cost differences may be accounted for by differential costs for medical equipment, medication, higher salaries and follow-up, but the variations suggests that there may be an error in one of these studies.

The ERG's clinical experts commented that the very high treatment costs of bladder cancer are related to the costs of managing surveillance and treatment for NMIBC. High-risk NMIBC requires lifelong cystoscopic surveillance, and recurrences require operative resection. Our clinical advisors commented that they expect the costs of locally advanced or metastatic disease to be relatively low by comparison as survival is short. Therefore, it appears misleading in the CS to lean too heavily a small number of cases to estimate the total costs for all bladder cancer and to justify the costs of second line treatment. The two groups are different and pembrolizumab treatment in second line should have little impact on the majority of healthcare costs for bladder cancer.

2.2 Critique of company's overview of current service provision

The company states that standard care for second-line treatment of urothelial cancer has remained the same in the last decade: platinum-based chemotherapies and taxane regimens are, according to the company, standard treatment (CS, p31). However, the use of taxane regimens is not regulated by National Institute for Health and Care Excellence (NICE) guidelines[6] and does not have Medicines and Healthcare Products Regulatory Agency (MHRA) marketing authorisation in

the UK for bladder or urothelial cancer; notwithstanding our clinical advisors tell us that taxanes are used in UK practice.

The company states that pembrolizumab has been granted a Breakthrough Therapy Designation for advanced melanoma, for advanced (metastatic) non-small cell lung cancer (NSCLC) and advanced NSCLC whose tumours express PD-L1 and for locally advanced or metastatic urothelial cancer with progression on or after platinum containing chemotherapy by the Food and Drug Administration (FDA). In the UK, pembrolizumab is recognised under the MHRA's Early Access to Medicines Scheme for unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care, and has received Promising Innovative Medicines (PIM) designation for treatment of metastatic NSCLC under certain circumstances (CS, p31).

The treatment pathway is, as the company states, determined by the performance status of the patient and the level of renal function. According to the NICE guideline[6] it also takes the recurrence history, size and number of cancers, histological type, grade and stage, risk category of the cancer and the predicted risk of recurrence into account. The company positions pembrolizumab as 2nd line treatment for locally advanced or metastatic MIBC. The current treatment pathway is a chemotherapy regimen for 2nd line and no regulated treatment for 3rd line, although the NICE scope suggests docetaxel and paclitaxel (see Figure 1).

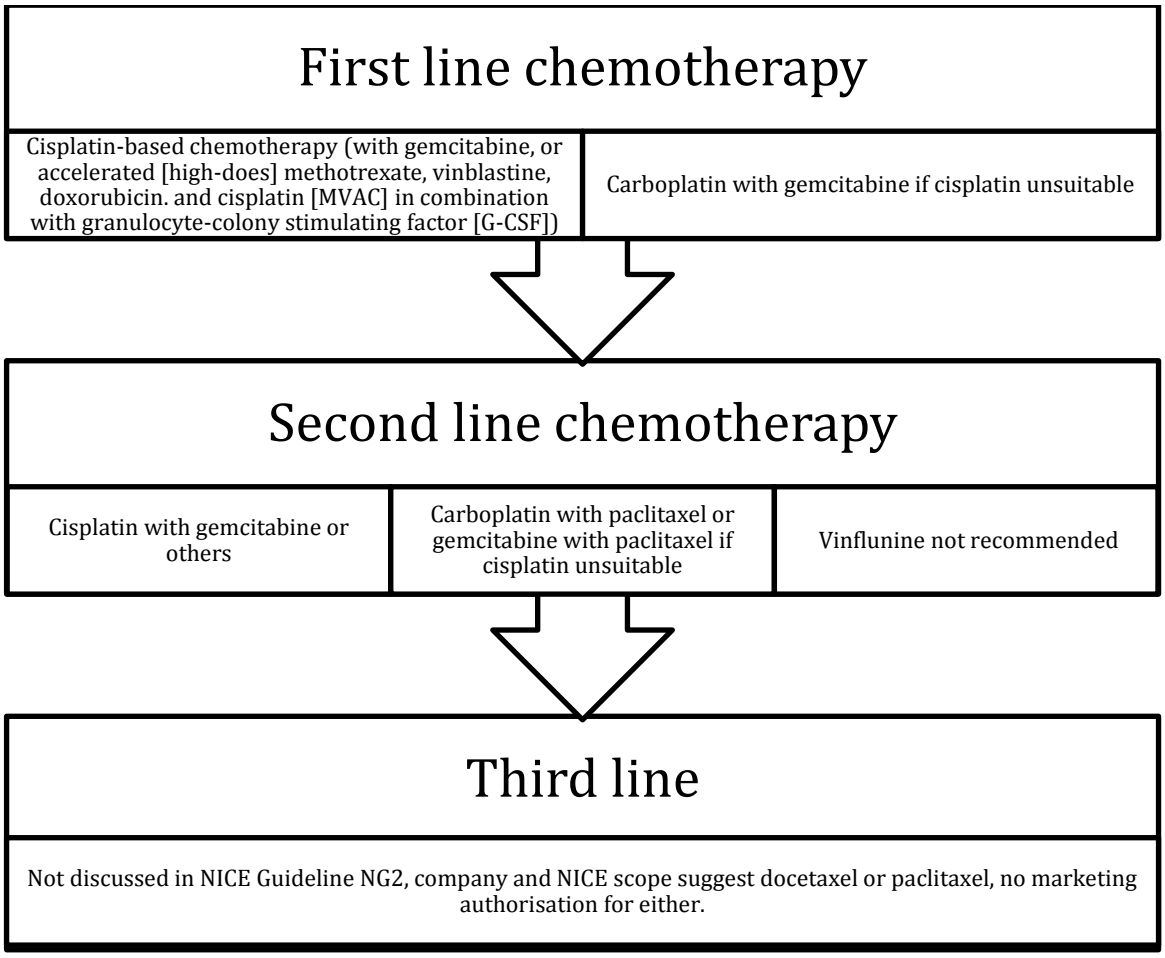


Figure 1: Treatment pathway

Cisplatin-combinations should be offered to patients with advanced or metastatic urothelial bladder cancer who are otherwise physically fit (Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1) and have adequate renal function (glomerular filtration rate (GFR) of 60 ml/min/1.73m^2 or more).[7] Carboplatin-combination chemotherapies should be offered if cisplatin-based chemotherapy is unsuitable, e.g. ECOG performance status is 2, renal function is inadequate or there are comorbidities.

The company points out that there is currently no UK marketing authorisation for urothelial cancer for the use of carboplatin with paclitaxel and gemcitabine with paclitaxel, the alternatives to cisplatin-combinations (CS, p36). The ERG can confirm that only cisplatin-combinations have a marketing authorisation. The ERG can also confirm that vinflunine is not recommended for treating advanced or metastatic transitional cell carcinoma of the urothelial tract after treatment

with platinum-based chemotherapy in the UK (CS, p37). The National Comprehensive Cancer Network (NCCN) even claims that there is no standard second line treatment (CS, p41).[8]

The company highlights that there is a "high unmet need for urothelial cancer therapies that prolong survival without greatly increasing toxicity or significantly compromising patients' quality of life" (CS, p31). The European Society for Medical Oncology (ESMO) practice guidelines for bladder cancer supports this claim by stating that "[a]bout 50% of patients are unfit for cisplatin-containing chemotherapy due to a poor Performance Score (PS), impaired renal function or comorbidity".[9] The company expects 502 stage IV patients to be eligible for treatment with pembrolizumab in 2017, rising to 532 in 2021. This accounts for less than half the stage IV patients each year.

2.3 Critique of changes to service provision

The company suggests introducing pembrolizumab as a 2nd line treatment for locally advanced or metastatic urothelial cancers after an initial first line chemotherapy and replacing platinum-based chemotherapy or gemcitabine with paclitaxel as 2nd line treatment. The company also suggests that pembrolizumab replaces docetaxel and paclitaxel as 3rd line treatment for patients with locally advanced or metastatic urothelial cancer. The NICE guideline for bladder cancer (NG2)[7] does not recommend a 3rd line treatment, but the final scope for pembrolizumab suggests, as does the company, that patients receive docetaxel or paclitaxel after two lines of chemotherapy. However, docetaxel and paclitaxel do not have marketing authorisation in the UK for urothelial or bladder cancer. There is also no report by the European Medicines Agency (EMA) for docetaxel or paclitaxel for urothelial or bladder cancer, although the ESMO practice guideline also mentions taxane-based regimes for 3rd line treatments.[9]

3 Critique of company's definition of decision problem

3.1 Population

The population in the decision problem, and subsequent clinical evidence matches the population described in the final scope. The population of relevance includes patients with locally advanced or metastatic urothelial cancer who have progressed on or after platinum-containing chemotherapy. In the KEYNOTE-045 trial,[10] 75.8% of patients had a prior cisplatin therapy while 23.2% of patients previously received carboplatin. The use of a prior platinum based-regimen could occur either at the stage of inoperable locally advanced/metastatic disease, or as part of adjuvant (following surgery) / neoadjuvant (prior to surgery) therapy for localised muscle-invasive urothelial cancer.

In the submission, the company stated that the anticipated label indication covers locally advanced/metastatic urothelial carcinoma in people who received prior chemotherapy, rather than prior platinum-based chemotherapy. The company did not provide any explanation for this. The Evidence Review Group have received in confidence information indicating that the proposed indication wording which has been submitted to the EMA by the company is:

- KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy.
- KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

This means that the anticipated label indication of pembrolizumab is broader than the population in the KEYNOTE-045. If the label indication does not restrict the use of pembrolizumab to patients who previously received a platinum-based regimen, the label indication cannot be supported by clinical evidence since 100% of people had a prior platinum-based regimen in KEYNOTE-045. Evidence on the effectiveness of pembrolizumab in people ineligible for cisplatin will be provided by the full results of KEYNOTE-052 study which enrolled 370 patients in a single-arm trial.[11, 12]

3.2 Intervention

The intervention in the decision problem is pembrolizumab as monotherapy, which matches the final scope. The company provides a description of the technology and the mechanism of action of pembrolizumab (CS p27) which the ERG's clinical advisors have confirmed is an accurate description. Pembrolizumab is an intravenously administered medication that has been authorised for use in indications other than this current appraisal including:

- treatment of advanced (unresectable or metastatic) melanoma in adults;
- first-line treatment of metastatic NSCLC in adults whose tumours express programmed cell death 1 ligand 1 (PD-L1) with a ≥50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations; and
- treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

With regards to the present submission, pembrolizumab is currently unlicensed in people with urothelial cancers, which means the benefit/risk balance has not been assessed by the European regulatory authority. In this report, the ERG will present the main clinical effectiveness and safety outcomes of pembrolizumab in adults with locally advanced/metastatic urothelial cancers. Based on this evidence, the ERG believes it is likely that the Committee for Medicinal Products for Human Use (CHMP) will conclude that the benefits of pembrolizumab outweighs the risks.

Pembrolizumab is a highly selective humanised monoclonal antibody against programmed death-1 (PD-1). It exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and programmed cell death 1 ligand 2 (PD-L2), on antigen presenting tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab activates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates antitumour immunity.

Pembrolizumab is part of a new class of immunotherapies which comprises drugs like nivolumab and atezolizumab. Pembrolizumab is not the only PD-1 inhibitor that has been evaluated within the scope of urothelial cancers. Atezolizumab is one of these and is currently subject to an ongoing appraisal (ID939). Nivolumab and durvalumab should also emerge in the coming months.

Pembrolizumab is given using an IV infusion, over a 30-minute period. The anticipated licensed dosing regimen is 200mg every 3 weeks with a treatment continuing until disease progression or unacceptable toxicity, whichever occurs first. Table 4 in the CS (p29) summarises administration and costs of pembrolizumab, and information provided in this table regarding the treatment administration concur with those in the KEYNOTE-045 trial.

3.3 Comparators

The comparators described in the decision problem are docetaxel and paclitaxel. This differs substantially from the NICE final scope given that the company excluded best supportive care (BSC) and retreatment with first line platinum based chemotherapy regimen as comparators.

The company indicated that alternative active treatments are available (e.g. docetaxel and paclitaxel) which means BSC is not a relevant comparator. The ERG does not fully agree with this since the company only considered people with locally advanced/metastatic urothelial cancers eligible for chemotherapy, which can be defined according to our clinical advisors as patients with an ECOG performance score of 0-2. Within the National Health Service (NHS), there is a significant proportion of people with locally advanced/metastatic urothelial cancer who have had one prior platinum-based regimen and who cannot undergo chemotherapy owing to a poor performance status (defined as ECOG PS 3-4). These patients are therefore only eligible to receive BSC. In the KEYNOTE-045 trial, the population included had an ECOG PS 0-2, which meant that patients with an ECOG PS $\geq$3 were excluded. Given that the KEYNOTE-045 is the only trial that evaluated pembrolizumab in people with locally advanced/metastatic urothelial cancer after failure to platinum-based therapy, there is no evidence to compare pembrolizumab to BSC in patients with ECOG PS 3-4 either directly or indirectly. The ERG is aware of a phase 3 randomised controlled trial (RCT) which compared vinflunine + BSC with BSC alone.[13] This trial could have been used to compare pembrolizumab to BSC indirectly but the relevance is questionable given that the trial only included people with PS 0-1.

In summary, although the ERG believes that BSC is a relevant comparator for people with PS 3-4, there was no evidence offered to compare pembrolizumab with BSC. While patients with an ECOG PS 4 would definitely not receive any treatment other than BSC, our clinical advisors suggested that treatment with pembrolizumab could be considered in people with an ECOG PS 3

given the relatively favourable safety profile of the drug. However, this would have to be supported by clinical effectiveness data in this subgroup.

With regards to retreatment with a platinum-based chemotherapy, the company indicated that no evidence exists for a comparison between pembrolizumab and retreatment with platinum-based chemotherapy, thus the latter was excluded. The ERG believes this is not a valid reason to exclude retreatment with platinum-based chemotherapy. Our clinical advisors indicated that retreatment with platinum-based chemotherapy can be considered within the NHS depending on the time to recurrence/progression after platinum therapy. In cases of early recurrence/progression (<12 months), which corresponds to the vast majority of patients, retreatment with platinum-based chemotherapy would in general not be considered while it could be considered in the rare cases of late recurrence (> 12 months). In case of relapse after 6-12 months, a carboplatin-gemcitabine therapy can be occasionally offered in second line (after first line platinum regimen) of locally advanced/metastatic urothelial cancers but only in patients with good PS.

With regards to the comparators, the ERG would like to highlight that neither the NICE scope nor the company submission have included other PD-L1 inhibitors such as atezolizumab, nivolumab, or durvalumab; although all these drugs are anticipated to have the same positioning should they be recommended by NICE within the NHS.

3.4 Outcomes

The outcome measures to be considered in the NICE scope have been reported in the decision problem. They are overall survival (OS), progression-free survival (PFS), response rates (RR), adverse effects (AE) and health-related quality of life (HRQoL).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the company's approach to systematic review

The CS undertook a systematic review for evidence of clinical effectiveness of relevance to the decision problem. The review included searches for studies on the intervention and comparators for a potential network meta-analysis (NMA).

The ERG's quality assessment of the CS, based on the Centre for Review and Dissemination (CRD) quality assessment questions for systematic reviews,[14] is summarised below (see Table 1). The quality of the company's systematic review is reasonable although very limited information was provided on the reason for exclusion of studies following full text review. The submitted evidence generally reflects the decision problem.

In the CS, the ERG noted that the numbers of full-text publications assessed for eligibility in Figure 5 (n=32) do not match the text on page 45 (text states 31 full-texts). In the CS clarification response, the company confirmed that 32 full-texts were reviewed.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Is sufficient detail of the individual studies presented?	Yes although this is limited to one study
5. Are the primary studies summarised appropriately?	Yes

4.2 Description of company's search strategy

The company reports two sets of broad searches for studies that could inform both direct and indirect comparisons (see CS section 4.1.2). The first set of searches, aiming to identify RCTs on pembrolizumab and several comparators chosen to satisfy a number of regulatory authorities, was undertaken in June 2016. The second set specifically sought additional comparators (cisplatin+gemcitabine and methotrexate, vinblastine, doxorubicin and cisplatin (MVAC)) and was undertaken in February 2017. Both sets of searches were undertaken in a reasonable range of

sources, including bibliographic databases, trials registers, conference proceedings and the company's own records. Database searches were limited to English language, but were not limited by date. Most search terms and lines were combined appropriately.

There are some issues that may have resulted in some records being missed: a) line 22 of the Embase cisplatin+gemcitabine / MVAC search misses out line 17; b) the use of 'NOT' combined with many study type terms in all the bibliographic database searches; and c) not hand searching the reference lists of relevant reviews or articles. However, the use of other search terms in the database searches and searching in other sources mean that overall the clinical effectiveness searches appear to be reasonably comprehensive. At the clarification stage, the ERG requested an update of the first set of searches and the company responded "it was not possible to run the updated search in the short timeline provided. However, we do not anticipate any new studies, given the limited clinical advancements in this area." The ERG's targeted independent searches for systematic reviews and longer term survival data identified two additional relevant studies.[13, 15, 16]

4.3 Inclusion / exclusion criteria used in the study selection

The eligibility criteria are listed in CS Table 6, CS page 44. The eligible population includes adults with advanced/metastatic urothelial carcinoma recurring or progressing follow platinum-based regimen. The intervention of interest for this single technology appraisal (STA) is pembrolizumab, which is stated in the Population Intervention Comparator Outcome Study Design (PICOS) table along with six different comparators (paclitaxel/gemcitabine; carboplatin/paclitaxel; cisplatin+gemcitabine; MVAC; docetaxel; and paclitaxel). The company indicated that the listed comparators were selected consistent with practice relevant to the UK setting. Therefore, vinflunine was not mentioned since this drug was issued with a negative recommendation by NICE in 2013.[17] The company has not listed BSC (see Section 3.3).

For the purpose of indirect and mixed treatment comparisons, the company included any RCTs with comparisons between any of the interventions of interest. This is why the vinflunine pivotal RCT [13] was included although vinflunine is not listed. To improve the quality of the reporting, the ERG believes that it would have been clearer to list all the potential comparators in the PICOS table (CS table 6, page 44) while identifying those of relevance to the UK setting. The company's eligibility criteria for the systematic review state that trials with outcome measures

including progression-free survival (PFS), overall survival (OS), objective response rate (ORR), adverse events (grade 3 and above), time to progression (TTP), duration of response (DoR), immune-related toxicity (any grade), health-related quality of life (HRQoL) should be included regardless of whether these were primary or secondary outcomes. These match the decision problem and the NICE scope although immune-related toxicity was not clearly specified. In terms of study design, the company included RCTs and excluded non-RCTs and observational studies. The ERG believes that the exclusion of non-randomised studies is justified owing to the risk of these studies presenting inadequate control of biases that could threaten the validity of indirect and mixed treatment comparisons.[18]

4.4 Identified studies

The main trial of the CS is the KEYNOTE-045 study (1 clinical study report (CSR) provided by the company, one conference proceeding,[19] plus one original article published after the company submission[10]). The company also included this trial in their indirect and mixed treatment comparison (for discussion of the NMA see relevant section). The trial was funded by Merck Sharp and Dohme (MSD).

The details of the trial were summarised and discussed in the CS on pages 49-84. The trial design was reported on page 49 of the CS. The KEYNOTE-045 study was an international, Phase III, randomised, open-label trial comparing pembrolizumab (200mg IV every 3 weeks) with investigator's choice of either paclitaxel (175mg/m^2 every 3 weeks), docetaxel (75mg/m^2 every 3 weeks), or vinflunine (320mg/m^2 every 3 weeks) in people with metastatic or locally advanced/unresectable urothelial cancer after recurrence or progression following platinum-based chemotherapy.

The dose regimen of vinflunine corresponded to that of the summary of product characteristics (SPC) for Javlor (brand name of vinflunine). Both docetaxel and paclitaxel are not licensed for urothelial cancers but these agents are commonly used in practice with dose regimens as in the KEYNOTE-045 trial.

Before randomisation, investigators had to select one treatment from the control arm to use in the event that the patient was randomised to the control arm. The ERG noted that there was no clear basis for the investigators' choice of comparators and asked the company to provide further

clarifications. In their clarification response, the company indicated that investigators were allowed to choose between paclitaxel, docetaxel and vinflunine, according to their clinical practice, provided vinflunine was approved in their countries. Paclitaxel and docetaxel were also available to investigators in countries where vinflunine was approved.

The company has not elaborated further on the choice of investigators according to their clinical practice. The choice between these three agents may differ across centres since, as emphasised in Bellmunt's paper,[10] there is no internationally accepted standard of care after platinum-based chemotherapy. At investigator level, the preference between the three chemotherapy regimen may also vary according to the patients' characteristics and history given that the safety profile of each drug is not exactly the same. The company has not reported baseline characteristics of KEYNOTE-045 patients according to the investigator's choice before randomisation. Consequently, the ERG is unable to confirm the strict comparability of patients depending on investigator's choice before randomisation, and cannot exclude the absence of significant heterogeneity within the KEYNOTE-045 population. Although a RCT comparing pembrolizumab with one single treatment would have been more methodologically acceptable, the ERG appreciate that the KEYNOTE-045 study was a pragmatic trial since the Standard of Care (SOC) arm, comprising several chemotherapy options, is a good reflector of current practices. The ERG is aware of another recent appraisal related to advanced breast cancer treatment where a new agent (eribuline) was compared to treatments chosen by the investigator.[20]

The randomisation was done in a 1:1 ratio: 270 patients were randomly assigned to the pembrolizumab group, and 272 to the SOC group (medication breakdown: 84 had paclitaxel, 84 had docetaxel, and 87 had vinflunine; missing for 17). Randomisation was stratified by ECOG performance score (0-1 vs. 2), presence or absence of visceral metastasis, haemoglobin (≥10g/dl vs. <10g/dl), and time to completion of most recent chemotherapy (<3 months or ≥ 3 months).

Treatment continued until radiographic disease progression, unacceptable toxicity, intercurrent illness that prevented further administration of treatment, investigator's decision to withdraw the subject, confirmed positive serum pregnancy test, non-compliance with trial treatment or procedure requirements, lost to follow-up, completed 24 months of treatment with pembrolizumab, administrative reasons, or withdrawal of consent for treatment.
Permitted concomitant medications were those considered necessary by the investigators and were recorded on the electronic case report forms (eCRF).

Eligibility criteria were reported on pages 52-53 of the CS and in table 10 on page 66. The trial was designed to select patients with locally advanced/metastatic urothelial cancers (histology: predominantly or exclusively transitional cell; upper tract [renal pelvis or ureter] or lower tract [bladder or urethra]) after recurrence or progression to a platinum-based regimen used either at first line (metastatic setting or inoperable locally advanced disease), at second line of metastatic disease, or as part of an adjuvant/neoadjuvant therapy for localised muscle-invasive urothelial cancer (post or prior to cystectomy).

Patients were recruited from November, 2014 to November, 2015 at 120 centres in 29 countries. The baseline characteristics of included patients are presented in Table 17 of the CS (p86-89). Although some of the baseline characteristics seem numerically different, there were no significant differences between the two treatment groups. The median age of patients was 67 years in the pembrolizumab group and 65 years in the SOC group and 74% were males. Almost 65% of patients were current or former smokers. The site of primary tumour was the lower tract in 86% of cases. The setting of the most recent prior therapy was first line in 62.7% of patients and second line in 21.2%. The proportion of patients with visceral metastasis was 89.2% in the pembrolizumab group and 86.0% in the SOC arm.

The company also presented the baseline characteristics according to biomarker assessment using the score of PD-L1 expression which was evaluated prospectively. PD-L1 expression was assessed in formalin-fixed tumour samples at a central laboratory using a commercially available assay kit. Only patients whose samples could be evaluated for PD-L1 expression were permitted to enrol in the study, regardless of the score of PD-L1 expression. PD-L1 assessment was expressed as a score defined as the proportion of PD-L1 expressing tumour and infiltrating immune cells relative to the total number of tumour cells. PD-L1 status was categorised as negative, positive, or strongly positive for combined positive scores (CPS) <1%, ≥1%, or ≥ 10% respectively.

In the clarification questions, the ERG asked the company to provide further justification for the cut-offs used (CPS≥1% or ≥ 10%). In their response, the company indicated that data external to KEYNOTE-045 informed the decision. The cut-off of ≥1% for positivity was determined with the analyses of tumour specimens from the KEYNOTE-012 trial (a phase 1 study that included a cohort of people of advanced urothelial cancer)[21] while the cut-off of ≥ 10% was based on a

review of data from the first 100 subjects enrolled in KEYNOTE-052 (a phase 2 study in people with advanced/metastatic urothelial cancer who are ineligible for cisplatin-based therapy).[22]

On page 90, the company referred to emerging evidence that PD-L1 expression level and clinical outcomes may be correlated. When asked to provide evidence for the link between PD-L1 expression and clinical outcomes, the company did not provide any evidence.

Based on these cut-offs, 55% of patients were negative for PD-L1 expression (CPS<1%) while 42.4% were positive (CPS≥1%) (40.7% in the pembrolizumab group vs. 44.1% in the SOC group). In KEYNOTE-045, 30.3% of patients were strongly positive for PD-L1 expression (CPS≥10%). The company noted that fewer subjects in the pembrolizumab group were strongly positive for PD-L1 expression compared to the SOC group (27.4% vs. 33.1%) which is explained as PD-L1 status was not a stratification factor.

Of the 542 randomised patients, only four were from the UK. In the clarification questions, the company were asked to comment on how representative the trial is to the UK population. In their response, the company indicated that the population is representative of the UK population since 13.8% of patients were from Western European countries (Belgium, France, Ireland, Netherlands, United Kingdom) and 41.1% were from European countries. Our clinical experts agreed on the generalisability of the KEYNOTE-045 trial to the UK population.

The data cut-off date for the second interim analysis was 7th September 2016. At that time, 40% of patients in the pembrolizumab group and 24.6% in the SOC group were continuing in trial, with 18.4% in the pembrolizumab group continuing to receive the drug on trial compared to 1.2% in the SOC group.

The most common reason for patients discontinuing treatment were progressive disease (54.9% and 50.6% in the pembrolizumab vs. SOC group), and adverse events (10.9% and 15.7% in the pembrolizumab vs. SOC group).

The description and critique of company's outcome selection is presented in section 4.7.

4.5 Relevant studies not included in the submission

To the best of our knowledge, the company included all the relevant studies related to pembrolizumab. The ERG has undertaken additional searches on long-term survival data to compare with the survival extrapolations from the company. This has been reported in the section 5.2.6.2.

4.6 Description and critique of the approach to validity assessment (quality assessment)

For RCTs, the company used specific criteria as described in the CRD's guidance for undertaking reviews in health care, which the ERG considers to be appropriate. However, the assessment undertaken by the company is inadequate because the ratings are study-specific but not outcome-specific. Ideally, one should be able to differentiate between the risk of bias (RoB) of PFS and OS if, for example, the outcome data completeness for these outcomes differs. The per study rather than per outcome RoB ratings conceal this distinction.

4.6.1 Quality assessment of the KEYNOTE-045 trial

CS Table 18 provides a quality assessment of the KEYNOTE-45 trial using criteria recommended by NICE. Table 2 summarises the ERG's check on this quality assessment (QA).

Table 2: Company and ERG assessment of trial quality

		KEYNOTE-045
1. Was randomisation carried out appropriately?	CS	Yes Electronic randomisation system (Interactive Voice Response System/ Interactive Voice and Web Response System (IVRS/IWRS))
	ERG	YES Subjects were assigned randomly to 1 of 2 treatment arms in a 1:1 ratio, i.e., to either pembrolizumab or the investigator's choice of paclitaxel, docetaxel, or vinflunine (chosen by the investigator before randomization occurred) (CS p49) Randomization was stratified by ECOG-PS (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months

		or ≥3 months). Subjects with ECOG-PS = 2 could not have additional poor prognosis factors (such as liver metastases, haemoglobin <10 g/dL, and time from completion of most recent chemotherapy <3 months [90 days]). Randomisation occurred centrally using an interactive voice response system/integrated web response system (IVRS/IWRS) (CS p49)
2. Was concealment of treatment allocation adequate?	CS	Yes, central allocation
	ERG	Yes (CS p89) See above
3. Were groups similar at outset in terms of prognostic factors?	CS	Yes The treatment arms were generally well balanced by all baseline characteristics, with the exception that slightly more subjects in the pembrolizumab arm were ≥65 years of age (61.1% vs 54.0%), ECOG PS = 0 (44.1% vs 39%) and in the never smokers (38.5% vs 30%) subgroups compared with the control arm.
	ERG	Some concerns: The treatment arms were generally well balanced by all baseline characteristics, with the exception that slightly more subjects in the pembrolizumab arm were ≥65 years of age (61.1% vs 54.0%), ECOG PS = 0 (44.1% vs 39%) and in the never smokers (38.5% vs 30%) subgroups compared with the control arm (CS p86). Slightly fewer subjects in the pembrolizumab arm were in the PD-L1 combined positive score (CPS) ≥10% group (27.4% vs 33.1%) compared with the control arm (CS p86) although this difference is not statistically significant.
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS	No (CS p89) Study is open label. No blinding of outcome assessment according to protocol
	ERG	No: open label trial with blinded outcome assessment This was an open-label trial; therefore, the applicant, investigator, and subject knew the treatment administered (CS p50). Imaging data for the primary analysis were centrally reviewed by independent radiologist(s) without knowledge of subject treatment

		assignment. The applicant and the trial team, consisting of clinical, statistical, statistical programming, and data management personnel, was blinded to subject-level PD-L1 biomarker results (including CPS ≥1%) until the cut-off value of PD-L1 expression level for CPS ≥10% was established and formally documented exclusively based on data outside of this trial. These steps were taken to ensure the unbiased use/integrity of the PD-L1 analysis. Access to the allocation schedule and/or the subject-level PD-L1 results for summaries or analyses were restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who had no other responsibilities associated with the trial. The statement in Appendix 7 (p85) mentioned above in the CS: "No blinding of outcome assessment according to protocol" is unclear or an error.
5. Were there any unexpected imbalances in drop-outs between groups?	CS	No
	ERG	Some comments: fewer subjects in the pembrolizumab arm compared with the control arm discontinued study treatment due to withdrawal by subject (1.1% vs 11.4%), or physician decision (2.3% vs 10.6%) (CS p166). However, all patients were included in the analysis (intention-to-treat (ITT)).
6. Is there any evidence that authors measured more outcomes than reported?	CS	No All outcomes listed in protocol appear in published paper
	ERG	No CS p61-65; protocol document
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS	Yes The analysis of primary efficacy endpoints was based on the ITT population, i.e. subjects were included in the treatment group to which they are randomised. The All Patients as Treated (APaT) population was used for the analysis of safety data in this study.
	ERG	ITT: yes

		The ITT population served as the primary analysis population in this trial (CS p86). Missing data: Some concerns From the CS (p103, 106): Objective Response Rate (ORR) per Confirmed Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 by Central Radiology Assessment, ITT population, p103 states: "In the pembrolizumab arm, 118 of 219 subjects (53.9%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 14. In the control arm, 109 of 200 subjects (54.5%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 15." The sample sizes (N's) given here are 219 for pembrolizumab (total 270, so 270-219 = 51 people missing [19%]) and 200 for control (total 272, so 272-200 = 72 missing [26%]), but this does not tally with Table 30 (p106; Summary of best overall response (BOR) based on RECIST 1.1 per central radiology assessment - All subjects (ITT population)) data for no post-baseline imaging (31 for pembrolizumab [11.5%] and 51 for control [18.8%]). A rate of around 20% of missing data in one of the groups could bias the results. Going back to the CS: Missing data adjusted for using a variety of censoring rules (p78) reproduced in CS

On page 144, the CS states that: "The risk of bias instrument can be used to assign summary assessments of within-study bias; low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high-risk of bias (high-risk of bias for one or more key domains)." On the basis of high risk of bias reported in the CS in the blinding domain (Appendix 14, p210), KEYNOTE-045 would be assigned an overall high risk of bias, although this is not emphasised in the CS (and blinding would be difficult or impossible due to the different adverse event profile of the interventions).

The ERG QA agrees with the company assessment of study quality for KEYNOTE-045 for randomisation and allocation concealment, blinding and reporting bias. Given the presence of a

key-domain rated as high-risk of bias (blinding or participants and personnel), the ERG also concludes that this study is at high risk of bias. Had the study been double-blinded, the ERG believes that the KEYNOTE-045 study would have still been at high-risk of performance bias. Indeed, given the very specific safety profile of the drugs evaluated in the KEYNOTE-045 trial, it is very likely that both patients and clinicians would have been able to correctly identify the allocated arm.

4.6.2 Quality assessment of the RCT evidence used in the indirect treatment comparison

The company has provided a quality assessment of four studies that were included within the scope of indirect and mixed treatment comparisons. Since no NMA was eventually conducted, the ERG did not comment on the quality assessment of these studies.

4.7 Description and critique of company's outcome selection

The NICE scope lists the specified the outcomes as:

- overall survival (OS)
- progression-free survival (PFS)
- response rates
- adverse effects of treatment
- health-related quality of life.

In the CS, the decision problem addressed all of the outcomes in the NICE scope since these were reported in the KEYNOTE-045 phase III study. The KEYNOTE-045 trial had co-primary endpoints that were PFS and OS. PFS and OS were assessed in the total population, in the population of patients positive for PD-L1 (CPS≥1%), and in the population of patients strongly positive for PD-L1 (CPS≥10%). Surprisingly, the recently published article reporting the results of KEYNOTE-045[10] does not state the assessment of PFS and OS in the population of patients positive for PD-L1 (CPS≥1%).

OS was defined as the time from randomisation to death from any cause and PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression or death due to any cause, whichever occurred first.

For the primary objective, PFS was assessed according to RECIST 1.1 based on blinded independent central radiologic (BICR) review. Tumour imaging was scheduled for week 9 followed by every 6 weeks during the first year and every 12 weeks thereafter. RECIST 1.1[23] corresponds to a revised guideline on response evaluation criteria in solid tumours (RECIST). These criteria are often used in clinical trials for anti-cancer therapies with the aim to assess tumour shrinkage (objective response) and disease progression. The RECIST 1.1 guideline defines key criteria on measurability of tumour at baseline (definition, methods of measurements), and tumour response evaluation (assessment of tumour burden and measurable disease, response criteria: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (StD)).

As part of the secondary endpoints, PFS was also assessed per RECIST 1.1 from randomisation to specific time points (6 and 12 months), and per modified RECIST (mRECIST) 1.1 based on BICR review. The mRECIST 1.1 corresponds to the RECIST 1.1 criteria with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1.

Other pre-specified secondary endpoints included ORR according to RECIST 1.1 and mRECIST 1.1 both based on BICR review, response duration according to RECIST 1.1 by BICR review, and occurrence of adverse events. ORR was defined as the proportion of patients who had either a CR or PR.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

The KEYNOTE-045 trial had several exploratory objectives which were mainly PFS assessed by RECIST 1.1 by investigator review along with the assessment of changes in HRQoL from baseline using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.

The ERG considers that the outcomes selected in the CS conform to those identified by NICE as relevant to the decision problem.

4.8 Description and critique of the company's approach to trial statistics

The primary objective of KEYNOTE-045 was to establish whether pembrolizumab was more effective than SOC (vinflunine, docetaxel or paclitaxel) for patients with platinum-refractory recurrent/progressive metastatic urothelial cancer, using OS and PFS as co-primary endpoints. This objective was extended to explore the effectiveness in both PD-L1 positive and PD-L1 strongly positive subgroups in addition to the general population, to give a total of 6 primary hypotheses.

In the clarification response related to the PD-L1 cut-offs, the company has indicated that the KEYNOTE-045 study was amended to include the analysis of efficacy outcomes based on data from KEYNOTE-012 and KEYNOTE-052. Since these two studies were designed to give information on the PD-L1 cut-offs, the ERG is concerned that the PD-L1 positive and strongly positive objectives were added as study amendments. It is also unclear why the company did not add evaluation of pembrolizumab effectiveness compared to SOC in PD-L1 negative (CPS<1%) patients as an additional primary objective.

The study initially aimed to recruit 470 participants, based on sample size calculations that were performed using both PFS and OS predictions. Details can be found in section 4.4.1 of the CS. Checks by the ERG show the trial to be suitably powered, particularly considering the trial actually recruited 542 subjects. Utility values for the economic analysis were obtained using the EuroQol 5 Dimensions (EQ-5D)-3L questionnaire.

Subjects were randomised using blocking and stratified based on haemoglobin level (≥10g/dL vs <10g/dL), presence/absence of liver metastases, ECOG performance score (0/1 vs 2) and time from most recent therapy (<3 months vs ≥3 months). Stratification did not consider response to previous chemotherapy and investigational centre or any other geographical factor, both of which were used in Technology Appraisal (TA) 272.[17] The block size of two was considered appropriate due to the international scale of the trial and the number of stratification variables.

KEYNOTE-045 planned for two interim analyses, the first being event related, estimated to occur at 11-14 months from the beginning of recruitment, with the second following 8 months later. The trial included an early stopping rule which could be triggered by an independent Data Monitoring Committee (DMC). The stopping rule was implemented following the second interim analysis, hence the data presented are not final.

The approach for missing data are presented in Table 13 of the CS. Overall, the ERG considers the statistical approach to be satisfactory. The ERG note that the company identifies that the proportional hazards assumption is not met in the data, yet refer to hazard ratios obtained from Cox proportional hazards (PH) models and their associated p-values, with no mention of their potential unsuitability.

There were six secondary outcomes focussing on PFS (using a modified RECIST), ORR and treatment duration. A further 17 subgroup analyses were pre-planned, looking at differences in typical baseline patient groups and tumour characteristics. Details of all planned analyses can be found in Table 10 of the CS. The ERG notes that whilst some consideration of multiplicity was made, the majority of results presented were not adjusted and so care should be taken when viewing p-values and confidence intervals due to the large number of analyses performed.

4.9 Description and critique of the company's approach to the evidence synthesis

4.9.1 Main RCT

The reporting of the KEYNOTE-045 trial was generally clear and comprehensive. Where possible the ERG has checked key data presented in the CS against those in the publication and clinical study report (CSR) provided by the company and summaries of the evidence can be seen in Section 4.10. The ERG did not find significant discrepancies between the CS and the published account of the trial.[10]

4.9.2 Indirect and mixed treatment comparisons

In section 4.10 of their submission the company presented, indirect and mixed treatment comparisons. These were conducted in order to provide information on the relative effectiveness of pembrolizumab compared to other interventions of interest given the absence of head-to-head

comparisons with these regimens. The company selected four trials in total, this includes the KEYNOTE-045 study. The characteristics of these studies were presented in a summary table on Table 49 (CS, p140) and with full details in Appendix 13. On pages 142-43, the company commented on the differences in patient populations across the trials and indicated that the vinflunine trial (NCT00315237) only included Asian patients. The ERG disagrees with this since, to the best of our knowledge, the ethnicity of included patients has been reported neither in the three main publications of the trial nor in the European Public Assessment Report (EPAR) for the drug when JAVLOR (brand name of vinflunine) was assessed by the CHMP. The vinflunine trial included 370 patients at 83 sites in 21 countries including Europe and North America. Although the ERG was unable to identify the distribution of people between Caucasians and Asians in the trial, it's very unlikely that the vinflunine trial only included Asian patients.

On page 142, the company indicated the choice of OS and PFS as outcomes of interest for the NMA, while adverse events and HRQoL outcomes were not proposed as these are inconsistently reported across trials. The company did not comment on the objective response rate.

On page 145, the company presented the network diagram of the four included studies and concluded that there was no possible way to connect the KEYNOTE-045 and the vinflunine trial (NCT00315237). The ERG believes that both trials have a common comparator (vinflunine + BSC in the vinflunine trial and vinflunine, which is one of the three treatments among the SOC arm in KEYNOTE-045). Although the KEYNOTE-045 trial did not refer to the use of BSC, it is the ERG's interpretation that patients in the SOC arm received chemotherapy alongside BSC.

Using this common comparator, the ERG considers that a NMA could in theory have indirectly compared pembrolizumab to BSC. As indicated in the critique of the decision problem, BSC is a relevant option in the UK setting in people with second-line metastatic urothelial cancer and with poor performance status (ECOG PS 3-4). However, the ERG noted that neither KEYNOTE-045 nor the vinflunine trial specifically included this subgroup of patients. Consequently, an exploratory NMA comparing pembrolizumab to BSC could have been considered, but the relevance of this indirect comparison would be questionable.

4.10 Summary of submitted evidence

4.10.1 Results from the pivotal trial

The evidence submitted by the company comes from the results of a single pivotal trial, KEYNOTE-045 (1 clinical study report (CSR) provided by the company, one conference proceeding,[19] plus one original article published after the company submission[10]).

Main outcomes

The primary efficacy endpoints were (CSR p86-90, p112):

- OS (i.e. time from randomisation to death due to any cause)
- PFS per RECIST 1.1 by BICR review (i.e. time from randomization to documented progressive disease or death due to any cause, whichever occurred first)

In:

- all subjects
- PD-L1 CPS ≥10%
- PD-L1 CPS ≥1%

The secondary endpoints were:

- ORR according to RECIST 1.1 by BICR review
- ORR according to mRECIST 1.1 by BICR review
- PFS according to mRECIST 1.1 by BICR review
- response duration.

Results are presented from a database cut-off date of 07 September 2016.

4.10.1.1 Effectiveness in the entire population (all subjects)

Overall survival was significantly improved in the pembrolizumab group compared to the chemotherapy group (hazard ratio for death, 0.73; 95% confidence interval (CI): 0.59 to 0.91; p = 0.002). The median overall survival was 10.3 months (95% CI: 8.0 to 11.8) in the pembrolizumab group, as compared with 7.4 months (95% CI: 6.1 to 8.3) in the chemotherapy group. The estimated overall survival rate at 12 months was 43.9% (95% CI: 37.8 to 49.9) in the pembrolizumab group, as compared with 30.7% (95% CI: 25.0 to 36.7) in the chemotherapy group.

A total of 437 events of disease progression or death occurred in the intention-to-treat population, with no significant difference in the duration of progression-free survival between the pembrolizumab group and the chemotherapy group (hazard ratio (HR) for death or disease progression, 0.98; 95% CI: 0.81 to 1.19; p = 0.42). The median progression-free survival was 2.1 months (95% CI: 2.0 to 2.2) in the pembrolizumab group and 3.3 months (95% CI: 2.3 to 3.5) in the chemotherapy group. The estimated progression-free survival at 12 months was 16.8% (95% CI: 12.3 to 22.0) in the pembrolizumab group and 6.2% (95% CI: 3.3 to 10.2) in the chemotherapy group (see Table 3).

Table 3: Analysis of OS and PFS per RECIST 1.1 by BICR review (ITT Population)

	Pembrolizumab	**Chemotherapy**
Number of patients	270	272
Number of progressions n (%)	218 (80.7)	219 (80.5)
PFS at 12 months (95% CI)	16.8 (12.3, 22.0)	6.2 (3.3, 10.2)
Median PFS (months) (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
HR for progression or death (95% CI)	0.98 (0.81, 1.19)	
p value	0.41648	
OS at 6 months (95% CI)	63.9 (57.9, 69.4)	56.7 (50.3, 62.6)
OS at 12 months (95% CI)	43.9 (37.8, 49.9)	30.7 (25.0, 36.7)
Median OS (months)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
HR for death (95% CI)	0.73 (0.59, 0.91)	
p value	0.00224	

In the total population, the objective response rate was significantly higher in the pembrolizumab group (21.1%; 95% CI: 16.4 to 26.5) than in the chemotherapy group (11.4%; 95% CI: 7.9 to 15.8) (p = 0.001) (see Table 4).

The results of the ORR analyses for confirmed response per mRECIST 1.1 by BICR review for all subjects in the ITT population are consistent with the RECIST Central Radiology Assessment.

Results of the analyses of PFS per mRECIST 1.1 by BICR review at 6 and 12 months among all subjects in the ITT population are consistent with results per RECIST 1.1.

The median time to response was 2.1 months in each group. The median duration of response was not reached in the pembrolizumab group (range, 1.6+ to 15.6+ months) and was 4.3 months (range, 1.4+ to 15.4+) in the chemotherapy group (plus signs indicate an ongoing response at data cut-off).

At the time of data cut-off, 41 of 57 patients (72%) with a response in the pembrolizumab group and 11 of 31 (35%) with a response in the chemotherapy group continued to have a response. Treatment was ongoing in 36 of 57 patients with a response (63%) in the pembrolizumab group and in 2 of 31 (6%) with a response in the chemotherapy group. The estimated percentage of patients with a duration of response of at least 12 months was 68% in the pembrolizumab group versus 35% in the chemotherapy group.[10]

Table 4: Analysis of ORR, time to response, response duration per RECIST 1.1 by BICR review; ORR and PFS per mRECIST 1.1 by BICR review; All subjects (ITT population)

	Pembrolizumab	**Chemotherapy**
Number of patients	270	272
Criteria: **RECIST 1.1 by BICR review**		
Number of Objective Responses	57	31
Objective Response Rate (%) (95% CI)	21.1 (16.4,26.5)	11.4 (7.9,15.8)
Difference for ORR (95% CI)	9.6 (3.5,15.9)	
p value	0.00106	
Mean (Standard Deviation (SD)) time to response† (months)	2.7 (1.2)	2.4 (0.8)
Median (range) time to response† (months)	2.1 (1.4-6.3)	2.1 (1.7-4.9)
Median (range)§ response duration‡ (months)	Not reached (1.6+ - 15.6+)	4.3 (1.4+ - 15.4+)
Number of Subjects with Response ≥ 6 Months (%)‡	41 (78)	7 (40)
Number of Subjects with Response ≥ 12 Months (%)‡	14 (68)	3 (35)
Criteria: **mRECIST 1.1 by BICR review**		
Number of Objective Responses	68	32
Objective Response Rate (%) (95% CI)	25.2 (20.1,30.8)	11.8 (8.2,16.2)
Difference for ORR (95% CI)	13.4 (7.0,19.9)	
p value	0.00002	
Number of PFS events	196 (72.6)	198 (72.8)
Median PFS (months) (95% CI)	2.2 (2.1, 3.4)	3.5 (3.1, 4.2)
HR for progression or death (95% CI)	0.91 (0.74, 1.11)	
p value	0.16411	

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.

‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.

§ "+" indicates the response duration is censored.

4.10.1.2 Effectiveness in people positive for PD-L1 expression (PD-L1 CPS ≥1%)

Pembrolizumab was associated with a survival benefit over chemotherapy among patients with a tumour PD-L1 CPS ≥1% (Table 5).

Analyses of PFS based on RECIST 1.1 by BICR review showed no reduction of risk of progression or death with pembrolizumab compared to SOC. The 6-month and 12-month PFS were higher for the pembrolizumab arm than in the control arm among subjects with PD-L1 CPS ≥1% (CSR p156).

Table 5 Analysis of OS; PD-L1 CPS ≥1% and PFS per RECIST 1.1 by BICR review

	Pembrolizumab	**Chemotherapy**
Number of patients	110	120
Number of progressions n (%)	85 (77.3)	98 (81.7)
PFS at 12 months (95% CI)	20.9 (13.6, 29.3)	4.4 (1.4, 10.4)
Median PFS (months) (95% CI)	2.1 (2.0, 2.4)	3.2 (2.2, 3.4)
HR for progression or death (95% CI)	0.91 (0.68, 1.24)	
p value	0.26443	
OS at 6 months (95% CI)	65.9 (56.1, 73.9)	51.6 (41.9, 60.4)
OS at 12 months (95% CI)	46.5 (36.4, 55.8)	28.8 (20.4, 37.7)
Median OS (months)	11.3 (7.7, 16.0)	6.9 (4.7, 8.8)
HR for death (95% CI)	0.61 (0.43, 0.86)	
p value	0.00239	

Results of the analysis of PFS per mRECIST 1.1 by BICR review at 6 and 12 months among subjects with PD-L1 CPS ≥1% are consistent with results per RECIST 1.1 (CS p117) (Table 6). The ORR per RECIST 1.1 and the ORR per mRECIST were higher with pembrolizumab than chemotherapy.

The median time to response is similar among patients with CPS ≥1% treated with pembrolizumab or chemotherapy (2.2 vs. 2.1 months).

Table 6 Analysis of ORR, time to response, response duration per RECIST 1.1 by BICR review; ORR and PFS per mRECIST 1.1 by BICR review; Subjects with PD-L1 CPS ≥ 1% (ITT population)

	Pembrolizumab	**Chemotherapy**
Number of patients	110	120
Criteria: **RECIST 1.1 by BICR review**		
Number of Objective Responses	26	10

Objective Response Rate (%) (95% CI)	23.6 (16.1,32.7)	8.3 (4.1,14.8)
Difference for ORR (95% CI)	16.9 (7.7,27.0)	
p value	0.00022	
Mean (SD) time to response† (months)	2.6 (1.0)	2.0 (0.1)
Median (range) time to response† (months)	2.2 (1.4-5.3)	2.1 (1.9-2.2)
Median (range)§ response duration‡ (months)	Not reached (1.6+ - 15.6+)	Not reached (1.5+ - 15.4+)
Number of Subjects with Response ≥ 6 Months (%)‡	21 (88)	3 (56)
Number of Subjects with Response ≥ 12 Months (%)‡	7 (78)	2 (56)
Criteria: **mRECIST 1.1 by BICR review**		
Number of Objective Responses	32	11
Objective Response Rate (%) (95% CI)	29.1 (20.8,38.5)	9.2 (4.7,15.8)
Difference for ORR	21.7 (11.8,32.2)	
p value	0.00001	
Number of PFS events	76 (69.1)	88 (73.3)
Median PFS (months) (95% CI)	2.1 (2.0, 3.9)	3.3 (2.6, 3.7)
HR for progression or death (95% CI)	0.86 (0.62, 1.19)	
P value	0.17024	

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates the response duration is censored.

4.10.1.3 Effectiveness in people strongly positive for PD-L1 expression (CPS ≥10%)

Pembrolizumab was associated with significantly longer overall survival than chemotherapy in people who had a tumour PD-L1 CPS ≥ 10% (hazard ratio for death, 0.57; 95% CI: 0.37 to 0.88; p = 0.005) (Table 7). The median overall survival was 8.0 months (95% CI: 5.0 to 12.3) in the pembrolizumab group, as compared with 5.2 months (95% CI: 4.0 to 7.4) in the chemotherapy group.

There was no significant difference between-group difference in the duration of progression-free survival (hazard ratio, 0.89; 95% CI: 0.61 to 1.28; p = 0.24).

Table 7: Analysis of OS; PFS per RECIST 1.1 by BICR review; PD-L1 CPS ≥10%

	Pembrolizumab	**Chemotherapy**
Number of patients	74	90
Number of progressions n (%)	59 (79.7)	72 (80.0)
PFS at 12 months (95% CI)	17.7 (9.5,27.9)	3.7 (0.7, 10.9)
Median PFS (months) (95% CI)	2.1 (1.9, 2.1)	3.1 (2.2, 3.4)
HR for progression or death (95% CI)	0.89 (0.61, 1.28)	
p value	0.23958	

OS at 6 months (95% CI)	58.5 (46.3, 68.9)	47.2 (36.0, 57.6)
OS at 12 months (95% CI)	39.8 (28.0, 51.3)	26.9 (17.5, 37.2)
Median OS (months)	8.0 (5.0, 12.3)	5.2 (4.0, 7.4)
HR for death (95% CI)	0.57 (0.37, 0.88)	
p value	0.00483	

Results for ORR were similar in the population of patients who had a tumour PD-L1 combined positive score ≥ 10% to those described for the whole population.

The results of the ORR analyses for confirmed response per mRECIST by BICR review are consistent with the RECIST 1.1 by BICR review (CS p 108). Results of the analysis of PFS per mRECIST by BICR review at 6 and 12 months are consistent with results per RECIST 1.1 (CS p117).

The median time to response (TTR) for responders was similar in both arms (pembrolizumab = 2.1 months, range: 1.4 to 5.3; control = 2.1 months, range: 1.9 to 2.2). Consistent with the overall ITT population, median DoR for 16 subjects with PD-L1 CPS ≥10% receiving pembrolizumab with a confirmed CR/PR had not yet been reached at the time of data cut-off (range: 1.6+ to 15.4+ months), whereas median DoR for the 6 subjects with PD-L1 CPS ≥10% receiving control was established at 4.4 months (range: 1.5+ to 10.8+ months). There were 14 subjects with PD-L1 CPS ≥10% in the pembrolizumab arm and 1 subject in the control arm with responses ≥6 months. There were 3 subjects in the pembrolizumab arm and no subjects in the control arm with response ≥12 months (CSR p152) (see Table 8).

Table 8: Analysis of ORR, time to response, response duration per RECIST 1.1 by BICR review; ORR and PFS per mRECIST 1.1 by BICR review; Subjects with PD-L1 CPS >= 10% (ITT population)

	Pembrolizumab	**Chemotherapy**
Number of patients	74	90
Criteria: **RECIST 1.1 by BICR review**		
Number of Objective Responses	16	6
Objective Response Rate (%) (95% CI)	21.6 (12.9,32.7)	6.7 (2.5,13.9)
Difference for ORR (95% CI)	19.3 (8.6,31.7)	
p value	0.00020	
Mean (SD) time to response† (months)	2.5 (1.0)	2.0 (0.1)
Median (range) time to response† (months)	2.1 (1.4-5.3)	2.1 (1.9-2.2)
Median (range)§ response duration‡ (months)	Not reached (1.6+ - 15.4+)	4.4 (1.5+ - 10.8+)

Number of Subjects with Response ≥ 6 Months (%)‡	14 (93)	1 (40)
Number of Subjects with Response ≥ 12 Months (%)‡	3 (76)	0
Criteria: **mRECIST 1.1 by BICR**		
Number of Objective Responses	19	7
Objective Response Rate (%) (95% CI)	25.7 (16.2,37.2)	7.8 (3.2,15.4)
Difference for ORR	22.5 (11.0,35.3)	
p value	0.00006	
Number of PFS events	52 (70.3)	65 (72.2)
Median PFS (months) (95% CI)	2.1 (2.0, 3.8)	3.3 (2.3, 3.7)
HR for progression or death (95% CI)	0.77 (0.52, 1.14)	
p value	0.09052	

† *Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.*
‡ *Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.*
§ *"+" indicates the response duration is censored.*

4.10.1.4 Effectiveness in further subgroup analyses

Subgroup analyses were pre-specified for the following variables (study protocol p100):

- Age category (< 65 vs. ≥ 65 years)
- PD-L1 subgroup (positive vs. negative)
- Strongly positive PD-L1 subgroup (to be defined based on emerging external data)
- Sex (female vs. male)
- Race (white vs. non-white)
- ECOG status (0/1 vs. 2 and 0 vs. 1/2)
- Geographic region of enrolling site (East Asia vs. non-East Asia, United States (US) vs. non-US, and EU vs. non-EU)
- Prior platinum therapy (carboplatin vs. cisplatin)
- Setting of most recent prior therapy (neoadjuvant vs. adjuvant vs. 1L metastatic vs. 2L metastatic)
- Presence or absence of liver metastases at baseline
- Baseline haemoglobin (≥ 10 g/dL vs. <10 g/dL)
- Time from completion/discontinuation of most recent prior therapy to baseline (< 3 months vs. ≥ 3 months)
- Histology (transitional cell vs. mixed transitional/non-transitional histology)
- Smoking status (never vs. former vs. current)
- Brain metastasis status (prior brain metastasis vs. no prior brain metastasis)
- Investigators' choice of paclitaxel, docetaxel or vinflunine
- Burden of disease in terms of baseline tumour volume

Primary outcomes

Analyses of OS by subgroup showed consistency of survival benefit favouring pembrolizumab across subgroups (CSR p116), with consistent point estimates for the HR in important subgroups such as ECOG-PS, liver metastasis, haemoglobin, time from prior chemotherapy, prior platinum (cisplatin versus carboplatin), investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine), and Bellmunt risk scores (see Table 9). Few exceptions were noted (e.g., 'non-White,' 'East Asia,' and 'never smoker'). The small numbers of events in some subgroups result in wide CIs and preclude an accurate interpretation of treatment effect.

Table 9: Overall survival by subgroup factors

	Control		Pembrolizumab		Hazard Ratio (95% CI)†
	N	Number of Events (%)	N	Number of Events (%)	
Overall	272	[redacted]	270	[redacted]	0.73(0.59,0.91)
<65 years	125		105		0.75(0.53,1.05)
≥65 years	147		165		0.76(0.56,1.02)
PD-L1 CPS < 1%	147		151		0.89(0.66,1.20)
PD-L1 CPS ≥ 1%	120		110		0.61(0.43,0.86)
PD-L1 CPS < 10%	176		186		0.80(0.61,1.05)
PD-L1 CPS ≥ 10%	90		74		0.57(0.37,0.88)
Female	70		70		0.78(0.49,1.24)
Male	202		200		0.73(0.56,0.94)
White	201		188		0.65(0.50,0.84)
Non-White	63		70		1.12(0.70,1.79)
ECOG 0/1	264		262		0.74(0.59,0.92)
ECOG 2	4		2		0.43(0.04,4.20)
ECOG 0	106		119		0.99(0.66,1.47)
ECOG 1/2	162		145		0.66(0.50,0.87)
East-Asia	48		58		1.25(0.72,2.18)
Non-East Asia	224		212		0.66(0.52,0.85)
EU	117		106		0.59(0.42,0.84)
Non-EU	155		164		0.79(0.60,1.06)
US	59		47		0.83(0.48,1.41)
Non-US	213		223		0.71(0.56,0.91)
Never Smoker	83		104		1.06(0.72,1.55)
Former Smoker	148		136		0.71(0.52,0.97)
Current Smoker	38		29		0.32(0.15,0.68)
Cisplatin	213		198		0.73(0.56,0.94)
Carboplatin	56		70		0.74(0.47,1.18)
Most Recent Prior Therapy:					
Neo Adjuvant	22		19		0.53(0.20,1.41)
Adjuvant	31	[redacted]	12	[redacted]	0.53(0.18,1.57)
1L Metastatic	157		183		0.72(0.54,0.95)
2L Metastatic	60		55		0.83(0.52,1.33)
Liver Metastases at Baseline:					
Presence	95		91		0.85(0.61,1.20)

Absence	176	[redacted]	179	[redacted]	0.67(0.50,0.89)
Hb ≥10 g/dL	223	[redacted]	219	[redacted]	0.71(0.55,0.91)
Hb <10 g/dL	44	[redacted]	43	[redacted]	0.75(0.46,1.22)
Time from Most Recent Chemo Therapy:		[redacted]		[redacted]	
≥3 Months	167	[redacted]	166	[redacted]	0.66(0.49,0.89)
<3 Months	104	[redacted]	103	[redacted]	0.82(0.58,1.15)
Transitional Cell	197	[redacted]	186	[redacted]	0.80(0.62,1.04)
Mixed Transitional/ nontransitional histology	73	[redacted]	82	[redacted]	0.58(0.37,0.89)
Prior Brain Metastasis	5	[redacted]	2	[redacted]	NA(NA,NA)
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	0.73(0.58,0.91)
Paclitaxel	84	[redacted]	266	[redacted]	0.76(0.55,1.04)
Docetaxel	84	[redacted]	266	[redacted]	0.76(0.55,1.05)
Vinflunine	87	[redacted]	266	[redacted]	0.69(0.51,0.94)
Burden of Disease on Baseline Tumour Volume:		[redacted]		[redacted]	
< Median	117	[redacted]	132	[redacted]	0.54(0.38,0.78)
≥ Median	135	[redacted]	115	[redacted]	0.91(0.68,1.23)
Risk Scores: 0	44	[redacted]	54	[redacted]	0.82(0.42,1.62)
1	97	[redacted]	96	[redacted]	0.73(0.49,1.08)
2	80	[redacted]	66	[redacted]	0.84(0.56,1.24)
3 or 4	45	[redacted]	45	[redacted]	0.76(0.47,1.24)
Site of Primary Tumour:		[redacted]		[redacted]	
Upper Tract	37	[redacted]	38	[redacted]	0.53(0.28,1.01)
Lower Tract	234	[redacted]	232	[redacted]	0.77(0.60,0.97)
Lymph Node Only	38	[redacted]	29	[redacted]	0.46(0.18,1.21)
Visceral Disease	233	[redacted]	240	[redacted]	0.75(0.60,0.95)

† Based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Score (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (Hb) (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
N = sample size
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

In the clarification questions, the ERG asked the company to provide further explanations of the cut-offs used to determine PD-L1 expression. In their response, the company commented that the OS benefit of pembrolizumab versus chemotherapy was observed across all PD-L1 CPS expression levels (page 8, clarification document). The ERG agree with this comment with respect to patients positive and strongly positive for PD-L1 expression. However, the ERG disagree with this statement pertaining to the group of patients negative for PD-L1 expression since the HR for death is 0.89 (95% CI 0.66, 1.20). Indeed, since the study was not designed to test the superiority of pembrolizumab in this subpopulation, the sample size may have been

insufficient to demonstrate a statistically significant difference in the risk of death. Therefore, the ERG believes that no conclusion, either positive or negative, can be drawn for the subgroup analysis in people with negative PD-L1 expression which would be eligible to pembrolizumab should this drug obtain a label indication regardless of PD-L1 expression.

Results for analyses of PFS by subgroup are consistent with the overall analysis and across subgroups (CSR p120) (see Table 10).

Table 10: Progression-Free Survival Based on RECIST 1.1 per Central Radiology Assessment (Primary Censoring Rule) by Subgroup Factors

	Control		Pembrolizumab		Hazard Ratio (95% CI)†
	N	Number of Events (%)	N	Number of Events (%)	
Overall	272	[redacted]	270	[redacted]	0.98(0.81,1.19)
<65 years	125	[redacted]	105	[redacted]	0.98(0.73,1.33)
≥65 years	147	[redacted]	165	[redacted]	1.08(0.83,1.40)
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	1.07(0.82,1.39)
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	0.91(0.68,1.24)
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	1.04(0.82,1.33)
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	0.89(0.61,1.28)
Female	70	[redacted]	70	[redacted]	0.96(0.63,1.44)
Male	202	[redacted]	200	[redacted]	1.01(0.81,1.28)
White	201	[redacted]	188	[redacted]	0.88(0.70,1.10)
Non-White	63	[redacted]	70	[redacted]	1.48(0.99,2.23)
ECOG 0/1	264	[redacted]	262	[redacted]	0.98(0.80,1.19)
ECOG 2	4	[redacted]	2	[redacted]	2.92(0.26,32.93)
ECOG 0	106	[redacted]	119	[redacted]	1.16(0.84,1.60)
ECOG 1/2	162	[redacted]	145	[redacted]	0.96(0.74,1.23)
East-Asia	48	[redacted]	58	[redacted]	1.68(1.05,2.67)
Non-East Asia	224	[redacted]	212	[redacted]	0.86(0.69,1.06)
EU	117	[redacted]	106	[redacted]	0.90(0.66,1.24)
Non-EU	155	[redacted]	164	[redacted]	1.03(0.80,1.33)
US	59	[redacted]	47	[redacted]	0.85(0.53,1.37)
Non-US	213	[redacted]	223	[redacted]	1.03(0.83,1.28)
Never Smoker	83	[redacted]	104	[redacted]	1.13(0.80,1.60)
Former Smoker	148	[redacted]	136	[redacted]	1.05(0.79,1.38)
Current Smoker	38	[redacted]	29	[redacted]	0.47(0.25,0.88)
Cisplatin	213	[redacted]	198	[redacted]	0.99(0.79,1.24)
Carboplatin	56	[redacted]	70	[redacted]	0.97(0.64,1.48)
Most Recent Prior Therapy:		[redacted]		[redacted]	
Neo Adjuvant	22		19		0.94(0.40,2.19)
Adjuvant	31	[redacted]	12	[redacted]	0.94(0.38,2.30)
1L Metastatic	157	[redacted]	183	[redacted]	0.88(0.69,1.14)
2L Metastatic	60	[redacted]	55	[redacted]	1.43(0.93,2.20)

Liver Metastases at Baseline:		[redacted]		[redacted]	
Presence	95		91		1.13(0.81,1.56)
Absence	176	[redacted]	179	[redacted]	0.93(0.73,1.18)
Hb ≥10 g/dL	223	[redacted]	219	[redacted]	0.94(0.76,1.17)
Hb <10 g/dL	44	[redacted]	43	[redacted]	1.26(0.77,2.05)
Time from Most Recent Chemo Therapy:		[redacted]		[redacted]	
≥3 Months	167		166		0.81(0.63,1.04)
<3 Months	104	[redacted]	103	[redacted]	1.28(0.94,1.76)
Transitional Cell	197	[redacted]	186	[redacted]	1.08(0.86,1.36)
Mixed Transitional/ nontransitional		[redacted]		[redacted]	
histology	73		82		0.84(0.57,1.24)
Prior Brain Metastasis	5	[redacted]	2	[redacted]	NA(NA,NA)
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	0.97(0.80,1.18)
Paclitaxel	84	[redacted]	266	[redacted]	0.94(0.71,1.24)
Docetaxel	84	[redacted]	266	[redacted]	0.97(0.73,1.28)
Vinflunine	87	[redacted]	266	[redacted]	1.09(0.83,1.44)
Burden of Disease on Baseline Tumour Volume:		[redacted]		[redacted]	
< Median	117		132		0.76(0.57,1.02)
≥ Median	135	[redacted]	115	[redacted]	1.22(0.93,1.61)
Risk Scores:		[redacted]		[redacted]	
0	44		54		0.83(0.52,1.33)
1	97	[redacted]	96	[redacted]	0.99(0.70,1.39)
2	80	[redacted]	66	[redacted]	1.09(0.75,1.58)
3 or 4	45	[redacted]	45	[redacted]	1.36(0.84,2.18)
Site of Primary Tumour:		[redacted]		[redacted]	
Upper Tract	37		38		1.18(0.67,2.07)
Lower Tract	234	[redacted]	232	[redacted]	0.97(0.78,1.19)
Lymph Node Only	38	[redacted]	29	[redacted]	0.56(0.30,1.07)
Visceral Disease	233		240	[redacted]	1.04(0.85,1.28)

† Based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Score (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
N = sample size
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Secondary outcomes

The company did not comment on the ORR by subgroups data. These were presented in Table 14.2-34 of the CSR (p398).

Table 11: Objective Response Rate Based on RECIST 1.1 per Central Radiology Assessment by Subgroup Factors

	Control		Pembrolizumab		Pembrolizumab vs Control
	N	Number of Responses (ORR%)	N	Number of Responses (ORR%)	Rate Difference (95% CI)†
Overall	272	[redacted]	270	[redacted]	[redacted]
<65 years	125	[redacted]	105	[redacted]	[redacted]
≥65 years	147	[redacted]	165	[redacted]	[redacted]
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	[redacted]
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	[redacted]
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	[redacted]
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	[redacted]
Female	70	[redacted]	70	[redacted]	[redacted]
Male	202	[redacted]	200	[redacted]	[redacted]
White	201	[redacted]	188	[redacted]	[redacted]
Non-White	63	[redacted]	70	[redacted]	[redacted]
ECOG 0/1	264	[redacted]	262	[redacted]	[redacted]
ECOG 2	4	[redacted]	2	[redacted]	[redacted]
ECOG 0	106	[redacted]	119	[redacted]	[redacted]
ECOG 1/2	162	[redacted]	145	[redacted]	[redacted]
East-Asia	48	[redacted]	58	[redacted]	[redacted]
Non-East Asia	224	[redacted]	212	[redacted]	[redacted]
EU	117	[redacted]	106	[redacted]	[redacted]
Non-EU	155	[redacted]	164	[redacted]	[redacted]
US	59	[redacted]	47	[redacted]	[redacted]

Non-US	213	[redacted]		223	[redacted]	
Never Smoker	83	[redacted]		104	[redacted]	
Former Smoker	148	[redacted]		136	[redacted]	
Current Smoker	38	[redacted]		29	[redacted]	
Cisplatin	213	[redacted]		198	[redacted]	
Carboplatin	56	[redacted]		70	[redacted]	
Most Recent Prior Therapy:		[redacted]			[redacted]	
Neo Adjuvant	22			19		
Adjuvant	31	[redacted]		12	[redacted]	
1L Metastatic	157	[redacted]		183	[redacted]	
2L Metastatic	60	[redacted]		55	[redacted]	
Liver Metastases at Baseline:		[redacted]			[redacted]	
Presence	95			91		
Absence	176	[redacted]		179	[redacted]	
Hb ≥10 g/dL	223	[redacted]		219	[redacted]	
Hb <10 g/dL	44	[redacted]		43	[redacted]	
Time from Most Recent Chemo Therapy: ≥3 Months	167	[redacted]		166	[redacted]	
<3 Months	104	[redacted]		103	[redacted]	
Transitional Cell	197	[redacted]		186	[redacted]	
Mixed Transitional/ nontransitional histology	73	[redacted]		82	[redacted]	
Prior Brain Metastasis	5	[redacted]		2	[redacted]	
No Prior Brain Metastasis	267	[redacted]		268	[redacted]	
Paclitaxel	84	[redacted]		266	[redacted]	
Docetaxel	84	[redacted]		266	[redacted]	
Vinflunine	87	[redacted]		266	[redacted]	
Burden of Disease on Baseline Tumour Volume: < Median	117	[redacted]		132	[redacted]	

≥ Median	135	[redacted]	115	[redacted]	[redacted]
Risk Scores:		[redacted]		[redacted]	[redacted]
0	44		54		
1	97	[redacted]	96	[redacted]	[redacted]
2	80	[redacted]	66	[redacted]	[redacted]
3 or 4	45	[redacted]	45	[redacted]	[redacted]
Site of Primary		[redacted]		[redacted]	[redacted]
Tumour:	37		38		
Upper Tract					
Lower Tract	234	[redacted]	232	[redacted]	[redacted]
Lymph Node Only	38	[redacted]	29	[redacted]	[redacted]
Visceral Disease	233	[redacted]	240	[redacted]	[redacted]

† Based on Miettinen & Nurminen method
N = sample size
ORR = Objective Response Rate
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Other secondary endpoints (ORR by mRECIST, PFS by mRECIST and response duration) were not presented by subgroup.

4.10.1.5 Health-related quality of life

Quality of life was assessed by EORTC-QLQ-C30 and EQ-5D questionnaires. The patient reported outcomes were to be collected prior to cycle 1, cycle 2, cycle 3, cycle 4 and every 2 cycles thereafter (e.g., cycle 6, cycle 8, cycle 10) up to a year or end of treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit (protocol p60).

EORTC-QLQ-C30:

Baseline global health status/quality of life (QoL) scores were similar between treatment arms (CS p122). At week 9, the global health status/QoL score was stable from baseline (least squares (LS) mean = -1.37 points; 95% CI: -4.10, 1.35) in the pembrolizumab arm, and a greater worsening of -5.75 points (95% CI: -8.62, -2.87) was observed in the control arm. The difference in LS means between pembrolizumab and the control arm at week 9 was 4.38 points (95% CI: 0.59, 8.16; two-sided p=0.02, not controlled for multiplicity). At week 15, there was an even greater difference in LS means between the pembrolizumab arm and control (9.05 points; 95% CI: 4.61, 13.48; two-sided p<0.001, not controlled for multiplicity) (see Table 12).

Table 12: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at Week 9 (FAS population)

	Pembrolizumab	Chemotherapy
Baseline: Number of patients	260	243
Baseline: Mean (SD)	61.51 (23.107)	59.12 (22.144)
Week 9: Number of patients	200	176
Week 9: Mean (SD)	63.04 (22.964)	58.48 (21.849)
Change from baseline at week 9	-1.37 (-4.10, 1.35)	-5.75 (-8.62, -2.87)
Difference in LS Means (95% CI)	4.38 (0.59, 8.16)	
p value	0.024	
Week 15: Number of patients	157	118
Week 15: Mean (SD)	67.57 (22.558)	57.91 (19.516)
Change from baseline at week 15	0.75 (-2.34, 3.83)	-8.30 (-11.76, -4.83)
Difference in LS Means (95% CI)	9.05 (4.61, 13.48)	
p value	< .001	
Time to first onset of a 10-point or greater score decrease from baseline in the EORTC QLQ-C30 global health status/QoL score: Hazard Ratio (95% CI)	0.70 (0.55, 0.90)	
p value	0.00182	

EQ-5D analyses

Results from EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses (CS p126). Both the EQ-5D visual analogue score (VAS) and the EQ-5D utility scores were stable over time for subjects in the pembrolizumab arm, whereas a worsening of EQ-5D VAS and utility scores was observed in the control group (see Table 13).

Table 13: Change from baseline in EuroQol EQ-5D VAS by time point - (FAS population)

	EuroQol EQ-5D VAS		EuroQol EQ-5D utility score	
	Pembrolizumab	Chemotherapy	Pembrolizumab	Chemotherapy
Baseline: Mean (SD) N Week 3: Mean (SD) N Mean (95% CI) change from baseline	68.0 (20.10) 232 69.1 (19.32) 232 1.1 (-1.1, 3.2)	67.3 (20.03) 209 66.1 (20.10) 209 -1.2 (-3.7, 1.2)	0.72 (0.22) 232 0.70 (0.24) 232 -0.02 (-0.05, 0.00)	0.70 (0.22) 209 0.68 (0.23) 209 -0.02 (-0.05, 0.00)
Baseline: Mean (SD) N Week 6: Mean (SD) N Mean (95% CI) change from baseline	68.8 (19.48) 210 69.3 (19.25) 210 0.5 (-1.8, 2.8)	69.8 (17.81) 191 65.6 (20.78) 191 -4.1 (-6.7, -1.5)	0.73 (0.22) 210 0.70 (0.25) 210 -0.03 (-0.06, 0.00)	0.73 (0.19) 191 0.66 (0.24) 191 -0.07 (-0.10, -0.04)
Baseline: Mean (SD) N Week 9: Mean (SD) N Mean (95% CI) change from baseline	69.2 (19.63) 195 70.0 (20.22) 195 0.8 (-1.8, 3.4)	70.5 (18.54) 169 66.5 (19.80) 169 -4.0 (-6.7, -1.4)	0.73 (0.22) 195 0.70 (0.27) 195 -0.03 (-0.07, -0.00)	0.73 (0.20) 169 0.65 (0.26) 169 -0.08 (-0.12, -0.05)
Baseline: Mean (SD) N Week 15: Mean (SD) N	71.8 (19.07) 153 73.4 (18.38) 153	70.8 (17.69) 112 67.7 (18.44) 112	0.76 (0.22) 153 0.74 (0.24) 153	0.76 (0.19) 112 0.67 (0.23) 112

Mean (95% CI) change from baseline	1.6 (-1.1, 4.4)	-3.1 (-6.4, 0.2)	-0.01 (-0.05, 0.02)	-0.09 (-0.12, -0.05)
Baseline: Mean (SD) N Week 21: Mean (SD) N Mean (95% CI) change from baseline	71.8 (18.75) 123 73.2 (18.65) 123 1.4 (-2.5, 5.3)	71.1 (18.20) 67 67.2 (18.75) 67 -3.9 (-8.5, 0.7)	0.77 (0.20) 123 0.77 (0.21) 123 -0.00 (-0.04, 0.03)	0.77 (0.19) 67 0.68 (0.22) 67 -0.09 (-0.14, -0.04)
Baseline: Mean (SD) N Week 27: Mean (SD) N Mean (95% CI) change from baseline	71.7 (18.49) 104 75.1 (19.00) 104 3.4 (-0.3, 7.1)	72.5 (16.99) 43 66.3 (19.48) 43 -6.2 (-13.3, 0.8)	0.77 (0.21) 104 0.76 (0.25) 104 -0.01 (-0.06, 0.03)	0.78 (0.19) 43 0.69 (0.25) 43 -0.09 (-0.16, -0.03)

The evaluation on quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, the validity of the findings is in question and conclusions may not be reliable from the quality of life results.

4.10.1.6 Safety: adverse events

Adverse events considered by the investigator to be "possibly," "probably," or "definitely" related to the study treatment were combined into the category drug-related AEs.

Adverse events that were considered by the investigators to be related to treatment occurred in 60.9% of the patients treated with pembrolizumab, vs. 90.2% of those who received chemotherapy (CS p152). Treatment-related events of grade 3, 4, or 5 severity were less frequent in the pembrolizumab group than in the chemotherapy group (15.0% vs. 49.4% of patients, CS p154), as was treatment-related discontinuation of therapy (5.6% vs. 11.0%). One pembrolizumab-treated patient died from treatment-related pneumonitis. Three other deaths in the pembrolizumab group were attributed by the investigators to study treatment, including one death related to urinary tract obstruction, one death related to malignant neoplasm progression, and one death of unspecified cause. In the chemotherapy group, treatment-related deaths were related to sepsis (in two patients), septic shock (in one), and unspecified cause (in one) (see Table 14). The ERG found surprising that the urinary tract obstruction and neoplasm progression that lead to two deaths in the pembrolizumab arm were attributed to study treatment.

The most common treatment-related adverse events of any grade were pruritus (19.5% of the patients), fatigue (13.9%), and nausea (10.9%) in the pembrolizumab group and alopecia (37.6%), fatigue (27.8%), and anaemia (24.7%) in the chemotherapy group.[10] There were no treatment-related events of grade 3, 4, or 5 severity that occurred with an incidence of 5% or more in the pembrolizumab group. In the chemotherapy group, treatment-related events of grade 3, 4, or 5

severity with an incidence of 5% or more were neutropenia (13.3%), decreased neutrophil count (12.2%), anaemia (7.8%), febrile neutropenia (7.1%), and decreased white-cell count (5.1%).

AEs of special interest (AEOSI) are immune mediated events and infusion related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab (CS p160). There were 45 (16.9%) subjects in the pembrolizumab arm with 1 or more AEOSIs. The only AEOSI of grade 3, 4, or 5 severity that were observed in two or more patients who were treated with pembrolizumab were pneumonitis (2.3% of the patients), colitis (1.1%), and nephritis (0.8%); there was only one grade 5 event (0.4%), which was pneumonitis.[10]

Table 14: Adverse Events in the As-Treated Population*

Event	**Pembrolizumab Group (N = 266)**		**Chemotherapy Group (N = 255)**	
	Any Grade	**Grade 3, 4, or 5**	**Any Grade**	**Grade 3, 4, or 5**
	Number of patients (percent)			
Treatment-related event†				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Event occurring in ≥10% of patients in either group‡				
Pruritus	52 (19.5)	0	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhoea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anaemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0	52 (20.4)	8 (3.1)
Peripheral sensory neuropathy	2 (0.8)	0	28 (11.0)	5 (2.0)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (14.1)	31 (12.2)
Peripheral neuropathy	1 (0.4)	0	27 (10.6)	2 (0.8)
Neutropenia	0	0	39 (15.3)	34 (13.3)
Alopecia	0	0	96 (37.6)	2 (0.8)
Event of interest§				

Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0
Infusion reaction	2 (0.8)	0	10 (3.9)	0
Nephritis	2 (0.8)	2 (0.8)	0	0
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0
Myositis	0	0	1 (0.4)	1 (0.4)

** The as-treated population included all the patients who received at least one dose of study treatment.*
† Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this was also the case for peripheral sensory neuropathy and peripheral neuropathy and for fatigue and asthenia.
‡ Events are listed in descending order of frequency in the pembrolizumab group.
§ The events of interest are those with an immune-related cause and are considered regardless of attribution to study treatment by the investigator.
They are listed in descending order of frequency in the pembrolizumab group. In addition to the specific preferred terms listed, related terms were also included.

4.10.2 Results from post-hoc analyses excluding vinflunine

The results from a post-hoc analysis where vinflunine was excluded from the SOC arm were presented in the CS. Since these analyses were conducted for the purpose of a cost-effectiveness within the UK perspective, these have been reported in the cost-effectiveness section.

4.10.3 Results from the NMA

No NMA was provided by the company.

4.11 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG on clinical effectiveness

4.12 Conclusions of the clinical effectiveness section

Pembrolizumab used as single agent was evaluated against SOC (either paclitaxel, docetaxel, or vinflunine) in the KEYNOTE-045 trial. This phase 3 trial was of good quality, with a low risk of

bias in most domains except for the blinding of participants and personnel since the study was open-label thus considered to be at high-risk of bias.

There were two co-primary endpoints that were assessed in the entire population, the population positive for PD-L1 expression, and the population strongly-positive for PD-L1 expression.

Regarding PFS, the risk of progression or death was similar between pembrolizumab and SOC in the three populations although the proportion of patients free from progression at 1 year was higher with pembrolizumab.

However, as far as OS is concerned, the risk of death was reduced with pembrolizumab compared to SOC in the three populations.

The results of PFS and OS in the numerous subgroups showed consistency with the overall findings for the entire population.

Evaluation of quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, it is difficult to draw reliable conclusions from the quality of life results.

The safety profile of pembrolizumab was more favourable than that of SOC. There was no treatment-related ≥3 event occurring with a frequency of ≥5% incidence in the pembrolizumab group.

As of April 2017, pembrolizumab is not licensed for urothelial cancers and a submission aimed to extend the marketing authorisation is currently being assessed with the CHMP. Based on the results of KEYNOTE-045 which presents the clinical effectiveness and safety profile of pembrolizumab in advanced/metastatic urothelial cancers after failure of platinum-based therapy, the ERG believes that it's likely that the CHMP will consider the balance between benefits and risks of pembrolizumab to be positive.

No indirect comparisons were presented by the company. There is no data comparing pembrolizumab to BSC which is a relevant comparator in people with poor performance status.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Objectives and search strategy

The CS states on p171 that the scope of the review was broadened to include patients with advanced or metastatic urothelial cancer irrespective of therapy line, in order to identify all relevant data that could inform development and population of the model. The company provided an appropriate description of the cost-effectiveness systematic, utility and cost/resource use reviews and details of the different search strategies were reported in Appendix 17 (the CS states on p171 that the detailed search strategy is in Appendix 23, however, there is no Appendix 23 in the CS). In brief, the company searched MEDLINE, Econlit, EMBASE, Cochrane library including the NHS Economic Evaluation Database and Health Technology Assessment (HTA) databases. Manual searches were also performed on oncology websites and conference proceedings. In addition, reference lists of included papers were also consulted. Original searches were carried out between 6th and 7th August 2015, and updated in December 2016. The search strategy was appropriate.

5.1.2 Inclusion/exclusion criteria used in the study selection

The CS on p172-173 (CS table 62) tabulated the inclusion and exclusion criteria for the systematic reviews of economic evaluations which included population, intervention/comparator, outcomes, study type, publication type, time limit, and language. The selection criteria limited studies to those published in English language, those in adult patients 18 years or older and studies published in the last 10 years. The study selection seemed appropriate. It is unclear what the inclusion/exclusion criteria was for either the cost and resource use; or HRQoL and utility systematic reviews.

5.1.3 Identified studies

CS Figures 32, 42 and 43 provided the flow diagrams for the economic evaluation; HRQoL and utility; and cost and resource use systematic reviews respectively. The company did state in the original CS that "a summary list of published cost-effectiveness studies has not been compiled".

The ERG requested at the clarification stage details of the 126 papers which were evaluated in full, including references and reasons why studies were excluded. For example, for the economic evaluation review in the original CS, 4 papers met the inclusion criteria from the original search but no further information or references were provided. Upon clarification the company excluded 3 of the 4 publications by stating "they should have been excluded during the secondary screening as although they provide relevant information in regards to the economic modelling, they were published prior to 2005". The company provided an excel document titled "ID1019 Economic SLR" which included references to the excluded studies.

The flow diagrams indicated that no studies were included for the original economic evaluation and the cost and resource use reviews; however, one study was identified from the updated cost and resource use search.[17] For the original HRQoL and utility review and updated search, 24 studies were extracted from 29 publications (the reference lists, characteristics and information on utility values for these studies were included in Appendix 18).

The CS did not state whether the studies were independently assessed by two reviewers. No quality assessment was conducted by the company, as stated on p175 "as no cost-effectiveness study meeting all inclusion criteria was identified". Furthermore, the CS does not formally report whether any of the modelling attributes from the included HRQoL and utility studies were used in the development of the *de novo* economic model of pembrolizumab.

Some additional studies relevant to the population were identified by the ERG through targeted searches of the CEA Registry, NHS EED and the HTA database, but none were relevant to the decision making context.

To summarise, no cost-effectiveness studies assessing pembrolizumab for patients with advanced or metastatic urothelial cancer were identified.

5.1.4 Conclusions

The company did not provide a formal conclusion from the data available of the three systematic reviews: economic evaluation, utility and cost/resource use.

5.2 Summary and critique by the ERG of the economic evaluation submitted by the company

5.2.1 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS. Including technologies regarded as current best practice for the two populations	UK SOC i.e. physicians choice of docetaxel or paclitaxel
Patient group	As per NICE final scope	Patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis (Cost per quality-adjusted life year (QALY))
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (lifetime duration)
Synthesis of evidence on outcomes	Systematic review	Data are drawn from one trial: KEYNOTE-045
Outcome measure	Quality-adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. Health states were evaluated using EQ-5D-3L data collected from KEYNOTE-045 trial

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefits	Yes
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		A range of sensitivity and scenario analyses are presented

5.2.2 Model structure

The company presented a *de novo* cost-utility partitioned survival model with a weekly cycle length and a lifetime time horizon. The model consisted of three health states: pre-progression, post-progression, and death (Figure 2). A half-cycle correction was applied in the base-case analysis.

The partitioned survival approach uses an "area under the curve" approach, where the number of patients in the two health states: PFS and OS, is taken directly from survival curves fitted to the clinical data. This approach did not consider post-progression survival directly. Instead, time in post-progression survival was derived from the difference in the area under the two survival health states (PFS and OS).

The model assumes all patients enter the model in the pre-progression health state. Patients in the pre-progression health state, stay in that health state until disease progression. Transitions to the death state could occur from either the pre-progression or post-progression health state. Costs of disease management, utilities and risks of death all differ between the pre-progression and the post-progression health states.

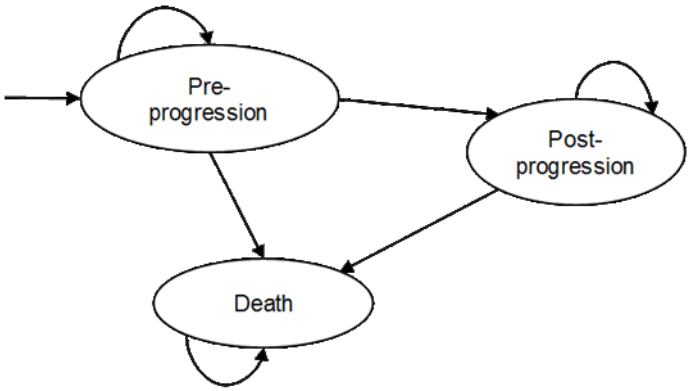


Figure 2: Model structure presented by the company

ERG summary

- Even though the model is a simple one with three health states, it is consistent with other models built in this disease area, and captures the two important clinical endpoints of OS and PFS. The cycle length of the model (1 week) should be sufficiently short to capture changes over the relevant time interval.

5.2.3 Population

The population modelled in the company's base case analysis included patients with metastatic or locally advanced/unresectable urothelial cancer which has recurred or progressed following platinum-containing chemotherapy.

The company also presented results for the following subgroups of patients in the CS Appendix:

1. patients with advanced or metastatic urothelial cancer of predominantly transitional cell histology.
2. patients with advanced or metastatic urothelial cancer of pure transitional cell histology.
3. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥1%) urothelial cancer.

4. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥10%) urothelial cancer.

Data for the base-case and the subgroup analyses were based on the KEYNOTE-045 study. The study population was assumed by the company to be reasonably similar to the UK population likely to receive treatment. However, out of the 542 patients recruited in the KEYNOTE-045 study, only 4 were from the UK (see section 4.4).

Individuals in the modelled cohort had an average starting age of 65.5 years and 74.2% were male. An average body surface area (BSA) of 1.90m^2 was used to estimate the dosing of paclitaxel and docetaxel. The average BSA value was taken from the European sites of KEYNOTE-045, whereas age and gender values were taken from the overall population recruited in KEYNOTE-045 (i.e. including patients from the US and Asia).

Information on patient characteristics for the subgroup analyses were provided in Appendix 9. However, in the economic model, the ERG found that the mean values of the patient characteristics used in the base-case analysis were used in all subgroup analyses. Furthermore, the ERG found that gender was not included as a model parameter.

For all subgroup analyses presented in the Appendix, the company stated that the results should be interpreted with caution as there is uncertainty around the estimates (due to small number of patients in the subgroups). However, only deterministic cost-effectiveness results were presented in the original submission. Upon request in the clarifications the company provided the probabilistic results.

ERG summary

- In the base-case analysis patients age and gender were taken from the overall trial population, however, the use of patient characteristics from only the European sites might result in more representative patients.
- The modelled population in all subgroup analyses were based on the characteristics of patients from the overall trial population.
- The impact of gender was not included in the estimation process in the economic model.

5.2.4 Interventions and comparators

In the company's base-case analysis, pembrolizumab is compared with UK standard of care (UK SOC) i.e. investigator's choice of paclitaxel or docetaxel. Based on the KEYNOTE-045 study, among patients who received paclitaxel or docetaxel (i.e. excluding vinflunine), 48.9% received paclitaxel and 51.1% received docetaxel. A scenario analysis is presented in which the UK SOC arm is based on the UK market share of paclitaxel and docetaxel (26% and 74%, respectively).

Pembrolizumab treatment is administered at a fixed dose every 3 weeks and should continue until radiologic disease progression, toxicities leading to discontinuation, physician's decision or 24 months of uninterrupted treatment with pembrolizumab. Based on clinical expert opinion, the company assumed that a maximum of 6 cycles were administered to reflect the UK clinical practice for the treatment regimens representing UK SOC. To estimate the duration of treatment in the pembrolizumab and comparator arms, time on treatment (ToT) data from KEYNOTE-045 was used. Separate parametric curves were fitted to the patient level treatment duration data from KEYNOTE-045 to represent ToT in the economic model (see Section 5.2.6 for more detail).

As part of the subgroup analyses presented in the CS Appendix, the company presented cost-effectiveness results for the overall patient population comparing pembrolizumab with individual regimens (i.e. pembrolizumab vs paclitaxel and pembrolizumab vs docetaxel).

The appropriateness of the pooled comparator treatment was considered by the ERG. Based on the ERG's clinical experts, paclitaxel and docetaxel were regarded as appropriate comparators in the UK setting. In addition, "lumping" the two treatment options as a single treatment was considered appropriate, since paclitaxel and docetaxel treatments are considered similar in terms of clinical effectiveness.

The economic model assumed that treatment effect with pembrolizumab lasted for a lifetime (35 years). Upon clarification, the company provided further scenario analyses looking at treatment effect which lasts only for 3, 5 or 10 years.

The ERG found an error in the application of maximum treatment duration of UK SOC in the model. That is, the duration of paclitaxel or docetaxel treatment continued beyond 18 weeks (6 cycles) and reached a maximum of 58 weeks. However, upon clarification the company provided the ERG with a new updated economic model correcting for this error.

The company added an option to the economic model to explore the possibility of patients continuing to take pembrolizumab for longer than maximum treatment duration. Whilst the maximum treatment duration was set to two years to match the KEYNOTE-045 trial, this could be changed within the model. However, the option to allow patients to exceed the maximum trial duration was labelled within the model as "% patients on treatment after 2 years", which the ERG believes to be inaccurate. A more suitable label should read "% patients on treatment after max treatment duration".

ERG summary

- The base-case analysis incorporates an appropriate comparator (UK SOC).
- After clarification, appropriate scenario analyses for the duration of pembrolizumab treatment effect have been performed by the company.
- The original economic model had an error in the application of maximum treatment duration for UK SOC treatment, this was corrected by the company.

5.2.5 Perspective, time horizon and discounting

The perspective is as per NICE reference case, with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. A lifetime horizon is modelled (35 years). In the base-case, costs and benefits were discounted at an annual rate of 3.5%.

ERG summary

- The perspective, time horizon and discount rates chosen by the company all follow NICE recommendations, and are appropriate to the decision problem.

5.2.6 Treatment effectiveness and extrapolation

Clinical outcomes from the KEYNOTE-045 trial were used to inform the transitions between health states in the model.

Primary endpoints

- Overall survival (OS)
- Progression-free survival (PFS)

Secondary endpoints

- Objective response rate
- Time to response
- Duration of response
- Adverse events of treatment
- Health-related quality of life

In this section we elaborate further on the co-primary endpoints: OS and PFS.

5.2.6.1 Overall survival

The estimation of long-term overall survival comprised the following methods:

1. Adjusting for treatment switching in the UK SOC arm
2. Overall survival extrapolation
3. Two-phase piecewise approach

1. Adjusting for treatment switching in the UK SOC

Three statistical techniques were used to adjust for treatment switching in the UK SOC arm, as some patients in this group received PD-L1 treatments following disease progression. These methods included the rank-preserving structural failure time (RPSFT), the simplified 2-stage method and the inverse probability of censoring weighting (IPCW). Treatment switching was accounted for in the survival models, with three different methods investigated in addition to an ITT analysis. Details of the methods can be found in the NICE Decision Support Unit (DSU) Technical Support Document 16 by Latimer and Abrams (2014).[24] Each was implemented and considered alongside their relative assumptions in section 4.7 and Appendix 10. There were 33 patients who switched from the control arm to other treatments; however, only 22 of these were actually eligible to switch with 11 patients appearing to switch prior to disease progression.

The ERG notes that three methods were investigated for adjusting for treatment switching: IPCW, RPSFT and 2-Stage.

- RPSFT was the least suitable for two reasons. Firstly, it censors patients prior to the time point at which they switched treatments in an attempt to remove bias, however this results in a loss of information. It then generates artificial survival times for those who switch. RPSFT also assumes a common treatment effect for both switchers to the experimental arm, and those who received it for the full trial. In KEYNOTE-045, subjects were able to

switch to a range of possible treatments, which included but were not limited to pembrolizumab. Hence, RPSFT was not a suitable choice.

- IPCW makes the assumption that there are no unobserved confounders. It relies on baseline and time dependent variables being available which predict prognosis and treatment switching. It censors patients at their point of switching, and weights the remaining patients according to their similarities to the censored patients in an attempt to remove any bias that the censoring has caused. Due to the uncertainty over the risk factors of bladder cancer and survival, it is difficult to gauge whether or not this is a suitable method in this case.
- The 2-Stage approach works when the treatment switching is linked to a particular event, e.g. disease progression, as occurred for the planned treatment switching in KEYNOTE-045. However, there were 11 subjects who switched without meeting the planned requirements, which will confound the analysis slightly. This method produces a treatment estimate for patients who switched and then shrinks their survival times accordingly to derive a survival time assuming they had not switched. However, as mentioned above, the subjects in KEYNOTE-045 did not switch to the same treatment, and so it may be incorrect to adjust their survival times by the same factor.

It is clear that none of these methods are perfect in this case. Whilst the RPSFT was the least suitable, it is difficult to decide between 2-Stage and IPCW. It is also difficult to conclude whether the methods are actually a significant improvement over the ITT analysis, or whether the adjustments go too far. The ERG would have liked to have seen further methods examined, including a simple censoring of patients at point of switch. Whilst this would have produced biased results and overestimated OS in the control arm, since it is known that switching was dependent on disease progression, it would have provided useful information in assessing the suitability of the other methods.

Table 15 and Table 16 present the treatment effect for overall survival and median overall survival, respectively. Results from the intention-to-treat (ITT) analysis (full analysis set) showed that pembrolizumab versus UK SOC had a treatment effect for overall survival of [redacted]. Treatment effectiveness results based on an adjustment method all had slightly greater treatment benefit, with hazard ratios (HR) ranging from [redacted] to [redacted]. The choice of the most appropriate adjustment method was based on the trial characteristics, the switching mechanism, the proportion of people switching, and the clinical validity of the

outcomes obtained. In the base case, the company chose the simplified two-stage method for people who switched to a PD-L1 treatment, and reported a treatment effect for overall survival of [redacted]. It was noted by the ERG that the 2-sided p-value of [redacted] for the simplified two-stage approach and the RPSFT had been retained from the ITT analysis.

On clarification, the company suggested that *'The p-value for the adjusted OS analysis using the RPSFT or the simplified 2-stage method is retained from the ITT analysis, provided that the same statistical test is used in the ITT analysis than in the adjusted analysis. The reason is that, under the null hypothesis of no treatment effect, there is no switchover effect and thus the test statistics of the RPSFT and the simplified 2-stage methods follow the same statistical distribution as the ITT test statistic. As the p-value is the probability to obtain a more extreme value than the observed one under the null hypothesis, the p-value from the ITT analysis is preserved in the 2-stage model approach and the RPSFT approach.*'. The ERG considers this response to be satisfactory.

Table 15: Treatment effect for overall survival for pembrolizumab versus UK SOC (table obtained from company submission)

	Pembrolizumab vs. UK SOC		
Switching adjustment correction method	**Hazard Ratio**	**95% CI**	**p-value (2-sided)**
Intention-to-treat	[redacted]	[redacted]	[redacted]
Simplified two-stage[$]	[redacted]	[redacted]	[redacted]
Rank-preserving structural failure time (RPSFT)[¶]	[redacted]	[redacted]	[redacted]
Inverse probability censoring weighting (IPCW)	[redacted]	[redacted]	[redacted]

¶ Re-censoring applied to all control patients
§ No re-censoring applied
* P-value retained from ITT analysis by design
†: Bootstrap p-value

Median overall survival for the UK SOC based on an ITT analysis was [redacted] months. Results based on an adjustment for treatment switching ranged from [redacted] to [redacted].

Table 16: Median OS based on the ITT, simplified two-stage, RPSFT and IPCW methods

Switching correction method	**Median OS (months) (95% CI)**
UK SOC (ITT)	[redacted]
UK SOC - Simplified two-stage correction (no re-censoring)	[redacted]
UK SOC – RPSFT correction	[redacted]
UK SOC – IPCW correction	[redacted]

2. Overall survival extrapolation

Figure 3: Kaplan-Meier plots of overall survival and adjustment for treatment switching using the two-stage analysis for pembrolizumab vs UK SOC (obtained from the company submission)

Parametric models were fitted to the Kaplan-Meier (KM) plots (see Figure 3) for overall survival for pembrolizumab and UK SOC of KEYNOTE-045 trial. Various parametric models were tested (for example, exponential, Gompertz, log-logistic, log-normal, generalised gamma and Weibull). The preferred model was chosen by the company based on a combination of visual inspection of goodness-of-fit, long-term plausibility informed by clinical expert opinion, and using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Figure 4 and Figure 5 show the parametric curves for the fully-fitted KM curves for pembrolizumab and UK SOC, respectively. Table 17 shows the AIC and BIC for each parametric model for pembrolizumab and UK SOC (using the two-stage approach for treatment switching only) to the fully-fitted data for overall survival. Based on AIC and BIC the log-normal parametric models provided the best fit to these data. It should be noted here that in the economic model, the same parametric fit for overall survival was selected for both the intervention and comparator.

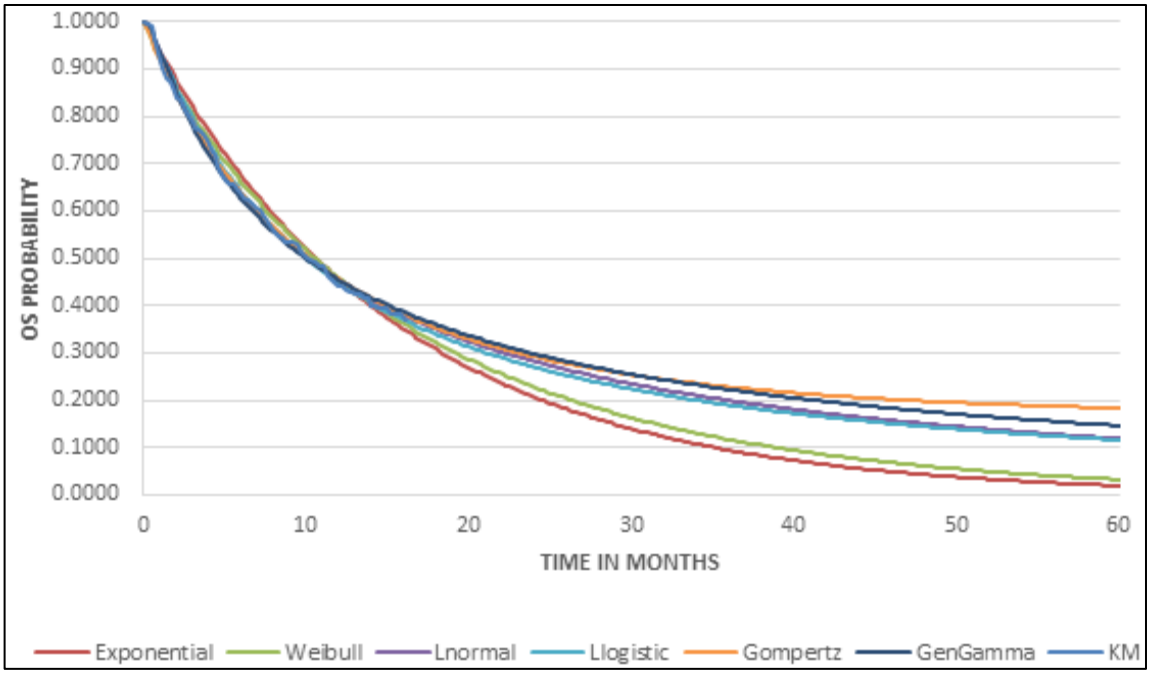


Figure 4: Kaplan-Meier plot along with parametric models for overall survival for pembrolizumab

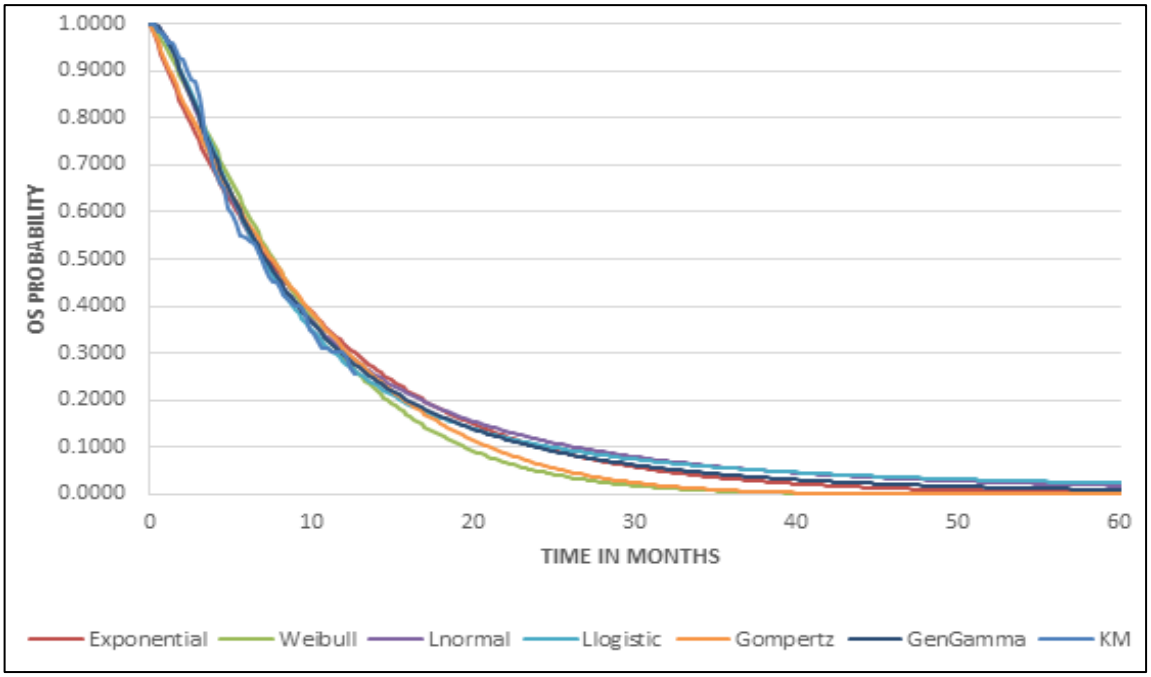


Figure 5: Kaplan-Meier plot along with parametric models for overall survival for UK SOC

Table 17: Goodness-of-fit statistics based on the fully-fitted parametric curves to data for overall survival

Parametric model	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC

Exponential	1612.4	1616	1092.5	1095.7
Weibull	1612.9	1620.1	1085.7	1092.2
Gompertz	1608.1	1615.3	1093.5	1099.9
Log-logistic	1606.3	1613.5	1075.1	1081.5
Log-normal	1601.5	1608.7	1078.2	1084.6
Generalised Gamma	1602.8	1613.6	1079.5	1089.1

Figure 6 shows the cumulative hazard associated with death following treatment with pembrolizumab compared to paclitaxel and docetaxel. As suggested by the company, these plots do not support the proportional hazards assumption, as the difference in hazard between treatments is not constant over time. In fact, the plots cross at approximately 14 weeks. The ERG agrees with the company that there is evidence to support the use of a piecewise model to extrapolate overall survival. The company suggested that the 40-week cut-off point is more appropriate than a 24-week cut-off to extrapolate beyond the observed data, because there is greater change in the slope before 40 weeks. Whilst this may be plausible, the ERG considers this to be a weak justification, because using the 40-week cut-off reduces the amount of observed data that could be used to extrapolate overall survival. It would have been helpful for the company to show how the various parametric models fitted the cumulative hazard plots to support/strengthen the justification for choosing a) a suitable cut-off point and b) an appropriate parametric model to extrapolate overall survival. The ERG has explored using a 24-week cut-off because at that time point we consider that the hazards follow a predictable path.

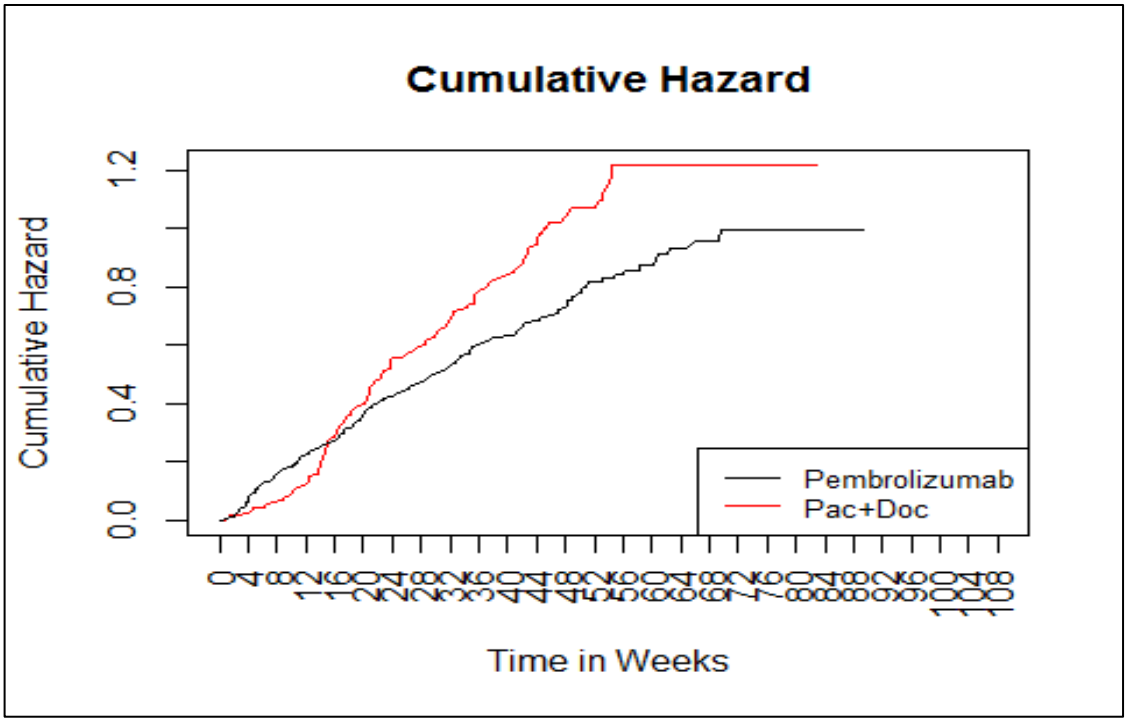


Figure 6: Cumulative hazard plot of overall survival for pembrolizumab versus UK SOC (obtained from company submission)

3. Two-phase piecewise approach

Estimation of long-term overall survival comprised of a two-phase piecewise approach. In the first phase, survival was estimated based on using the observed Kaplan-Meier survival data in KEYNOTE-045 up to a 40-week cut-off point. In the second phase, a series of parametric models were fitted to the observed data beyond the 40-week cut-off point. Figure 7 and Figure 8 show the Kaplan-Meier plots for overall survival for the UK SOC and pembrolizumab, respectively, along with parametric fits. Table 18 shows the AIC and BIC for each parametric model for pembrolizumab and UK SOC for overall survival using data beyond the 40-week cut-off. Based on the AIC/BIC and clinical opinion on the plausibility of these survival models, the log-normal parametric models were considered the most appropriate to project overall survival.

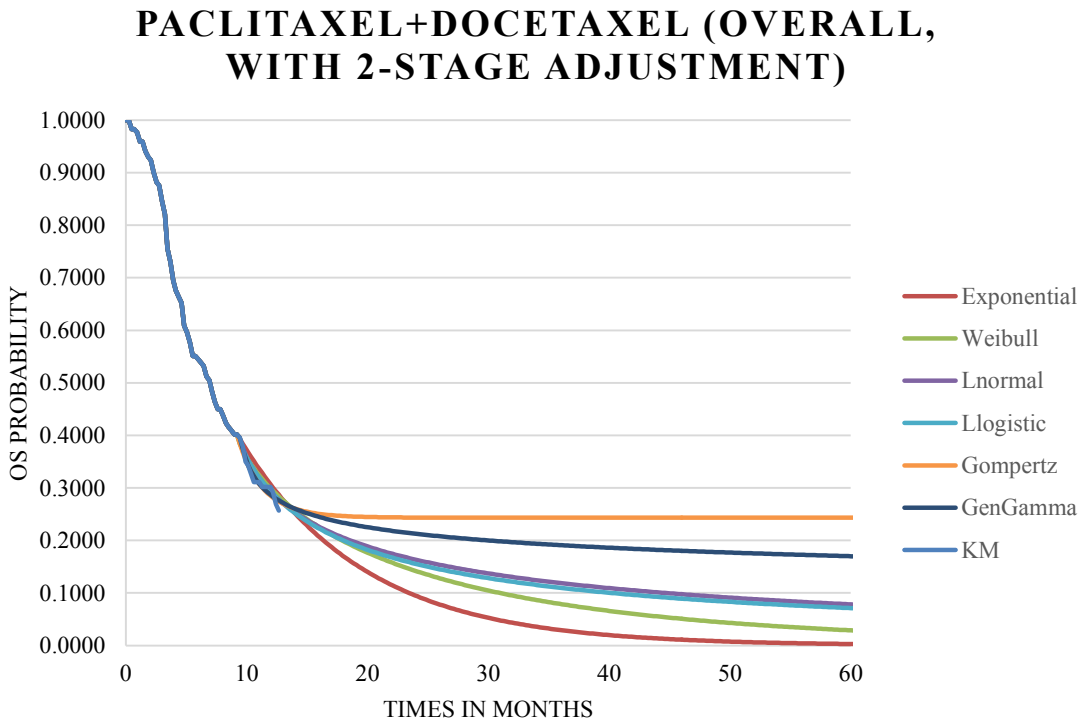


Figure 7: Kaplan-Meier plot for overall survival for UK SOC (2-stage adjustment applied), with various parametric models (obtained from the economic model)

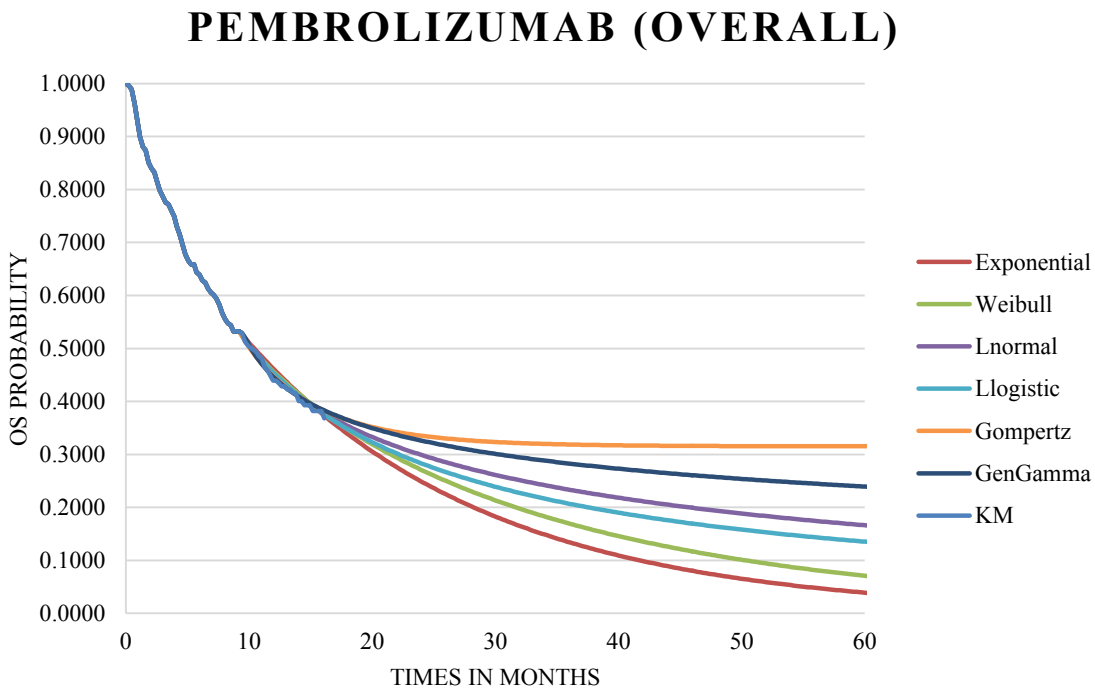


Figure 8: Kaplan-Meier plot for overall survival for pembrolizumab, with various parametric models (obtained from the economic model)

Table 18: Goodness-of-fit statistics based on the extrapolations using data beyond the 40-week cut-off, for pembrolizumab and UK SOC

Parametric model	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC
Exponential	339.1	342.1	165.1	167.1
Weibull	340.5	346.4	165	169.1
Gompertz	338.1	344	160.4	164.5
Log-logistic	339.4	345.3	163.7	167.7
Log-normal	337.5	343.4	161.8	165.9
Generalised Gamma	338.5	347.3	160.2	166.3

Figure 9 shows the estimated long-term overall survival using the two-phase piecewise approach, which is based on observed Kaplan-Meier data and log-normal extrapolations.

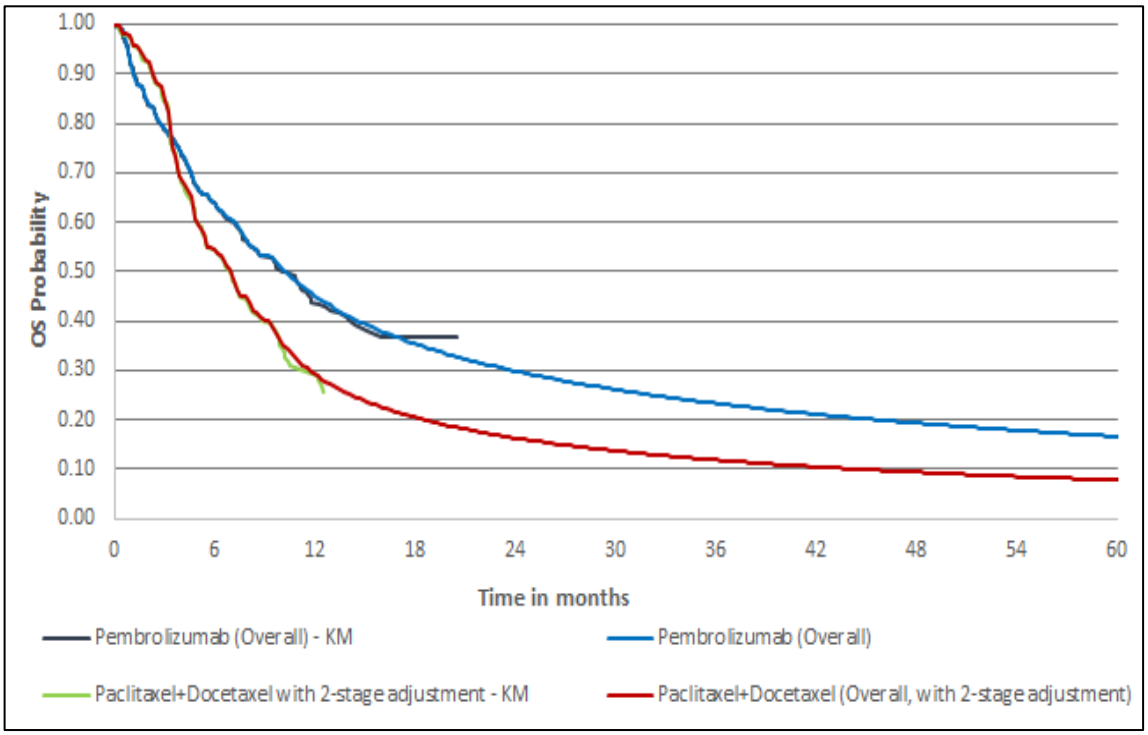


Figure 9: Kaplan-Meier plots for overall survival for pembrolizumab and UK SOC (2-stage adjustment applied), using a phase piecewise model

5.2.6.2 Critique of the Company's survival extrapolations

On page 183 in the CS, the company has compared the extrapolated OS for people in the UK SOC with that reported by Cancer Research UK for patients with stage IV bladder cancer.[1] They indicate that the 5 year OS from log-normal distribution is projected at 7.8% and consider this is

close to that of the observed data in the Cancer Research UK database (adults aged 15-99; period 2002-2006), which is 9.2% in men and 10.8% in women.

The ERG however, have some concerns around the comparability of people in the KEYNOTE-045 trial with those from Cancer Research UK. The data from Cancer Research UK are people with stage IV bladder (100%) cancer at diagnosis. While the staging of people in KEYNOTE-045 is similar (99.6% were stage IV), the rate of bladder cancer was lower in KEYNOTE-045 since 86.0% of patients had a site of primary tumour in the lower urinary tract (bladder or urethra) and 14.0% in the upper tract (renal pelvis or ureter). Arguing that upper tract urinary cancers (UTUC) have a poorer prognosis compared to lower tract urinary cancers (LTUC), the company explains that the 5 year OS found at 7.8% in UK SOC arm is lower than 9-11% as reported in Cancer Research UK owing to the inclusion of UTUC in KEYNOTE-045.

The ERG's clinical experts agreed on the general notion that UTUC are more aggressive and respond less well to chemotherapy compared to LTUC. Although the cancer staging was similar in KEYNOTE UK SOC and the population from Cancer Research UK, the ERG believes that people in KEYNOTE-045 were in a more advanced disease stage compared to the Cancer Research UK population. Our understanding of the data from Cancer Research UK is that it corresponded to people at diagnosis of metastatic disease who therefore were at first line therapy. In KEYNOTE-045, the setting of most recent prior therapy of included SOC patients, as per the inclusion criteria, was first line in 57.7% of cases, and second line in 22.1%. According to the listed inclusion criteria, the first-line platinum-containing regimen could have been in the metastatic setting or for inoperable locally advanced disease. The distribution among metastatic setting vs. inoperable locally advanced disease within the prior first-line therapy is not stated but we assume that it was mainly patients treated at the stage of metastatic setting.

Consequently, while people from Cancer Research UK were at the stage of diagnosis of metastatic disease, around 80% of people in the KEYNOTE SOC arm were likely to be either at second or third line of metastatic disease which makes this population at even greater risk.

Therefore, the ERG believes that the 7.8% five-year OS noted in the KEYNOTE UK SOC arm is very likely to be lower. Little else is known about the baseline characteristics of the patients who have generated the Cancer Research UK data, and so the ERG has reservations about using this data as a reference point.

The ERG has conducted a literature search in order to identify other sources of comparison from published data on similar population. Two studies were considered of potential interest. The ERG compared inclusion criteria, baseline characteristics, and survival outcomes of these populations and results are presented in Table 19, Table 20 and Table 21. These were not consistently reported in the trials which makes the comparisons difficult.

The von der Maase study[15, 16] seems to have included patients with the best prognostic features among the three studies: patients included for first-line treatment of metastatic disease, lowest proportion with metastases (65% vs. 75% for Bellmunt 2008[13] and 96% for KEYNOTE-045); lowest proportion with visceral metastases (47% vs. 75% and 88%); and lowest proportion with Hb <10g/dL (0% [exclusion criterion] vs. 14% vs. 16%).

Patients in KEYNOTE-045 had a better baseline ECOG than in Bellmunt 2008[13] (ECOG score 0 = 42% vs. 32%), although they had more metastases (96% vs. 75%) and more visceral involvement (88% vs. 75%) and were of similar age at baseline. Most importantly, the patients in KEYNOTE-045 could be included after failure to platinum-based regimen given as adjuvant/neoadjuvant therapy while patients in the vinflunine trial could only be included after failure to chemotherapy given at the stage of locally advanced/metastatic disease.

The ERG considers that among the three studies presented, the baseline characteristics of KEYNOTE-045 patients were less favourable compared to that of the von der Maase study[15, 16] and more favourable compared to that of the Bellmunt 2008 study.[13] Although the von der Maase study[15, 16] included people only at first line treatment of metastatic disease, this trial is of relevance since the authors presented a subgroup analysis depending on the presence of visceral metastasis which is a well-known risk factor. Interestingly, the 5 year OS was 6.8% in people with visceral metastasis at inclusion. Given that 85.7% of people in the KEYNOTE-045 study had visceral metastasis at inclusion, this confirms that the 5-year OS 7.8% in the UK SOC arm from KEYNOTE-045 is likely to be overestimated in the CS.

Overall, the ERG believes the 5-year OS in the UK SOC of KEYNOTE-045 should be below that observed in the von der Maase study, and above that in the vinflunine trial (which is not reported but should be below 2% since there was only 6 survivors at 40 months of the 253 included patients).

Table 19: Inclusion criteria of studies considered to be comparable with KEYNOTE-045

Study	KEYNOTE-045 from Bellmunt 2017	von der Maase 2000, von der Maase 2005 [15, 16]	Bellmunt 2008/Bellmunt 2013 [13, 25]
Age	≥18 years	-	≥18 years
Histology/location of cancer	Histologically or cytologically confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra	Histologically proven transitional-cell carcinoma of the urothelium	Histologically confirmed transitional cell carcinoma of the urothelial tract
Cell type	Predominantly transitional-cell features on histologic testing	Transitional-cell carcinoma	Transitional cell carcinoma
Stage	Progression after platinum-based chemotherapy for advanced disease or recurrence within 12 months after platinum-based adjuvant or neoadjuvant therapy for localised muscle-invasive disease	First-line stage IV: locally advanced (T4b, N2, N3) or metastatic (M1)	Locally advanced or metastatic; documented progression after first-line platinum-containing chemotherapy
Prior chemo (line of therapy)	Had received ≤2 lines of systemic chemotherapy for advanced disease previously	Prior systemic chemotherapy was not allowed	Documented progression after first-line platinum-containing chemotherapy
Measurable lesion	Had at least one measurable lesion according to RECIST	Measurable or assessable	-
Performance status	ECOG PS score of 0, 1, or 2	Karnofsky performance status ≥ 70	ECOG performance status (PS) of 0 or 1
Other prior therapy allowed	-	Prior local intravesical therapy, immunotherapy, or radiation therapy was allowed if completed at least 4 weeks before enrolment.	Prior radiation was allowed if affecting less than 30% of the bone marrow and completed 30 days before random assignment with full recovery of related toxicity

Table 20: Baseline characteristics of included patients

Baseline characteristics of included patients	Keynote-045 from Bellmunt 2017	von der Maase 2000, von der Maase 2005 [15, 16]		Bellmunt 2008/Bellmunt 2013 [13, 25]
	SOC (Docetaxel or paclitaxel or vinflunine) (n=272)	Gemcitabine/cisplatin (GC) (n=203)	Methotrexate/vinblastine/ doxorubicin/cisplatin (MVAC) (n=202)	Vinflunine + BSC (n=253)
Male n (%)	202 (74.3%)	160(78.8%)	160 (79.2%)	197 (77.9%)
Age < 65	125 (46%)	-	-	135 (53.4%)
Age >= 65	147 (54%)	-	-	118 (46.6%)
Mean	65.1	-	-	63.5
Median	65	63	63	64.2
Asian	58 (21.3%)	-	-	-
White	201 (73.9%)	197 (98%)	197 (97.5%)	-
ECOG PS 0	106 (39%)	82.5% with Karnosfky PS ≥80	81.1% with Karnosfky PS ≥80	72 (28.5%)
ECOG PS 1	158 (58.1%)	-	-	181 (71.5%)
M1	261 (96%)	141 (69.5%)	127 (62.9%)	Around 75% had at least 2 organs involved
Staging IV	271 (99.6%)	-	-	/
Prior Cisplatin therapy	213 (78.3%)	-	-	164 (64.8%)
Prior Carboplatin therapy	56 (20.6%)	-	-	75 (29.6%)
Baseline Hb >=10 g/dL	223 (82%)	100%	100%	214 (85%)
Prior Cystectomy	51 (18.8%)	77 (37.9%)	79 (39.1%)	/
Prior radiation therapy	-	27 (13.3%)	23 (11.4%)	22.5 %
Visceral Disease	233 (85.7%)	99 (48.8%)	93 (46%)	187 (73.9%)
Abnormal alkaline phosphatase	-	56 (28.6%)	51 (26%)	75 (30%)
Creatinine clearance ≥ 60 mL/min	-	100%	100%)	134 (54%)

Table 21: Survival outcomes

	Keynote-045 from Bellmunt 2017	**von der Maase 2000, von der Maase 2005** [15, 16]		**Bellmunt 2008/Bellmunt 2013** [13, 25]
Survival outcomes	**SOC (Docetaxel or paclitaxel or vinflunine) (n=272)**	**GC (n=203)**	**MVAC (n=202)**	**Vinflunine + BSC (n=253)**
Median OS	7.4 months	13.8 months	14.8 months	6.9 months
12 months OS	30.7%	58.4%	62.6%	27%
24 months OS	-	25%	31%	11%
30 months OS	-	-	-	5.5% (14/253)
36 months OS	-	19.0%	20.4%	-
40 months OS	-	-	-	2.3% (6/253)
48 months OS	-	16.4%	17.3%	-
60 months OS	-	13.0%	15.3%	-
		20.9% without / 6.8% with visceral metastases		

As stated in section 5.2.6.1, the ERG considers that from 24-weeks (approximately 5.52 months), the cumulative hazard follows an internally consistent pattern (see Figure 6), and so it would have been more appropriate to extrapolate overall survival on the Kaplan-Meier curve from this time point to maximise the data used in the model. Using the company's economic model, the ERG has obtained overall survival estimates for the UK SOC (Table 22) and pembrolizumab (Table 23) arms based on a 24-week and 40-week cut-off. Survival estimates are provided at one, three, five and ten years. The 5-year overall survival estimates for the UK SOC, using the 24-week cut-off ranged from 0.1% to 8.9% across the parametric models. From the 40-week cut-off, survival estimates ranged from approximately 0.3% to 24.33%. Given the paucity of published evidence on the long-term overall survival in this population, the ERG consulted their clinical expert who suggested that they would expect a 5-year overall survival to be approximately 2-3% consistently with our previous statement comparing KEYNOTE-045 to two other trials. Hence, an extrapolation based on a log-normal or log-logistic parametric distribution, added to the observed 24-week Kaplan-Meier data, gives an appropriate 5-year estimate. These results show that the expected 5-year overall survival is 2.9% and 3.1%, using the log-normal and log-logistic parametric distributions, respectively.

Table 22: UK SOC overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using a 24-week cut-off						
1-year	0.3019	0.3006	0.2926	0.2888	0.3014	0.2939
3-year	0.0349	0.0198	0.0686	0.0654	0.0913	0.1272
5-year	0.0040	0.0010	0.0290	0.0315	0.0585	0.0891
10-year	0.0000	0.0000	0.0073	0.0117	0.0460	0.0556
Using a 40-week cut-off						
1-year	0.3002	0.2941	0.2880	0.2882	0.2811	0.2831
3-year	0.0290	0.0785	0.1185	0.1095	0.2433	0.1908
5-year	0.0028	0.0288	0.0782	0.0712	0.2433	0.1700
10-year	0.0000	0.0035	0.0421	0.0396	0.2433	0.1475

The 5-year overall survival estimates for pembrolizumab, using the 24-week cut-off ranged from approximately 3.3% to 22.48%. From the 40-week cut-off, survival estimates ranged from approximately 3.9% to 31.53%. To the ERG's knowledge, there is no published evidence on the long-term overall survival in this population. It can be seen in Table 23 that the 5-year overall survival estimate using the log-normal and the log-logistic parametric distributions were 16.91% and 13.40% respectively. Here, it can be seen that there is a noticeable difference in the 5-year survival estimates. Given that the same functional form/parametric distribution are to be used in the economic model, the ERG preferred to prioritise the fitting of the parametric curves to

pembrolizumab due to the larger differences that were observed. Based on the AIC/BIC, the log-logistic compared to using the log-normal distribution provided a better fit to the pembrolizumab data.

Therefore in the ERG's base-case, estimated overall survival is based on extrapolations using the log-logistic distributions, added to the observed 24-week Kaplan-Meier data. Additionally, the ERG has undertaken further analyses to show the impact of using different parametric distributions to extrapolate from the 24-week time-point on the Kaplan-Meier curve for overall survival.

Table 23: Pembrolizumab overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using a 24-week cut-off						
1-year	0.4570	0.4542	0.4487	0.4497	0.4480	0.4508
3-year	0.1235	0.1546	0.2407	0.2073	0.2542	0.1940
5-year	0.0334	0.0581	0.1691	0.1340	0.2248	0.1070
10-year	0.0013	0.0059	0.0966	0.0707	0.2174	0.0352
Using a 40-week cut-off						
1-year	0.4566	0.4520	0.4467	0.4493	0.4429	0.4416
3-year	0.1335	0.1689	0.2330	0.2065	0.3186	0.2825
5-year	0.0391	0.0708	0.1663	0.1353	0.3153	0.2394
10-year	0.0018	0.0095	0.0985	0.0731	0.3152	0.1926

5.2.6.3 Progression-free survival

In KEYNOTE-045, progression-free survival was defined as per RECIST 1.1[23] the first assessment was performed at week nine, then every six weeks. Like overall survival, projection of long-term progression-free survival was based on a two-phase piecewise model, which was derived by using Kaplan-Meier data up to week 21, then fitting parametric models to the remaining observed data. The 21-week cut-off was chosen based on the separation of the cumulative hazards for pembrolizumab and UK SOC as shown in Figure 10.

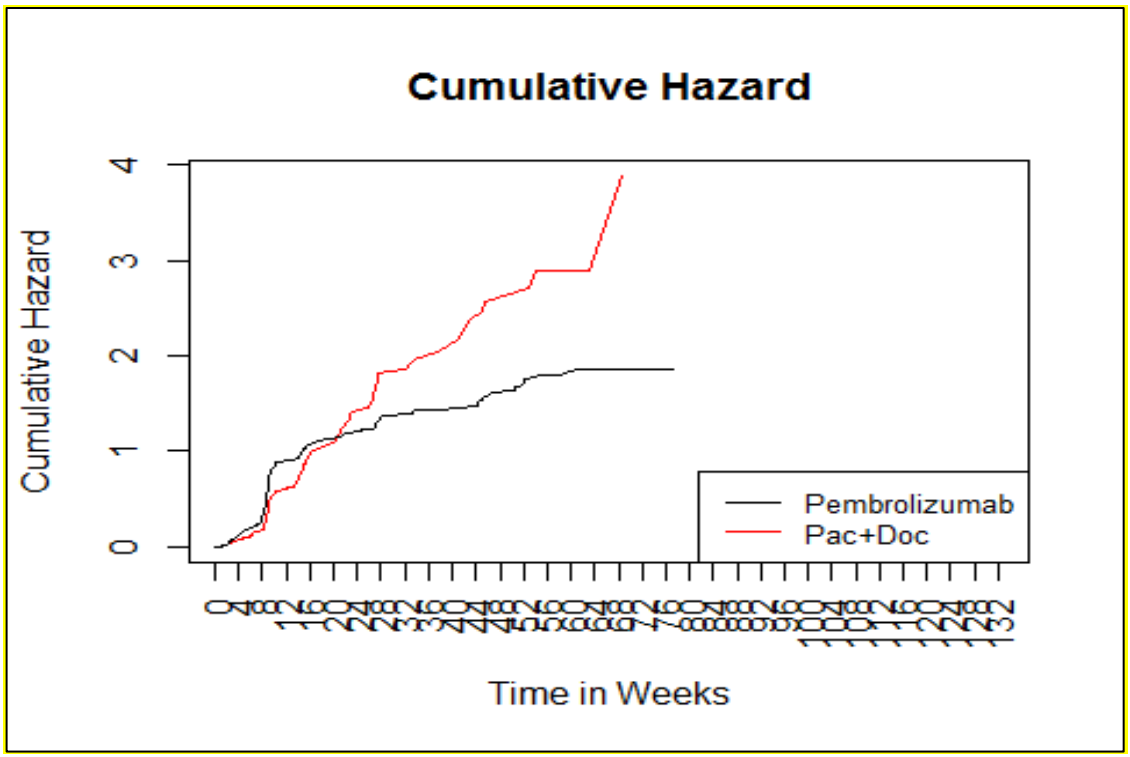


Figure 10: Cumulative hazard plots for progression-free survival for pembrolizumab and UK SOC

The company further suggested that the proportional hazard assumption did hold because the Kaplan-Meier plots crossed, therefore separate parametric models were fitted to project progression-free survival. Figure 11 and Figure 12 show the Kaplan-Meier plots with parametric models fitted to pembrolizumab and UK SOC, respectively. These figures show the various parametric fits to the observed data beyond the 21-week cut-off.

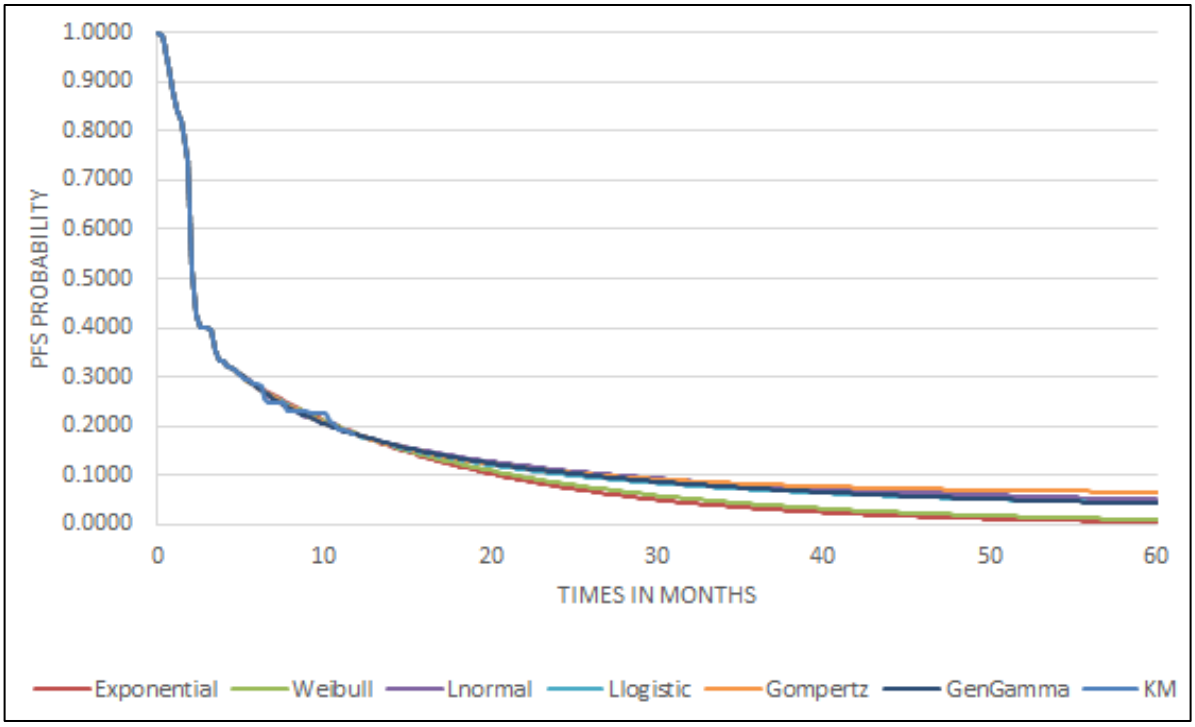


Figure 11: Kaplan-Meier plot for progression-free survival for pembrolizumab, with extrapolations using a 21-week cut-off point

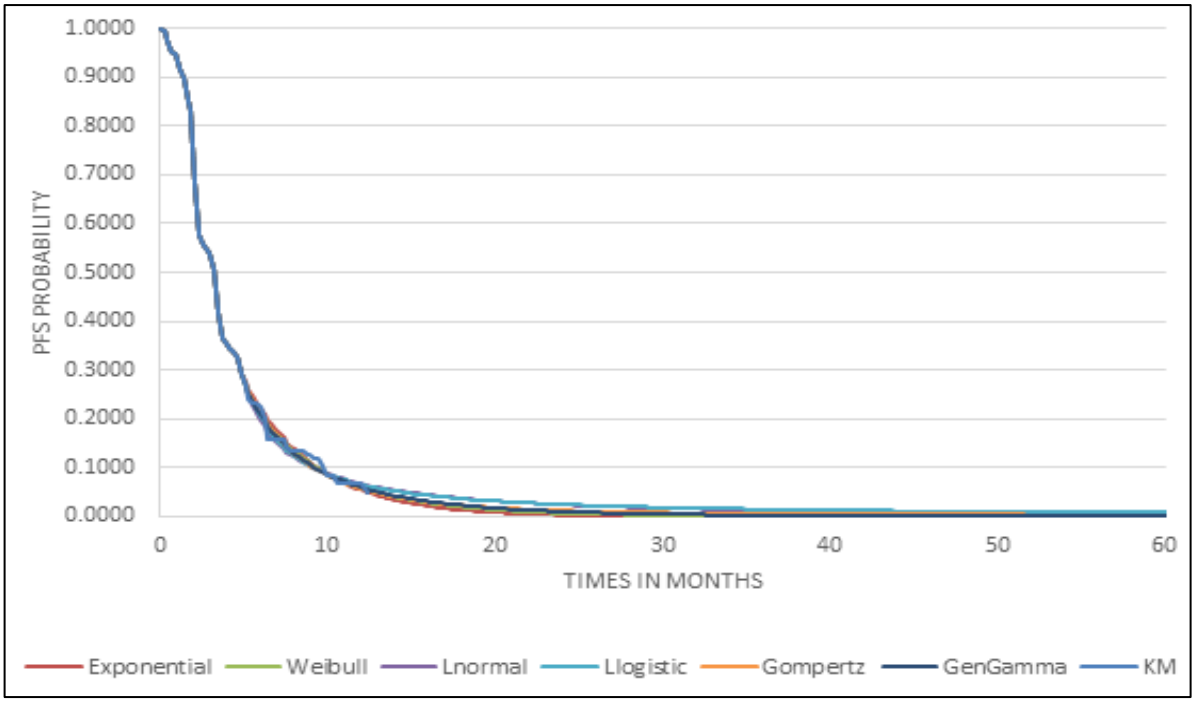


Figure 12: Kaplan-Meier plot for progression-free survival for UK SOC, with extrapolations using a 21-week cut-off point

Projection of PFS was based on AIC/BIC for the second phase of the piecewise model (based on data beyond the 21-week cut-off). Table 24 shows these goodness-of-fit measures for pembrolizumab and UK SOC.

Table 24: Goodness-of-fit statistics based on the extrapolations of data beyond the 21-week cut-off, for pembrolizumab and UK SOC

Parametric model	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	339	341.4	154.1	155.4
Weibull	340.7	345.5	150.6	153.1
Gompertz	340.2	345	155.9	158.4
Log-logistic	340.2	344.9	153.6	156.1
Log-normal	339.9	344.6	153.4	155.9
Generalised Gamma	341.8	348.9	149.8	153.6

As suggested by the company, there was no clear best parametric fit for pembrolizumab or UK SOC, as all the distributions were very similar. This was seen in the parametric fits (Figure 11 and Figure 12) and AIC/BIC (Table 24). In the base case, the company has chosen the exponential model to extrapolate PFS for the UK SOC and for consistency, used the exponential model for pembrolizumab. Figure 13 shows the two-phase piecewise approach to extrapolate PFS beyond the trial time horizon for pembrolizumab and UK SOC.

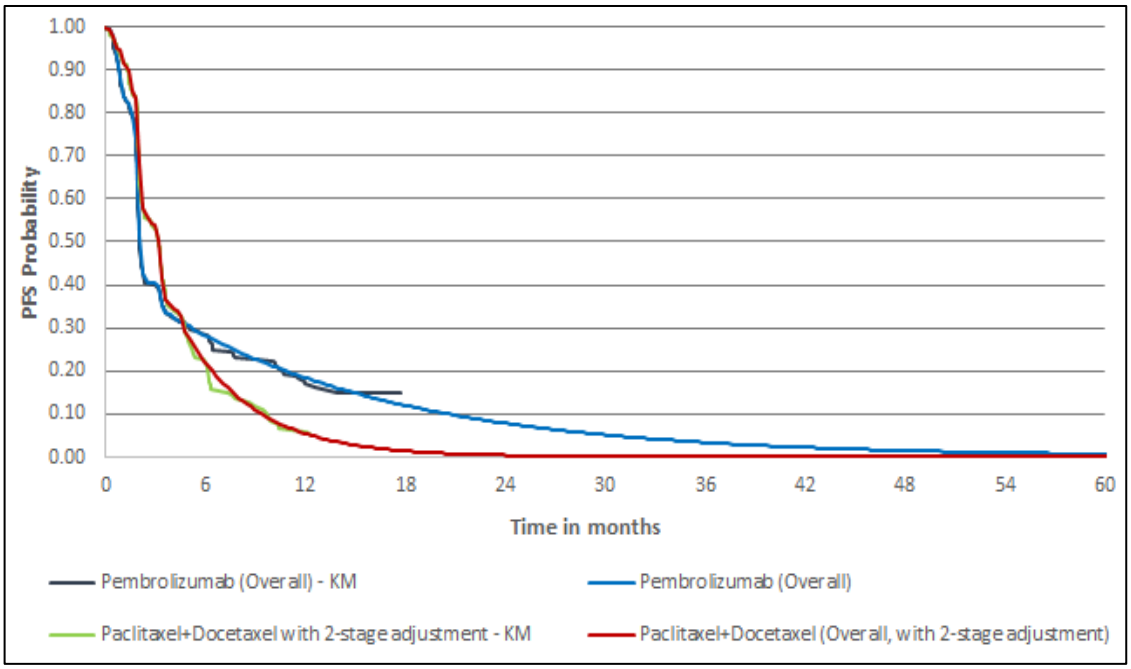


Figure 13: Kaplan-Meier plot for progression-free survival for pembrolizumab and UK SOC, with extrapolations using a 21-week cut-off point

Subgroup analysis 1: Overall survival for PD-L1 strongly positive (CPS≥ 10%)

The first subgroup that the CS considered was that of patients who were strongly PD-L1 positive (CPS≥ 10%). The key results are shown in Table 25. There were 164 patients in this group, with a total of 104 deaths observed. Pembrolizumab has a lower event rate than the control arm (59.5% vs. 66.7%) suggesting the immunotherapy is the superior treatment. Pembrolizumab also has a higher OS at both six and twelve months, but the differences are not statistically significant, likely due to power. The Kaplan Meier diagram also suggests pembrolizumab is beneficial for overall survival, as shown in Figure 14.

Overall, this group has an event rate of 63.4%, which is slightly higher than of the whole population (61.6%) which could suggest the strongly positive group have a higher risk of death, however, the difference is slight. The median OS for both arms is lower in this subgroup than their relative median OS from the whole population, along with the OS at 6 and 12 months, again suggesting a worse prognosis for subjects in the strongly PD-L1 positive subgroup. The HR suggests that pembrolizumab is more effective in this subgroup with HR of 0.57 though the difference in OS suggested no change in effectiveness with a difference in median OS of 2.8 months.

Table 25: Results of PD-L1 CPS ≥ 10% Subgroup Analysis

						Pembrolizumab vs. Control
Treatment	**N**	**Number of events (%)**	**Median OS (months) (95% CI)**	**OS at 6 months in % (95% CI)**	**OS at 12 months in % (95% CI)**	**Hazard Ratio (95% CI)**
Control	90	60 (66.7)	5.2 (4.0, 7.4)	47.2 (36.0, 57.6)	26.9 (17.5, 37.2)	
Pembrolizumab	74	44 (59.5)	8.0 (5.0, 12.3)	58.5 (46.3, 68.9)	39.8 (28.0, 51.3)	0.57 (0.37, 0.88)

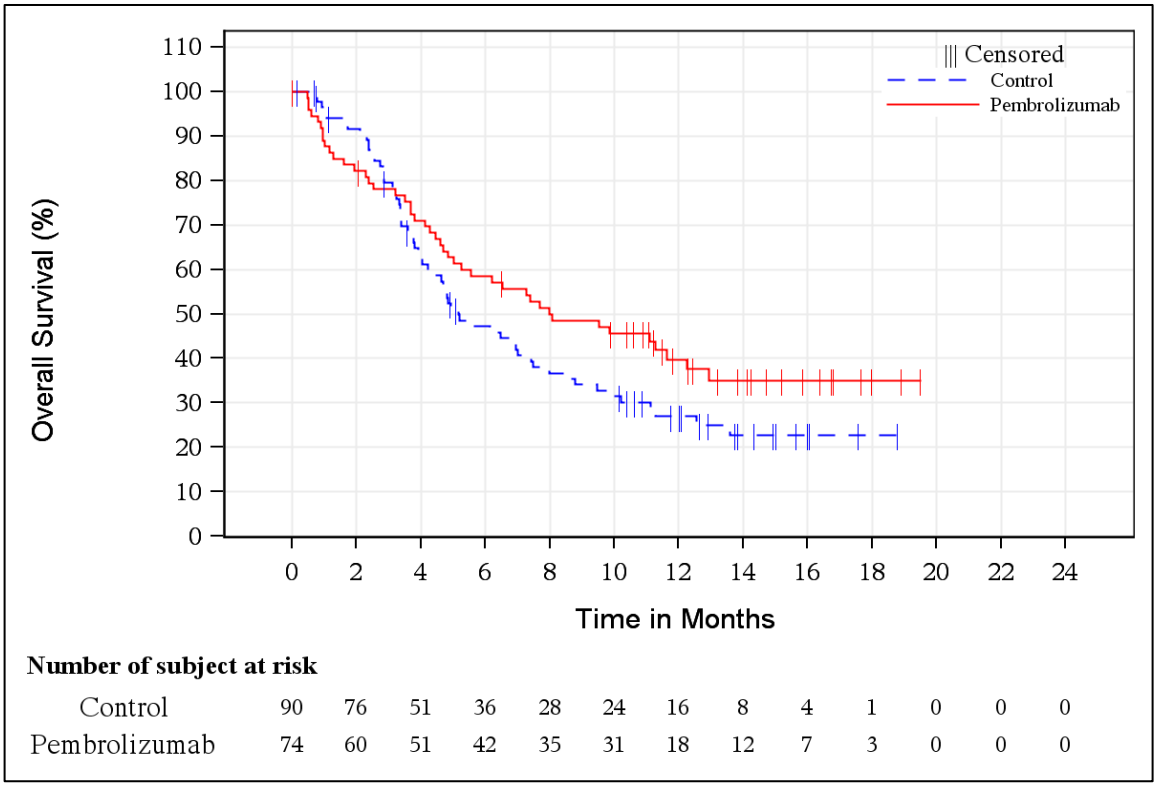


Figure 14: KM plot of PD-L1 CPS ≥ 10% Subgroup

The PD-L1 ≥ 10% subgroup was also investigated using PFS as the outcome measure. The results are shown in Table 26. There was little to distinguish between the groups, with pembrolizumab having a lower median PFS (2.1 vs 3.1 months) but a higher 6 month (24.7% vs 18.5%) and 12 month PFS (17.7% vs 3.7%). The percentage of events was almost identical, both between and arms and compared to the whole trial population, all around 80%. However, the HR has decreased to 0.89 in favour of pembrolizumab, perhaps influenced by the more noticeable difference in tails between the treatment arms, as shown in Figure 15. However, the difference was not statistically significant.

Table 26: Results of PD-L1 CPS ≥ 10% Subgroup Analysis (PFS)

Treatment	N	Number of events (%)	Median PFS (months) (95% CI)	PFS at 6 months in % (95% CI)	PFS at 12 months in % (95% CI)	Pembrolizumab vs. Control Hazard ratio (95% CI)
Control	90	72 (80.0)	3.1 2.2, 3.4)	18.5 (10.6, 28.1)	3.7 (0.7, 10.9)	
Pembrolizumab	74	59 (79.7)	2.1 (1.9, 2.1)	24.7 (15.5, 34.9)	17.7 (9.5, 27.9)	0.89 (0.61, 1.28)

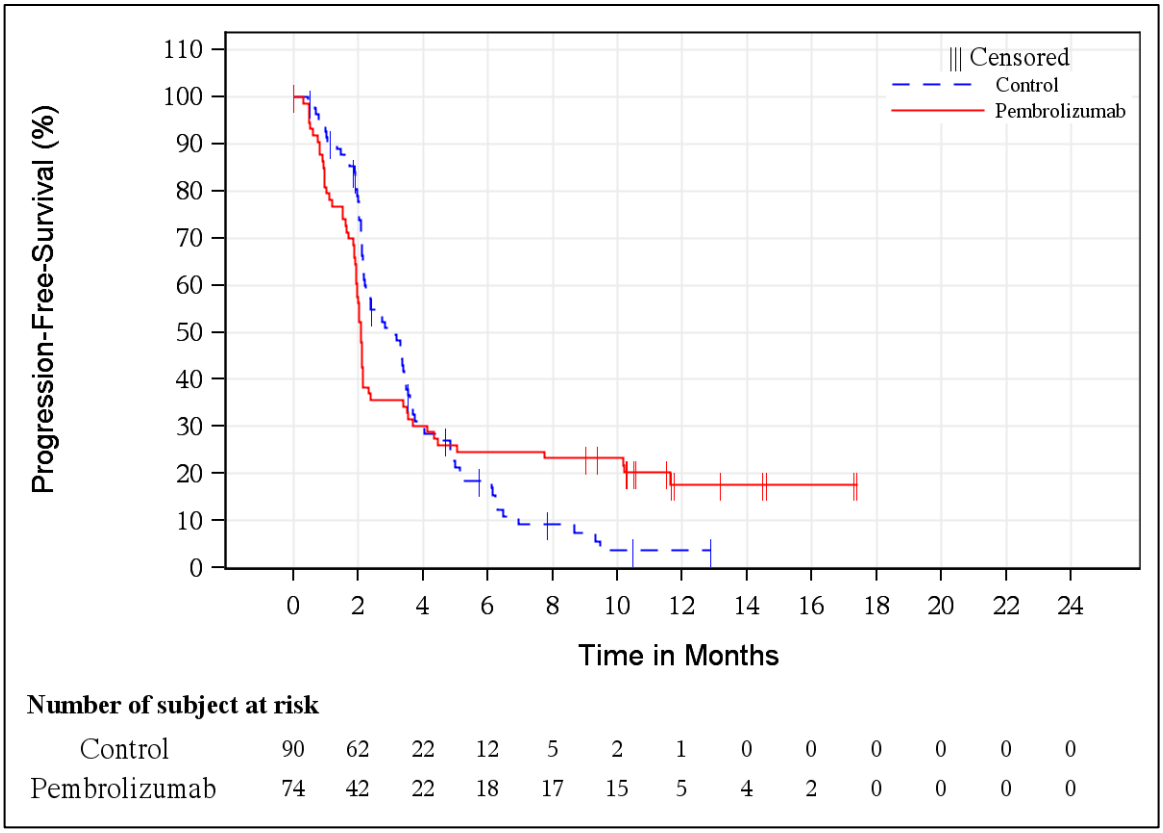


Figure 15: KM plot of PD-L1 CPS ≥ 10% Subgroup (PFS)

Subgroup analysis 2: Overall survival for PD-L1 positive (CPS≥ 1%)

The second subgroup considered by the company was that of patients who were PD-L1 positive (CPS≥1%), and the summary of results is shown in Table 27. A total of 230 patients fell into this category, 120 in the control arm, and 110 in the pembrolizumab arm. One-hundred and forty-two deaths were observed, with a higher event rate in the control arm (67.5% vs. 55.5%). This suggests pembrolizumab is superior in this subgroup, supported by a HR of 0.61, higher OS at 6 (65.9% vs 51.6%) and 12 (46.5% vs 28.8%) months and the Kaplan Meier plot is shown in Figure 16.

The combined event rate of 61.7% showed no difference to that of the whole population (61.6%). The control arm appears to have a slightly worse prognosis in this subgroup, with a lower median OS when compared to the control arm of the entire population. It also has lower OS at 6 and 12 months. In contrast, pembrolizumab appears to be more effective in this subgroup, having a higher median OS by 1 month, and increased 6 and 12 month survival rates when compared to the pembrolizumab arm of the whole trial population. However, all of these differences between the subgroup and trial population are slight and not statistically significant.

Table 27: Results of PD-L1 CPS ≥ 1% Subgroup Analysis

Treatment	N	Number of events (%)	Median OS (months) (95% CI)	OS at 6 months in % (95% CI)	OS at 12 months in % (95% CI)	Pembrolizumab vs. Control Hazard Ratio (95% CI)
Control	120	81 (67.5)	6.9 (4.7, 8.8)	51.6 (41.9, 60.4)	28.8 (20.4, 37.7)	
Pembrolizumab	110	61 (55.5)	11.3 (7.7, 16.0)	65.9 (56.1, 73.9)	46.5 (36.4, 55.8)	0.61 (0.43, 0.86)

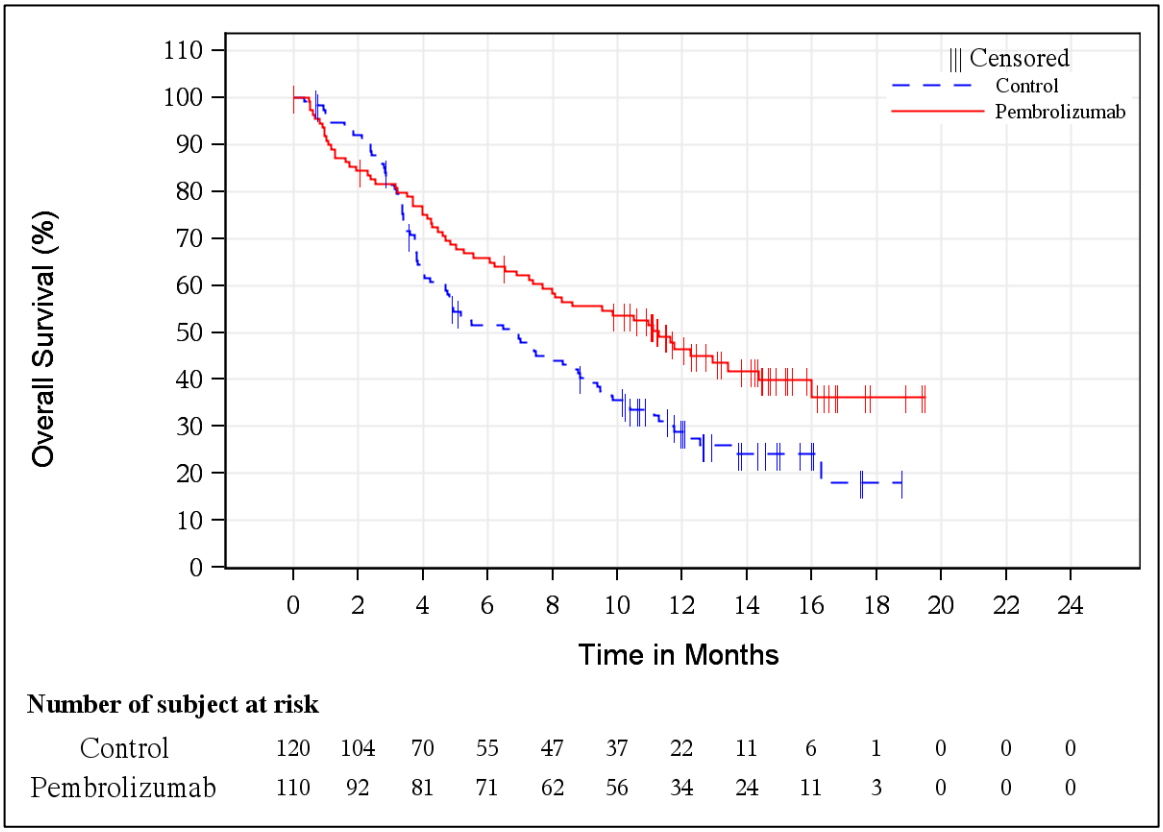
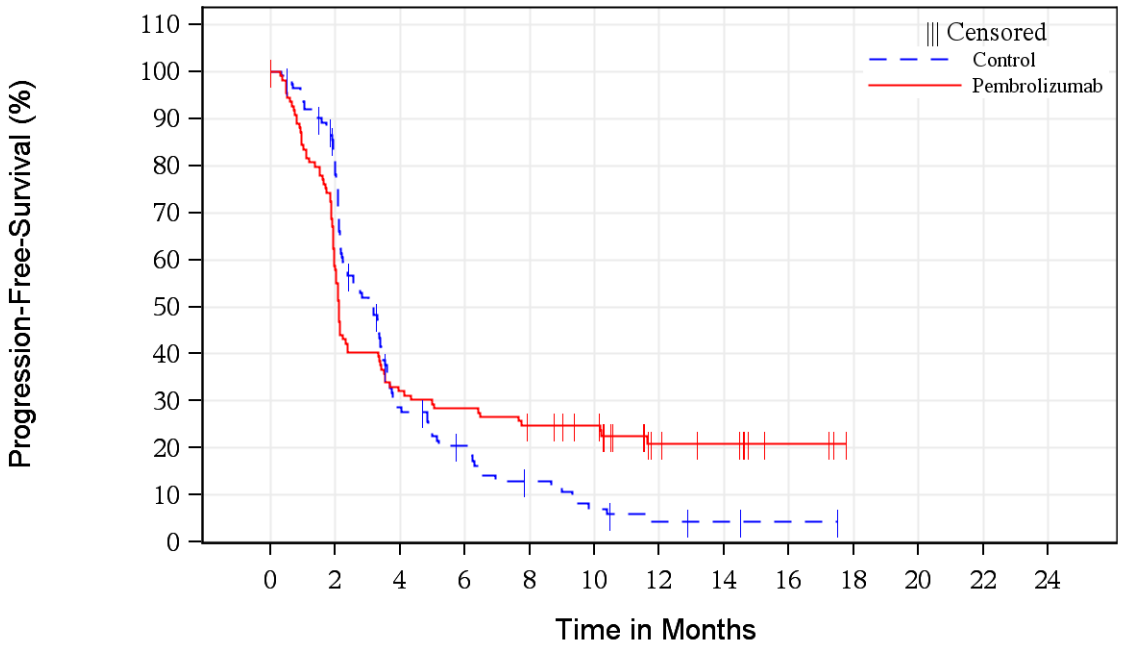


Figure 16: KM plot of PD-L1 CPS ≥ 1% Subgroup

The PFS of the PD-L1 ≥ 1% subgroup was also investigated by the company. The results are shown in Table 28. As before, there is little to distinguish this subgroup from the whole trial population, with a HR of 0.91 weakly favouring pembrolizumab. There is a difference in median PFS of 1.1 months in favour of the control arm, however pembrolizumab appears superior when comparing the 6 month (28.4% vs 20.5%) and 12 month (20.9% vs 4.4%) PFS. For completeness, the KM diagram is shown in Figure 17.

Table 28: Results of PD-L1 CPS ≥ 1% Subgroup Analysis (PFS)

Treatment	N	Number of Events (%)	Median PFS† (Months) (95% CI)	PFS at Months 6 in % (95% CI)	PFS at Months 12 in % (95% CI)	Pembrolizumab vs. Control Hazard Ratio (95% CI)
Control	120	98 (81.7)	3.2 (2.2, 3.4)	20.5 (13.3, 28.8)	4.4 (1.4, 10.4)	0.91 (0.68, 1.24)
Pembrolizumab	110	85 (77.3)	2.1 (2.0, 2.4)	28.4 (20.3, 37.1)	20.9 (13.6, 29.3)	



Number of subject at risk

Control	120	87	29	19	11	6	3	2	1	0	0	0	0
Pembrolizumab	110	64	35	31	26	23	10	8	3	0	0	0	0

Figure 17: KM plot of PD-L1 CPS ≥ 1% Subgroup (PFS)

5.2.6.4 Time on treatment

The company anticipates that the licence would indicate that people would receive treatment until disease progression. As per the KEYNOTE-045 protocol, a stopping rule was implemented whereby people could not receive pembrolizumab for longer than 24 months. Duration of treatment in pembrolizumab and UK SOC was based on time-on-treatment (ToT) data obtained from KEYNOTE-045. In addition to patients switching due to progressive disease, the time-on-treatment data was also influenced by those who discontinued treatment as a result of adverse events and other reasons listed in section 4.3.1 in the CS. The data also contained people who received additional weeks of treatment whilst their disease progression was confirmed.

Parametric curves were fitted to the Kaplan-Meier plot for time-on-treatment for pembrolizumab and UK SOC. Various parametric models were tested, with the preferred model chosen by examination of goodness-of-fit and using AIC/BIC. Figure 18 and Figure 19 show the Kaplan-Meier plots with fully fitted parametric models for pembrolizumab and UK SOC, respectively. It should be noted that in the Kaplan-Meier plot of pembrolizumab (Figure 18), the data appears to have been truncated, whilst in the electronic model it suggested that people received treatment beyond 70 weeks (approximately). As a result, it is unclear to the ERG whether a) the parametric curves have been fitted to all the data or b) the parametric curves have been fitted to truncated data.

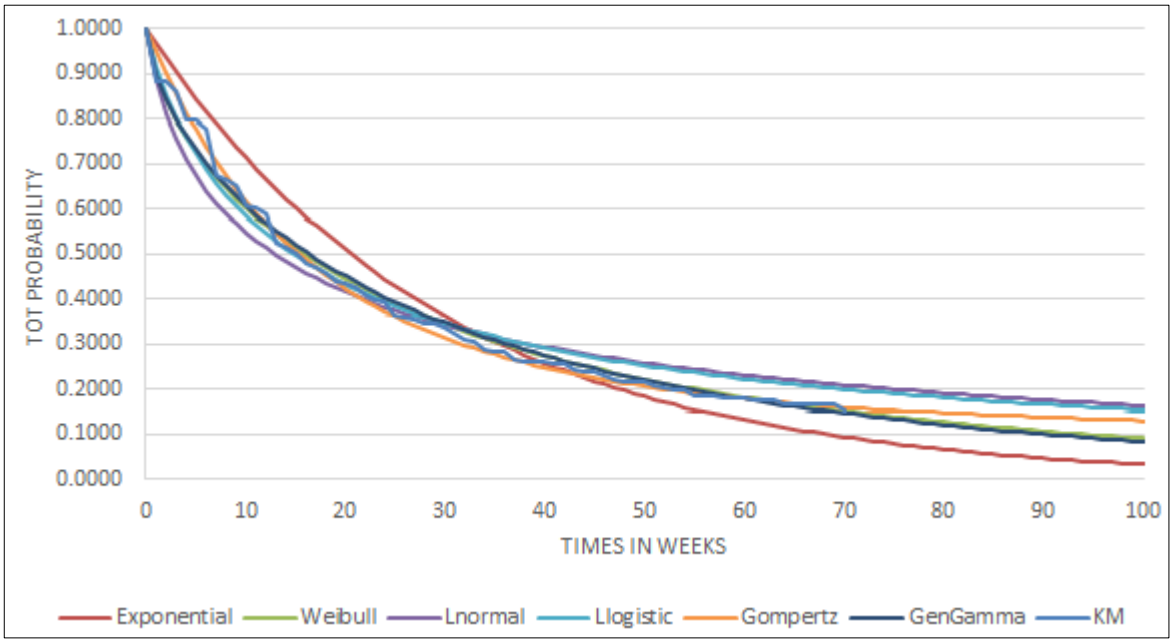


Figure 18: Kaplan-Meier plot for time-on-treatment for pembrolizumab, with various parametric models

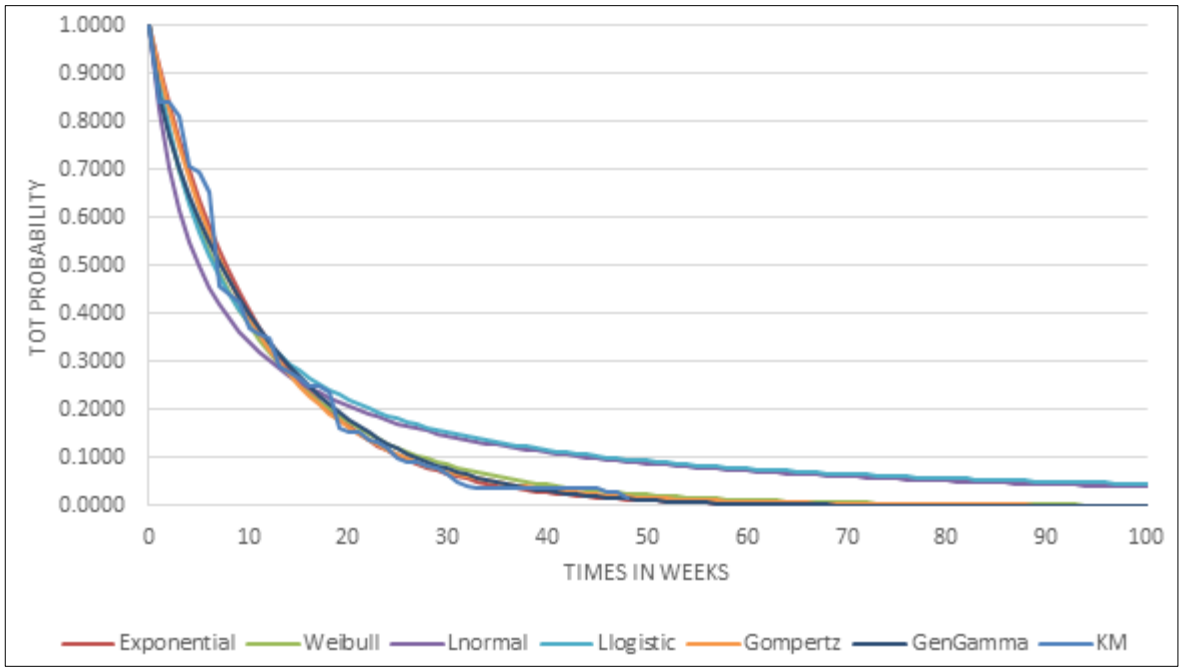


Figure 19: Kaplan-Meier plot for time-on-treatment for UK SOC, with various parametric models

Table 29 shows the AIC and BIC for each parametric model to the fully-fitted data on time-on-treatment. Results of the goodness-of-fit measures suggested that the Weibull and the generalised gamma parametric curves provided the best fits for time-on-treatment for pembrolizumab and UK SOC respectively. The resulting Kaplan-Meier plots with best fitting parametric curves are shown in Figure 20.

Table 29: Goodness-of-fit statistics based on the fully-fitted parametric curves to data on time-on-treatment

	Pembrolizumab		UK SOC, 2-stage adjusted	
Parametric model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1923.8	1927.4	1133.1	1136.3
Weibull	1870.5	1877.7	1126.8	1133.1
Gompertz	1890.9	1898.1	1134.1	1140.4
Log-logistic	1885	1892.2	1167.2	1173.5
Log-normal	1899.8	1906.9	1177.1	1183.3
Generalised Gamma	1872.1	1882.8	1122.2	1131.6

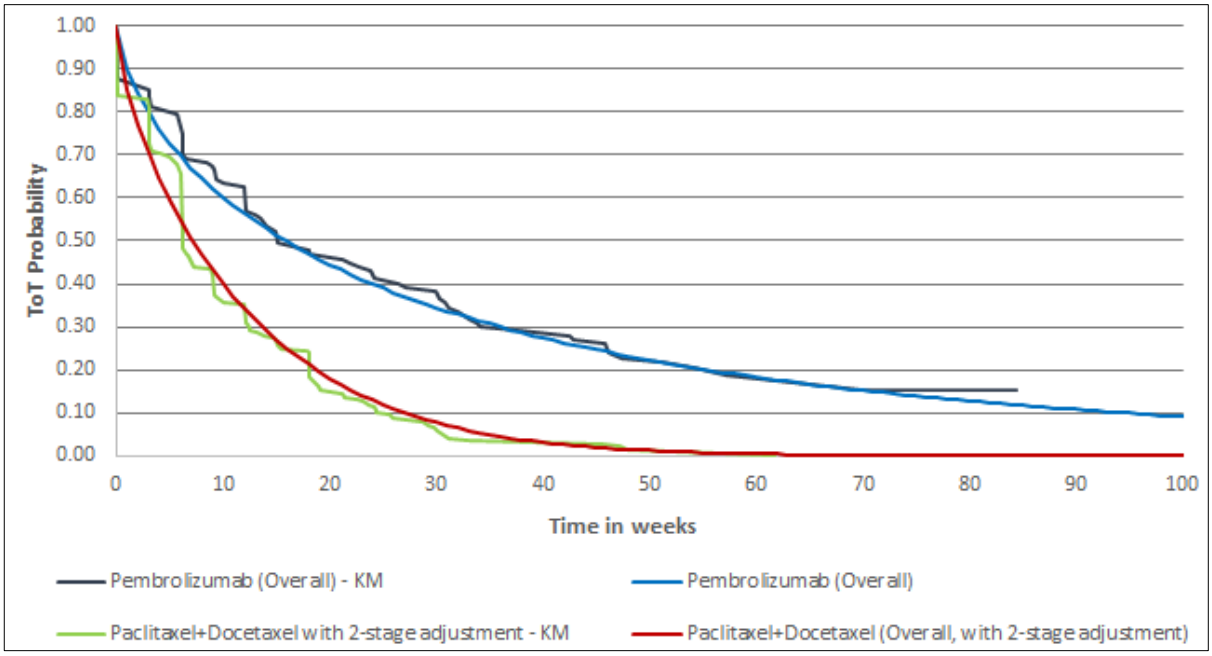


Figure 20: Kaplan-Meier plots for time-on-treatment for pembrolizumab and UK SOC (2-stage adjustment applied)

It appears that the Kaplan-Meier plot for pembrolizumab in Figure 18 is not identical to the Kaplan-Meier plot for pembrolizumab in Figure 20.

In the base case, it was assumed that people received pembrolizumab for a maximum of 35 cycles (24 months) (based on anticipated licence) and a maximum of six cycles (18 weeks) treatment with UK SOC, which is in line with clinical practice in England. Additionally, the company stated that adjustments were made to reflect the proportion of people who received a full treatment dose within each 3-week cycle. Data on dose intensity were analysed and results showed that the average dose intensity for people treated with pembrolizumab and UK SOC was 100.42%, 102.75% (docetaxel) and 100.02% (paclitaxel), respectively. The company considered these estimates not to be realistic in clinical practice whereby dose intensity is likely to be below 100%; hence the company applied a conservative 100% dose intensity in the economic model.

5.2.7 Mortality

General population background mortality was estimated using the latest UK life tables from the Office of National Statistics.[26] In line with common practice, overall survival in the economic model was estimated as the minimum of general population survival (i.e. one minus general population mortality) and trial patients' overall survival.

5.2.7.1 Adverse events

The base-case model included adverse events graded 3+ which occurred in at least 5% of patients (at any grade) in either treatment arm, with two exceptions:

- Grade 2 diarrhoea was also included to be consistent with previous NICE appraisals.[27, 28]
- Febrile neutropenia (with a 2% incidence in the UK SOC arm) was also included as clinicians suggested that this adverse event has significant impact on quality of life and costs and is consistent with recent NICE appraisal.[27]

The incidence of adverse events was taken from the KEYNOTE-045 trial for each treatment arm (see Table 30). It is evident that patients in UK SOC arm experienced more AEs compared to patients in the pembrolizumab arm; according to the ERG's clinical advisor this is expected due to the different toxicity profiles of the drugs. The CS stated that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. However, limiting adverse events to those graded 3 or 4 in severity and affecting ≥5% patients, and without providing count data, means that multiple adverse events suffered by the same patients may be under-represented within the model. For example, a patient may experience an adverse event on multiple occasions, but this will only be modelled as a single occurrence.

For the economic model, the total number of adverse events for both pembrolizumab and UK SOC arms are all applied in the first cycle (in the first 7 days), without any further consideration of adverse events in the duration of the model. This approach in the CS model may have under-estimated costs and over-estimated benefits associated with the two treatment arms.

Table 30: Grade 3+ AE rates for AEs included in the economic model based on KEYNOTE-045 data (CS Table 72)

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for UK SOC (Grade 3+)
Anaemia	8.3%	11.9%
Febrile neutropenia	0.0%	4.76%
Neutropenia	0.0%	11.9%
Diarrhoea	5.3%	5.36%
Fatigue	3.8%	5.95%
Neutrophil count decreased	0.4%	14.29%
White blood cell count decreased	0.4%	5.95%

Pneumonia	2.6%	4.17%
Hypophosphatemia	0.80%	3.57%

ERG summary

- The ERG considers the methods used to adjust for treatment switching in the UK SOC to be satisfactory.
- The ERG agrees with the company that the proportional hazards assumption does not hold and that it is feasible to use the two-phase piecewise approach.
- In our ERG base-case, the estimated overall survival is based on extrapolations using the log-logistic distributions, added to the observed 24-week Kaplan-Meier data.
- The incidence of AEs seems to be in line with the expectation for each treatment in the KEYNOTE-045 trial.
- There is a concern that AEs may have been under-represented in the economic model due to being applied only in the first cycle of the model.

5.2.8 Health related quality of life

For the CS, HRQoL was estimated using the EQ-5D-3L, collected every 3 weeks for the first 9 weeks, and then every 6 weeks subsequently. EQ-5D data was also collected at the discontinuation visit, and at a safety follow up 30 days later. Two approaches to the analysis were performed: the primary analysis used utilities based on (categorised) time to death, and the secondary analysis used utilities based on the two progression states (progression-free and progressed). All baseline utility values were generated using the full analysis set (FAS) of the KEYNOTE-045 trial, which consisted of subjects who had received at least one dose of study treatment and completed at least one patient reported outcome analysis. FAS included patients who were allocated to vinflunine prior to randomisation and contained 266 patients in the pembrolizumab arm and 254 in the control arm. The ERG requested utility values from the company based on the UKSOC population excluding vinflunine. These were provided by the company upon clarification. The utilities are shown in Table 31.

Table 31: Mean utility values

	Pembrolizumab	Control (paclitaxel, docetaxel and vinflunine)	Pembrolizumab and control pooled (used in CS)	UKSOC (paclitaxel and docetaxel)	Pembrolizumab and UKSOC pooled	NICE TA272[17]
Time to death based (days)						
≥ 360	0.765	0.804	0.778	0.823	0.780	-
(180 to 360)	0.686	0.699	0.693	0.673	0.680	-
(90 to180)	0.566	0.612	0.590	0.595	0.578	-
(30 to 90)	0.457	0.446	0.451	0.414	0.435	-
<30	0.336	0.311	0.325	0.337	0.337	-
Progression based						
Progression-free	0.757	0.698	0.731	0.709	0.741	0.65
Progressed	0.680	0.565	0.641	0.554	0.647	0.25

The company points out that, due to the timing of the questionnaires, it is unlikely that the utility score captured the expected decline of health prior to death. The company found no significant differences in EQ-5D at baseline, and so decided to use pooled utility values for both arms. The ERG notes that statistically significant differences were observed in the progression based values (see CS table 75), and borderline statistically significant differences in the survival based utility values (see CS table 74). Hence the ERG explored using un-pooled utility values in a scenario analysis.

Furthermore, the ERG noted that treatment-specific utility values are lower for pembrolizumab compared to UK SOC when measured based on time to death, except for the (180 to 360) and (30 to 90) categories. However, patients in such categories only account for about 13% of all patients in the model. And, in fact, utility values were reported as considerably higher for pembrolizumab compared to UK SOC when measured based on progression status. Such findings appear to be counter-intuitive, as using one method of valuation of HRQoL over the other should not result in higher utility estimates for a particular treatment. The ERG does not have a particular explanation for such disparity, apart from the potential lack of accounting for treatment switching when estimating treatment-specific utility values and prolonged survival of unhealthy participants in the pembrolizumab arm. Due to this inconsistency, the ERG have also used pooled utility values in a scenario analysis.

In the CS base-case analysis, pooled utility values based on time to death were used. Estimated life years were based on time to death (i.e. categorising life years based on the 5 time to death

points (see Table 31)) and then assigned the respective utility values in each life year category to estimate QALYs. To the best of the ERG's knowledge, this approach is not common in practice, and has only been used for previous studies investigating melanoma treatments.[29, 30] The ERG has concerns over the reliability of the survival based utility estimates, with a large amount of missing data. The pembrolizumab arm has a median ToT of 15 weeks, meaning all patients should have completed on average four EQ-5D questionnaires whilst on treatment, excluding baseline, plus two follow-up questionnaires giving a total of six responses per person. It is likely that the subgroup of patients living beyond 360 days actually has a higher median ToT meaning six responses is an underestimate. However, examination of Table 74 of the CS concludes that the ≥ 360 day survival pembrolizumab group averaged 3.4 responses per person, suggesting almost half of their possible data is missing for this subgroup. The CS fails to mention how missing EQ-5D data was managed. Similarly, patients surviving < 30 days should only have completed one EQ-5D questionnaire, so the ERG is unsure how there can be more responses than people in these subgroups for both treatment arms. Additionally, despite the fact that these survival-time based groups are mutually exclusive, they appear to contain more members than were in the trial, with a total 596 subjects obtained from Table 74 when only 542 were recruited. The ERG would expect the total to be below 542 when accounting for patients who were censored prior to 360 days. It is also unknown how the company obtained their average estimates for each group, and whether they calculated an average per person, and averaged this, or whether they averaged across all questionnaire responses. Due to the uncertainty associated with the survival based utility estimates, the ERG chose to use progression based estimates in their scenario and base case analyses.

A literature search conducted by the company yielded 18 comparable HRQoL studies, however none presented utilities as a function of time to death and therefore were not included in any sensitivity analysis by the company. A previous TA[17] reported related utilities for comparison which are shown in Table 31, though they were not specific to bladder cancer. The lower values seen in Table 31 (despite the CS stating the utility values in KEYNOTE-045 are comparable with these in TA272) support the view that the post-progression score is overestimated by the CS data. It is also plausible that the time to death utilities are also overestimated as a result of the data collection. In a scenario analysis, the ERG will explore the impact on the incremental cost-effectiveness ratio (ICER), by using the utility values reported in TA272.

Please note that there is typo in CS Table 77, where the mean value for time to death in days ≥ 360 should be 0.778 (as used in the model and as reported in CS Table 74) as opposed to 0.761. Furthermore, the value for progressed health state for the pembrolizumab and UKSOC pooled arm is 0.647 (see CS clarification section B Table 3); however, the ERG believe that this value should be lower than 0.641 (pembrolizumab and control pooled). The ERG were unsure whether this was a typo or some confusion in their analysis (see Table 31).

Disutilities for ageing and adverse events were included in the model and are shown in Table 32. The decision to assume no further decline past the age of 75 years is based on Kind et al. (1999), who did not report any change in EQ-5D utility score beyond age 75 years (i.e. utility value was constant for anyone over the age of 75 years).[31] There is the possibility that the manner in which the company derived the age disutilities may have underestimated the effect of ageing on quality of life. More recently, Ara and Brazier (2010) have provided an algorithm that estimates general population utility scores as a function of age and gender.[32] The ERG believes that using Ara and Brazier[32] to derive age-related disutilities is more appropriate as: (a) the study by Kind et al. (1999) is outdated; and (b) the algorithm can provide age-related utility decrements for people beyond the age of 75. The ERG will present updated results in the scenario analysis using updated disutility values.

Adverse event disutility values were applied only in the first cycle of the economic model and were not considered for the remaining time horizon of the model. This approach may have overestimated the resulting QALYs from both pembrolizumab and UK SOC. The ERG notes that adverse event disutilities were not accounted for in related STAs.[17]

Whilst the frequency of adverse events suggests that pembrolizumab has a favourable profile, the adverse event disutility suggests otherwise. If the adverse event disutility is broken down by arm it can be seen that adverse events have a much greater impact on quality of life in the pembrolizumab arm, as shown in Table 32. The ERG presents results based on using separate adverse event utility values for each arm in the scenario analysis.

Table 32: Disutility values

Disutility type	Inc. vinflunine patients	Exc. vinflunine patients	Details
Age	0.0045	Not applicable	Per year increase in age from 65 to 75.

Adverse event (pooled)	0.117	0.137	Average disutility of a Grade 3+ AE, with a duration of 13.9 days per event.
Adverse event pembrolizumab arm	0.195	0.195	Average disutility of a Grade 3+ AE, with unknown duration.
Adverse event control arm	0.043	0.058	Average disutility of a Grade 3+ AE, with unknown duration.

ERG summary

- Utility values used in the economic model were generated from KEYNOTE-045 trial data. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results
- The ERG has reservations about using separate utilities for each treatment arm, due to counter-intuitive estimates.
- Estimating life years and subsequent QALYs using utility values based on time to death results is an unusual method. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC.
- The company provided utility values without vinflunine after clarification.
- Disutilities were also used for the effect of adverse effects, with the values pooled for both arms.

5.2.9 Resources and costs

5.2.9.1 Intervention and comparator costs

All interventions were administered once per three week cycle. The total costs of pembrolizumab consisted of drug costs and administration costs with a single dose of 200mg typically administered intravenously over a 30 minute time period. The administration cost estimate was conservative assuming an administration period of 60 minutes (Healthcare Resource Group (HRG) code SB12Z).[33] Costs are shown in Table 33.

Table 33: Drug and administration costs

Costs	Dose per administration	Cost per mg	Cost per dose	Administration cost per dose	Total cost per dose	Source
Pembrolizumab	200mg	£26.30	£5260.00	£253.32*	£5513.32	MSD
Docetaxel	75mg/m^2	£0.13	£18.09	£253.32*	£271.41	eMIT
Paclitaxel	175mg/m^2	£0.07	£23.81	£406.63#	£430.44	eMIT
UK SOC	-	-	£20.88	£328.44	£349.32	CS

* HRG code: SB12Z – deliver simple parenteral chemotherapy at first attendance; # HRG code SB14Z – deliver complex parenteral chemotherapy at first attendance; eMIT – electronic market information tool

The CS stated that an average body surface area of 1.9m^2 was used to calculate the average dose of the UK SOC arm; this was calculated based on a weighted average of patients in KEYNOTE-045. The ratio of control treatments used in the model was obtained from the trial, 0.511:0.489 in favour of docetaxel, whereas the ratio of control treatments administered in the UK is 0.74:0.26 in favour of docetaxel. Docetaxel administration lasted for up to 60 minutes and was costed using a simple chemotherapy delivery. Paclitaxel administration had a duration of 3 hours, and so the administration costs were based on complex chemotherapy delivery (HRG code SB14Z).[33] The drug costs for the comparator arm were obtained from eMIT (2015-2016),[34] and the administration costs were obtained from the latest NHS Reference costs (2015-2016).[33] No drug wastage costs were included in the model.

The duration of treatment in the pembrolizumab and UK SOC arms were based on extrapolation of time on treatment (ToT) data from the KEYNOTE-045 trial. Different parametric curves were fitted to the patient level data to represent ToT in the economic model. The choice of the parametric curves were based on AIC/BIC values and visual inspection of the curves to the data. The function with the lowest AIC/BIC was Weibull for pembrolizumab, and GenGamma for UK SOC (Table 79 in CS) (see section 5.2.6.4 for more detail). These functions were chosen to inform patients' ToT in the economic model. A maximum treatment duration of 35 cycles (i.e. 24 months) was assumed for pembrolizumab, in line with the KEYNOTE-045 protocol and a maximum treatment duration of 6 cycles (i.e. 18 weeks) was used for the comparator therapies to reflect clinical practice in the UK. The average number of cycles received per patient in KEYNOTE-045 was 5.00 cycles for paclitaxel and 3.90 cycles for docetaxel.

5.2.9.2 Other health state costs

Routine costs of care

Resource use frequency for the progression-free and progressed health states along with the routine costs of care which take into account costs for routine monitoring and disease management were presented in Tables 81 and 82 of the CS, respectively. Resource use consisted of visits to various healthcare professionals such as general practitioners, oncologists and health visitors. The related unit costs were obtained from the NHS reference costs (2015-2016) and the Personal Social Services Research Unit (PSSRU) 2016 report.[33, 35]

The estimated monitoring and disease management costs per week were £154.61 and £136.07 (not per month as the CS states on p209), respectively for the pre-progression and post-progression health states.

Adverse Events (AEs)

The costs presented for adverse events were reported in Table 84 in the CS and are replicated in Table 34. The majority of costs in the CS were obtained using NHS reference costs (2015-2016).[33] When costs were not available from the NHS reference list, costs were acquired from other sources such as NICE DSU Reports,[36] and inflated using the appropriate indices.[35] Also included in the table are costs for adverse events from other recent publications, which demonstrates the uncertainty in costs. Whilst some of this may be explained by the different health areas and the varying severity of adverse events in each study, it is likely that there is still potential for under- or over-estimation of costs.

Table 34: Adverse event unit costs

Adverse event	Costs used in CS	Costs used by other publication*
Anaemia	£1,315.94	-
Febrile neutropenia	£2,641.80	£3,538.00 [17] £7,066.63 [37] £7352.54 [38]
Neutropenia	£70.80	£1733.22 [37]
Diarrhoea	£919.84	£8.59 per day [39] £1050.76 [37]
Fatigue	£2,499.99	£2233.40 [37]
Neutrophil count decreased	£70.80	-
White blood cell count decreased	£70.80	-
Hypophosphataemia	£1,212.89	-
Pneumonia	£1,751.08	-
Rash	None	£4.30 per day [39] £109.77 [37]
Nausea/vomiting	None	£1050.76 [37]
Dyspnoea	None	£97.00 - £139.00 [39]

* These costs have not been inflated to current price year for the economic model

Only adverse events of severity grade 3 or greater with a prevalence of >5% in at least one arm were included in the economic analysis. However, the ERG noted that data related to fatigue, pneumonia and hypophosphataemia were included in the utility calculations despite these adverse

events not meeting these criteria and no other justification for their inclusions was provided. For these adverse events, the ERG has performed a scenario analysis setting their prevalence and cost to zero. The ERG also has some concerns over the methods used to determine which adverse events were drug related, which may possibly create bias in favour of pembrolizumab.

Unit costs and incidence of additional adverse events that cancer patients typically exhibit, such as dyspnoea, hypertension, and abdominal pain were not considered in the CS model.

Adverse event costs were applied only in the first cycle of the economic model in the CS, without considering their impact in the remaining time horizon of the model; however, this is in line with previous STAs that the ERG have been involved with. However, this approach may underestimate adverse event costs associated with both pembrolizumab and UK SOC arms.

Terminal care costs

Terminal care costs were included in the economic model in the form of a one-off cost for all patients who transitioned to the death health state. The CS acknowledges the limited data available for terminal care in the urothelial cancer field. Estimates were calculated in line with a previous HTA report.[40]

Resource use estimates were obtained from both Marie Curie reports[41] and NICE guidance.[17, 42] Cost data was taken from a combination of the latest NHS reference costs and the PSSRU Report 2016.[33, 35] The total cost of terminal care per patient was £7252.82 for both treatment arms.

ERG Summary

- Drug dosing schedules and costs were provided by the company.
- No drug wastage costs were included.
- UK SOC treatment costs were estimated based on the KEYNOTE-045 trial docetaxel-paclitaxel administration ratio instead of the UK market administration ratio.
- Adverse event costs may have been underestimated in the economic model due to: (a) excluding some common adverse events that occur in cancer patients; (b) considering adverse events only in the first cycle of the model.

5.2.10 Cost effectiveness results

5.2.10.1 Base-case analysis

The CS provided updated cost-effectiveness results for the base-case and the subgroup analyses in their response to the ERG's clarification questions (CS clarification response: Appendix 5 - Addendum 1).

For the base-case analysis, deterministic and probabilistic results are presented in Table 35 comparing pembrolizumab with UK SOC for the overall patient population. All analyses are presented with the discounted patient access scheme (PAS).

Table 35: Base-case results (CS clarification response: Appendix 5 -Addendum 1 - Tables 87 and 91)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Deterministic results					
UK SOC	£20,938	1.10	-	-	-
Pembrolizumab	£60,053	1.95	£39,115	0.85	£45,833
Probabilistic results					
UK SOC	£21,367	1.13	-	-	-
Pembrolizumab	£60,634	1.98	£39,267	0.85	£46,194

The CS found that for the overall patient population pembrolizumab was more expensive than UK SOC; however, it generated more QALYs than the comparator. This resulted in a deterministic ICER of £45,833/QALY gained. The results of the probabilistic sensitivity analysis (PSA) are similar with an expected ICER of £46,194/QALY.

5.2.10.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed, which involved a random sampling of the parameters used in the cost effectiveness model using a 1,000 samples. The ERG examined convergence of the PSA by running a simulation with 5,000 samples, which resulted in similar probabilistic estimates to those reported in the CS. Whilst such an analysis goes some way to checking the validity, it does not guarantee consideration of particular combinations of parameter values, nor the potential for correlation between parameters. It would be useful to identify which

(if any) combination of parameter values led to the control arm resulting in more QALYs than the pembrolizumab arm, and to establish the feasibility of these combinations.

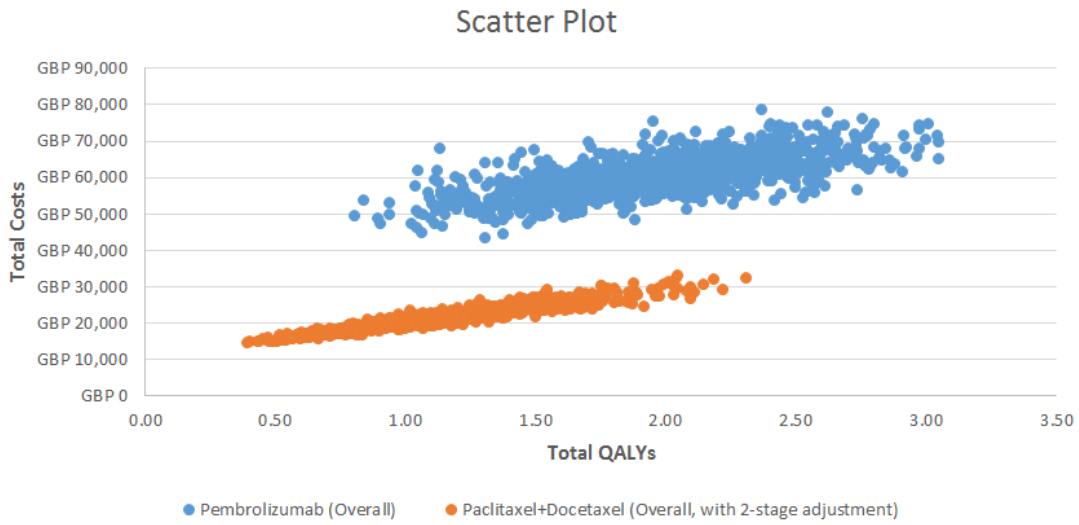


Figure 21: Cost-effectiveness plane

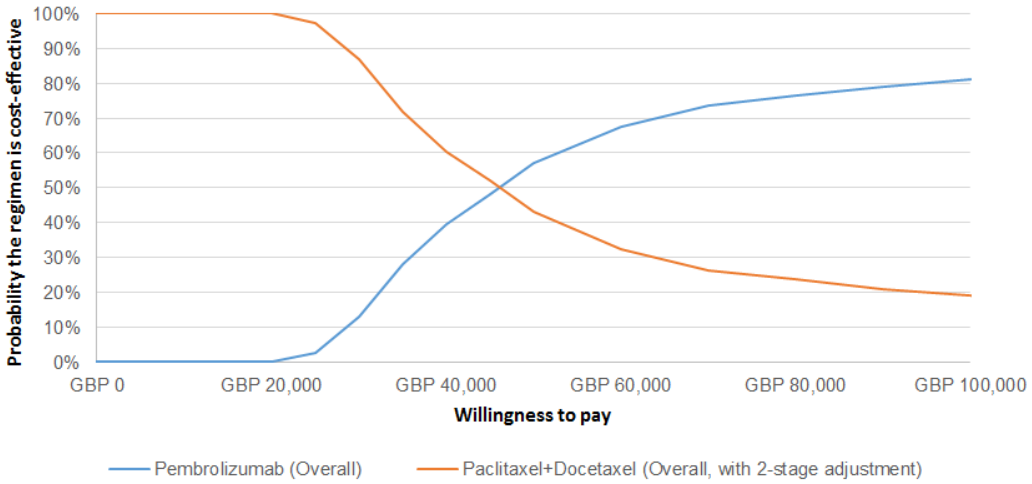


Figure 22: Cost-effectiveness acceptability curve

Cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) are shown in Figure 21 and Figure 22, respectively (CS clarification response: Appendix 6 - Addendum, Figures 49 and 50 respectively). A scatter plot of the PSA results in Figure 21 shows that patients on pembrolizumab have higher costs, but generally have more QALYs. There is also a wider variation in costs and QALYs associated with pembrolizumab than the control arm. At a willingness to pay (WTP) threshold of £50,000 per QALY (see section 7 for further details for

end-of life criteria), the probability of pembrolizumab being cost-effective when compared to UK SOC is 0.57.

Variation in costs appears to be considerably less compared to variation in QALYs in Figure 21. The ERG explored the reason for such finding. Since all relevant cost and resource use parameters were assigned appropriate distributions, the ERG believes that such underestimation of variation is due to assigning a coefficient of variation of 0.1 (10%) in all cost and resource use parameters. The ERG have explored the use of a coefficient of variation of 0.2 (20%) and present the findings in Figure 23 and Figure 24. Compared to the CS, the probabilistic ICER has slightly increased to £46,898 per QALY and the probability of pembrolizumab being cost-effective has slightly decreased to 0.55.

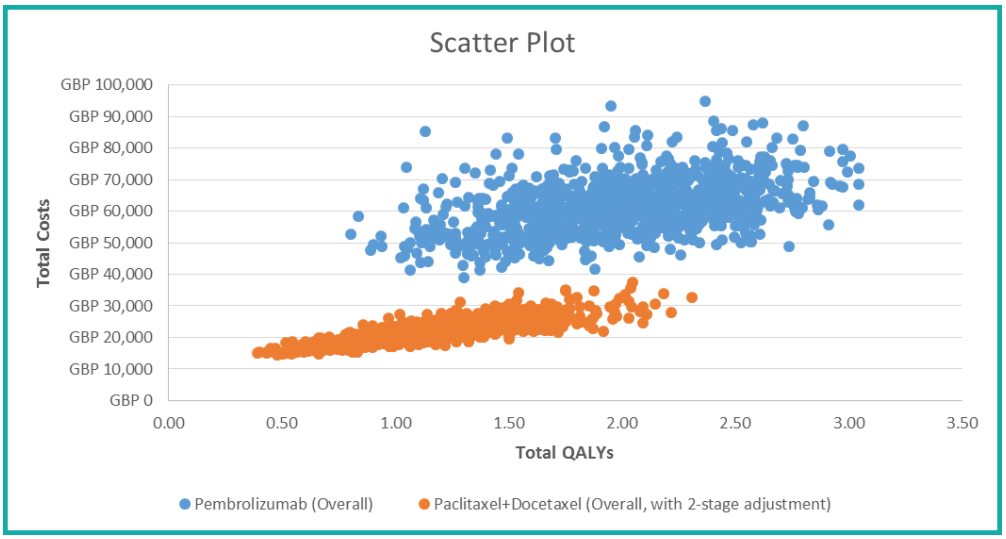


Figure 23: Cost-effectiveness plane - variation 0.2

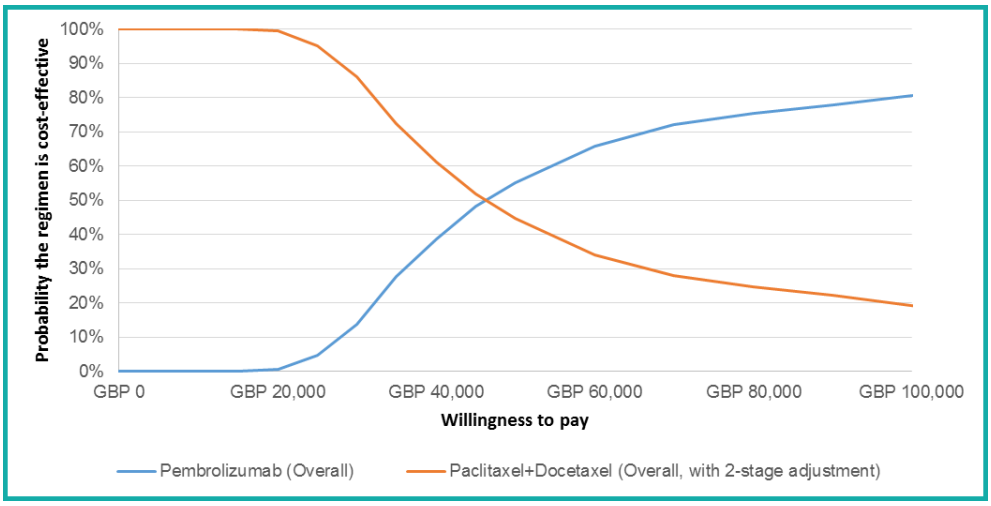


Figure 24: Cost-effectiveness acceptability curve - variation 0.2

5.2.10.3 Subgroup analyses

The CS presented subgroup cost-effectiveness results in Appendix 22 in the CS clarification response and are reproduced in the following tables: Table 36 to Table 40. The CS stated that "the results of the subgroup analyses are exploratory and should be interpreted with caution, especially since these are based in small sample sizes and some of the switchover analyses to adjust for OS could not be performed".

Table 36: Cost-effectiveness results for the comparison of pembrolizumab vs. paclitaxel (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 5 page 37						
Crossover adjustment: none (ITT)						
Paclitaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
Paclitaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage and IPCW adjustments could not be implemented in this population* *[#]These are the corrected figures (the figures were incorrect in the CS)*						

The CS found that for the overall patient population pembrolizumab was more expensive than when paclitaxel or docetaxel were considered as individual regimens on their own; however, it generated more QALYs than the comparator (see Table 36 and Table 37). As noted in Table 37

when comparing pembrolizumab with docetaxel, when no adjustment was made this resulted in a deterministic ICER of [redacted] per QALY gained when RPSFT adjustment method was used the ICER fell to [redacted] per QALY gained.

Table 37: Cost-effectiveness results for the comparison of pembrolizumab vs. docetaxel (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 5 page 37						
Crossover adjustment: none (ITT)						
Docetaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
Docetaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
Docetaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage adjustment could not be implemented in this population*						

Table 38: Cost-effectiveness results for histology subgroups (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 6 page 38						
1) Patients with predominantly transitional cell urothelial carcinoma						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2) Patients with pure transitional cell urothelial carcinoma						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**No adjustment method could be implemented in this population*						

The CS found that for patients with predominantly transitional cell urothelial carcinoma when no adjustment was made the deterministic ICER was [redacted] and for patients with pure transitional cell

urothelial carcinoma when no adjustment was made pembrolizumab was [redacted] by UK SOC (see Table 38).

Table 39: Cost-effectiveness results for patients whose tumours express positive PD-L1 (CPS≥1%) (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 6 page 39						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage adjustment could not be implemented in this population*						

For patients whose tumours express positive PD-L1 (CPS≥1%), the deterministic ICERs were the £50,000/QALY threshold (see Table 39). Whereas for patients whose tumours express positive PD-L1 (CPS≥10%), the deterministic ICERs [redacted] the £50,000/QALY threshold (see Table 40).

Table 40: Cost-effectiveness results for patients whose tumours express strongly positive PD-L1 (CPS≥10%) (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 6 page 40						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage and IPCW adjustments could not be implemented in this population*						

In their clarification response the company presented cost-effectiveness results for patients who were negative for PD-L1 (CPS<1%) (see Table 41), where it is evident that cost-effectiveness results depend on whether or not patient crossover is accounted in the estimation. The deterministic results showed an ICER of [redacted] per QALY for the ITT population and an ICER of per QALY for the RPSFT method of crossover adjustment.

Table 41: Cost-effectiveness results for patients with CPS<1% (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
deterministic results						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage and IPCW adjustments could not be implemented in this population*						

Also, upon request from the ERG, the company presented CEACs for all subgroup analyses undertaken, in the clarification response letter. Upon examination by the ERG they are in agreement with the deterministic cost-effectiveness results (the CEACs are not presented here).

The ERG has some reservations regarding the subgroup analyses presented in the CS. To the best of the ERG's knowledge, subgroup results were obtained using the same model parameters (such as age and gender) as in the base-case analysis (i.e. the overall patient population) and varying only the survival modelling part of the economic model. Since the populations are not the same as in the base-case analysis, we would expect the patient cohort to exhibit differences in model parameters beyond these informing OS and PFS.

5.2.11 Sensitivity analyses

5.2.11.1 Deterministic sensitivity analysis

A deterministic sensitivity analysis was performed using the 5% and 95% confidence interval estimates (unless otherwise stated in the CS), exploring the effect of key variables on the net monetary benefit (NMB) using a willingness to pay threshold of £50,000. A tornado diagram of the results is shown in Figure 25.

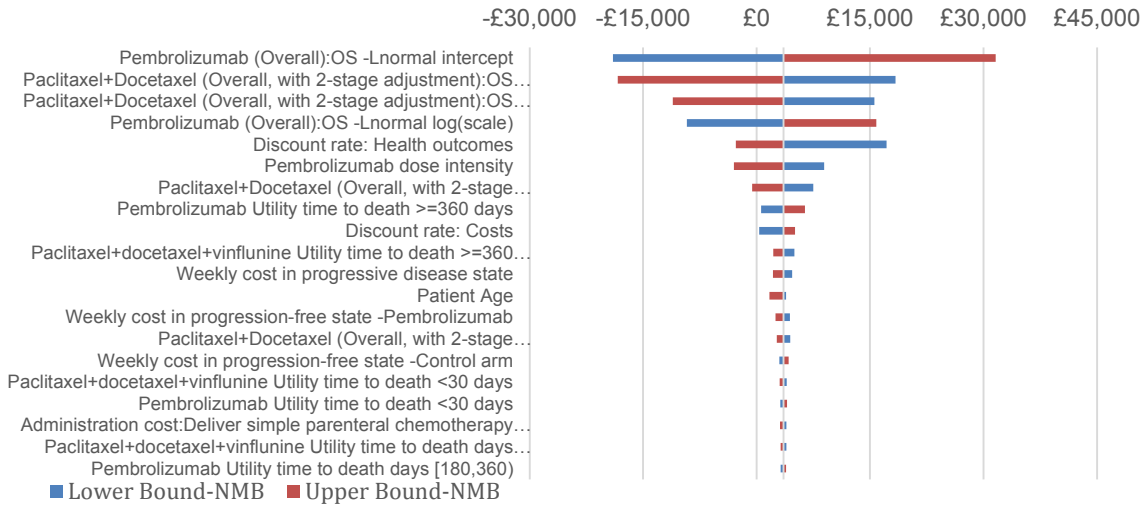


Figure 25: Tornado Diagram based on NMB

No tornado plot for the effects on the ICER were presented in the original CS, however it was included in the CS clarification response letter as shown in Figure 26. It is unknown what criterion were used for the selection of key variables. Looking at both Figure 25 and Figure 26, the most influential variables had a strong enough impact to suggest the control arm was more cost-effective when the 5% and 95% confidence intervals were used. The most influential of these were the parameters of the log normal distribution for overall survival of both arms, the discount rate of the health outcomes, the pembrolizumab dose intensity, and the assumptions around the time on treatment for the UK SOC arm. No combinations of these factors were explored in terms of two-way sensitivity analyses. The fact that the choice of model for OS is one of the most influential factors, illustrates how important this variable is in influencing the ICER.

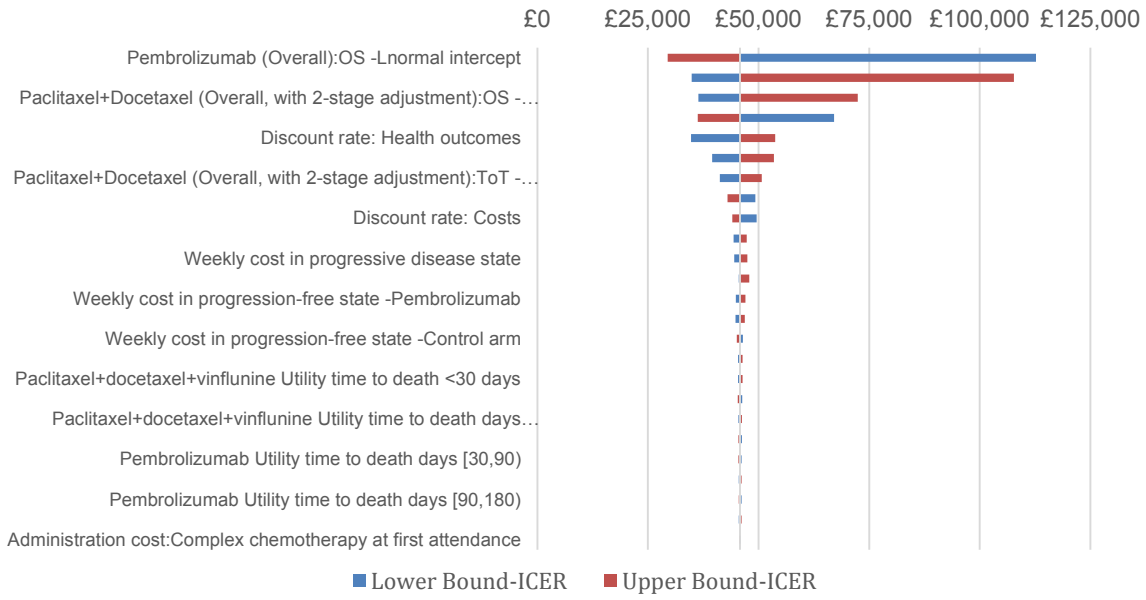


Figure 26: Tornado Diagram based on ICER

5.2.11.2 Scenario analyses

Nine alternative scenarios were analysed to assess the impact of assumptions on the ICER, two of these analyses raised the ICER per QALY over £50,000. These were: failing to adjust for treatment switching using an ITT analysis (ICER = £64,101) and using pooled progression based utility values (ICER = £54,665). The ERG feels that both these approaches represent valid estimates and that these results should be carefully considered. There were three scenarios that reduced the ICER to below £35,000. These were: using the RPSFT method for treatment switching (ICER = £31,509), and changing the cut off used for the piecewise modelling of overall survival (to 24 weeks or to 32 weeks). Further details can be found in Table 92 of the CS clarification response appendix.

The results of the scenario analysis showed that relatively few of the investigated scenarios had a meaningful effect on the ICER. However, the ERG would like to have seen a greater consideration of other survival curves included in the scenario analysis, for both PFS and OS particularly as the justification of the base-case selection is weak and also as the OS and PFS extrapolation are highly influential to the ICER, any changes could be quite significant. Yet only one alternative distribution was examined in the scenario analysis, modelling the PFS of the UKSOC arm with a generalised gamma distribution.

An additional sensitivity analysis was performed as requested by the ERG and NICE in the clarifications. This analysis explored how changing the duration of treatment effect and changing the percentage of patients that remained on pembrolizumab after 2 years affected the ICER. The results of this analysis are shown in Table 42. It can be seen that if the maximum treatment duration is not capped at 2 years, then the ICER exceeds the £50,000 threshold, regardless of the duration of the treatment effect (100% of progression-free patients on treatment after 2 years). Similarly, limiting the treatment effect to 3 years also raises the ICER above £50,000, even if no subjects were to take pembrolizumab for longer than 2 years. However, when the treatment effect is limited to 5 years, then the ICER is only below £50,000 if no patients were take pembrolizumab beyond 2 years. Most combinations of scenarios other than the base-case scenario raise the ICER to over £50,000, which casts some uncertainty over the true cost-effectiveness of pembrolizumab.

Table 42: Effects of changing duration of treatment effects and time on treatment duration on ICER

Continued treatment effect duration post treatment	ICER	Percentage of progression-free patients on treatment after 2 years		
		0%	25%	100%
Lifetime (base-case)	Deterministic	£45,833	£47,795	£52,806
10 years	Deterministic	£46,722	£48,732	£53,864
5 years	Deterministic	£49,442	£51,597	£57,100
3 years	Deterministic	£53,208	£55,564	£61,582

ERG summary

- A wide range of different approaches to a sensitivity analysis were conducted.
- Statistical approach to treatment switching and pooled utility values pushed ICER to over £50,000/QALY threshold.
- The ICER was sensitive to survival model parameters
- The ICER was also sensitive to time on treatment and to the treatment effect duration.

5.2.12 Model validation and face validity check

The company stated that they validated the clinical benefit by comparing model outcomes to clinical trial outcomes. Specifically, they compared the OS and PFS estimates obtained from the model at 6 months and 1 year with the respective estimates obtained from the KEYNOTE-045 trial. The ERG have some reservations with this approach for two reasons.

The first relates to the comparability of OS estimates at 6 months. Since the cut-off point in OS modelling is 40 weeks and before the cut-off the company used KM data from the KEYNOTE trial, the model and KEYNOTE outcomes for OS at 6 months should be the same. Despite that, OS estimates are slightly higher in the model relative to KEYNOTE both in the pembrolizumab and the UK SOC arms (Table 43). Upon inspection of the economic model, the ERG found that such disparity is due to a half cycle correction applied in the model and if the half cycle correction is removed such outcomes are the same.

The second reason relates to the fact that model predictions beyond 1 year were not validated, as OS and PFS estimates from KEYNOTE were not presented for a time point beyond 1 year in the CS. This is the case despite having follow up trial data beyond 1 year. Upon inspection of OS outcomes at 14.5 months, model outcomes were slightly higher compared to trial outcomes in the pembrolizumab arm (40.2% vs 39.3%) and slightly lower in the UK SOC arm (24.6% vs 25.7%). The same is true at 16.1 months (pembrolizumab: 37.8% vs 36.8%; UK SOC: 22.5% vs 25.7%). If we compare OS outcomes at 20 months, model outcomes are lower compared to trial outcomes in both pembrolizumab (33.3% vs 36.8%) and UK SOC (18.9% vs 25.7%). Despite that, the underestimation of OS is more profound in the UK SOC arm.

Table 43: Comparison of model and trial outcomes (In CS Table 88)

Outcome	Pembrolizumab		UK SOC	
	Base case	KEYNOTE-045	Base case	KEYNOTE-045
Progression-free survival				
Median PFS (months)	2.3	2.1	3.4	3.2
6-month PFS	28.6%	28.8%	22.8%	22.7%
Overall survival				
Median OS (months)	10.3	10.3	7.1	6.9
6-month OS	64.1%	63.9%	54.8%	54.5%
1-year OS	45.5%	43.9%	29.6%	30.2%
2-year OS	30.0%	-	16.4%	-
5-year OS	16.7%	-	7.8%	-
10-year OS	9.9%	-	4.2%	-

Another limitation of the clinical benefit validation process is that no external data more relevant to the target population were examined in order to validate long-term outcomes and examine the generalisability of the KEYNOTE-045 trial to the UK setting.

Regarding the model cross validation process, the company stated that the current economic model was adapted from a cost-effectiveness model for patients with NSCLC. The current model used identical base-inputs for example, costs, utilities, survival from the NSCLC model and the results obtained were the same; therefore, the company suggested that the current model is structurally sound. The ERG cannot comment on such finding since they cannot validate these results.

Finally, the model was validated by an external health economist and by using a "black box" testing method, in which a range of extreme value sets were used to highlight any errors. In addition, a simplified version of the model was written and individual formulae in the model were checked. Upon inspection of the Excel economic model, the ERG did not find any errors and believe the model is methodologically robust.

ERG summary

- The method used to validate clinical benefit was not optimal. The ERG has some concerns regarding the validation of long-term survival outcomes and a potential overestimation of OS in the pembrolizumab arm relative to the UK SOC arm.
- The Excel model presented by the company appears to be methodologically robust.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Only the deterministic results for the exploratory and sensitivity analyses undertaken by the ERG have been presented, as the probabilistic results were similar to the deterministic results. A list of all changes is reported in Appendix 11.1.

Table 44: Excluding vinflunine patients when estimating utility values in the pooled analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death based						
UK SOC	£20,938	1.59	1.09	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,115	0.86	£45,712
Progression based						
UK SOC	£20,938	1.59	1.04	-	-	-
Pembrolizumab	£60,053	2.71	1.76	£39,115	0.72	£54,063

Table 44 shows the base-case results when vinflunine patients were excluded from the calculation of EQ-5D utility values for the pooled analysis. Compared to the company base-case analysis (Table 35), when vinflunine is excluded for time to death utilities the ICER slightly decreases by £121/QALY, however, the alternative scenario is to use progression based utilities without vinflunine patients and the ICER compare to the base-case analysis increases by £8,230/QALY.

When vinflunine patients were excluded from the calculation of EQ-5D utility values specific for each treatment arm, compared to the base-case analysis (Table 35), the ICER increases when time to death utilities are used by £4,241/QALY; however, when progression based utilities are used the ICER falls by £3,532/QALY (see Table 45).

Table 45: Excluding vinflunine patients when estimating utility values specific for each treatment arm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death based						
UK SOC	£20,938	1.59	1.14	-	-	-
Pembrolizumab	£60,053	2.71	1.92	£39,115	0.78	£50,074
Progression based						
UK SOC	£20,938	1.59	0.92	-	-	-
Pembrolizumab	£60,053	2.71	1.84	£39,115	0.92	£42,301

Using utility values (including vinflunine patients) which are progression-based, the ICER increases to [redacted] (see Table 46).

Table 46: Progression-based utilities (inc. vinflunine patients)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Progression based						
UK SOC	£20,938	1.59	1.03	-	-	-
Pembrolizumab	£60,053	2.71	1.74	£39,115	0.72	£54,665

As mentioned in Section 5.2.8, the ERG has used progression based utilities based on TA272, as we believe that the time to death utilities are overestimated. The ICER using utility values based on TA272 increases dramatically from £45,833 per QALY (Table 35) to £114,082 per QALY, this is due to the substantially smaller differences in QALYs between the two treatment arms (see Table 47).

Table 47: Utility values from TA272 (pooled utility values excluding vinflunine)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Progression based						
UK SOC	£20,938	1.59	0.52	-	-	-
Pembrolizumab	£60,053	2.71	0.87	£39,115	0.34	£114,082

Also, in Section 5.2.8, we mentioned that disutility for ageing used in the model assumed no further decline past the age of 75 years. Using a more up-to-date reference, Ara and Brazier, 2010[32] when calculating age-related utility decrements the ICER slightly increases (time to death based utilities: +£840/QALY) – see Table 48.

Table 48: Applying age-related utility decrements based on values from Ara and Brazier (2010)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death based						

UK SOC	£20,938	1.59	1.09	-	-	-
Pembrolizumab	£60,053	2.71	1.92	£39,115	0.84	£46,673
Progression based						
UK SOC	£20,938	1.59	1.02	-	-	-
Pembrolizumab	£60,053	2.71	1.72	£39,115	0.70	£55,861

Using the adverse event disutility values as presented in Table 32, for the pooled analysis (see Table 49) the ICER is very similar to the base-case analysis (£49,814/QALY). However, when separate adverse event disutility values are used for each specific treatment arm the ICER increases considerably. For example, the ICER increases from £45,833 per QALY (base-case) to £60,714 per QALY when using time to death utilities (see Table 50), as mentioned earlier adverse events have a much greater impact on the quality of life in the pembrolizumab arms.

Table 49: Adverse event utility values excluding vinflunine patients in the pooled analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death						
UK SOC	£20,938	1.59	1.10	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,115	0.85	£45,814
Progression based						
UK SOC	£20,938	1.59	1.03	-	-	-
Pembrolizumab	£60,053	2.71	1.74	£39,115	0.72	£54,638

Table 50: Adverse event utility values excluding vinflunine patients for each specific treatment arm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death						
UK SOC	£20,938	1.59	1.08	-	-	-
Pembrolizumab	£60,053	2.71	1.72	£39,115	0.64	£60,714
Progression based						
UK SOC	£20,938	1.59	0.86	-	-	-
Pembrolizumab	£60,053	2.71	1.65	£39,115	0.79	£49,652

Table 51 shows the sensitivity analysis performed when removing the adverse events that did not meet the company's own inclusion criteria (pneumonia, hyphosphataemia and fatigue) – costs and

prevalence were set to 0. As shown the impact of these costs were negligible (ICER increased by £151/QALY). Furthermore, the table also shows results when using the most recent adverse event costs and again the impact of these costs were negligible (ICER decreased by £866/QALY).

Table 51: Adverse event costs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Removal of unjustified AE costs and prevalence (pneumonia, hypophosphataemia and fatigue)						
UK SOC	£20,673	1.59	1.10	-	-	-
Pembrolizumab	£59,903	2.71	1.95	£39,230	0.85	£45,984
Using AE costs from alternative sources (most recent publication used where multiple options possible)*						
UK SOC	£21,638	1.59	1.10	-	-	-
Pembrolizumab	£60,014	2.71	1.95	£38,376	0.85	£44,967

***ERG unable to add costs of rash, nausea/vomiting or dyspnoea**

Table 52: Estimation of cost of UK SOC based on UK market share of docetaxel and paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£20,814	1.59	1.10	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,239	0.85	£45,978

Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel, the ICER is very similar to the base-case analysis (£45,978 – see Table 52).

As mentioned in Section 5.2.6.1, the ERG considers that an extrapolation based on a log-logistic parametric distribution, added to the observed 24-week data may give plausible estimates for overall survival. Changing from log-normal to log-logistic only, the company's base-case ICER increases from £45,833 per QALY to £59,246 per QALY gained (see Table 53); and changing the cut-off from 40 weeks to 24 weeks only, the company's base-case ICER decreases from £45,833 per QALY to £34,168 per QALY (see Table 53). However, the ERG considers that both of these points should be considered together to give plausible estimates for overall survival, hence the

company's base-case ICER decreases from £45,833 per QALY to £42,343 per QALY (see Table 53).

Table 53: Changing overall survival functions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Log-logistic model for overall survival						
UK SOC	£20,609	1.54	1.06	-	-	-
Pembrolizumab	£57,638	2.36	1.68	£37,029	0.62	£59,246
24 week cut-off for overall survival						
UK SOC	£17,334	1.06	0.70	-	-	-
Pembrolizumab	£60,027	2.71	1.95	£42,693	1.25	£34,168
Log-logistic model and 24 week cut-off for overall survival						
UK SOC	£17,563	1.09	0.72	-	-	-
Pembrolizumab	£57,457	2.34	1.67	£38,894	0.94	£42,343

ERG preferred base-case analysis

Our overall preferred ERG base-case is presented in Table 54. Changes include:

- Exclusion of vinflunine patients from estimation of utility values.
- Estimation of age-related utility decrements based on Ara and Brazier (2010).
- Use of utility values based on progression status.
- Use of pooled utility and adverse event disutility values.
- Setting adverse event prevalence and costs related to pneumonia, hypophosphatemia and fatigue to zero.
- Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel.
- Use a cut-off point of 24 weeks for the overall survival modelling approach.
- Use a log-logistic distribution for overall survival modelling for pembrolizumab and UK SOC.

Table 54: ERG preferred base-case analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£17,174	1.09	0.73	-	-	-
Pembrolizumab	£57,307	2.34	1.51	£40,132	0.78	£51,405

As shown in Table 54, for the ERG preferred base-case the ICER is slightly higher at £51,405 per QALY compared to the CS base-case analysis ICER of £45,833 per QALY.

5.3.1 ERG's preferred base-case model using different parametric distributions for overall survival

Due to the paucity of published information on the long-term overall survival for people with advanced or metastatic urothelial cancer, the ERG considers there to be some uncertainty in the extrapolations. It can be seen from Figure 7, Figure 8, Table 22 and Table 23 that the three-, five- and ten-year overall survival estimates differ based on the parametric curve used, and this will have an impact on the life years gained and QALYs gained. It should be noted that the company's results are based on a 35-year (lifetime) time horizon, which is in line with the NICE reference case. However, using the ERG's preferred assumptions (see section 5.3) we show in Table 55 that the majority of these benefits are based on the extrapolated difference and not based on the observed difference. To estimate the proportion of clinical benefit (expressed as life years gained (LYG)) that comes from the observed data or the extrapolated survival, we first estimated the LYG between pembrolizumab and UK SOC from the data over the period of observation in KEYNOTE-045. Given the availability of the data (median follow-up duration 14.1 months, range: 9.9 to 22.1), we considered two time points, 10 months and 22 months. We assumed that the LYG from observed data at these two time points could be calculated using the survival models for pembrolizumab and UK SOC as in the cost-effectiveness model (log-logistic distribution; 24 weeks cut-off) and changing the time horizon to 10 and 22 months. Indeed, we assumed these models were very much reliable to predict the life expectancies over a short-term period as in the actual observed data.

At a 35-year time horizon, the model yielded a 1.25 LYG (2.34 life years with pembrolizumab vs. 1.09 life years for UK SOC). Using the 10 month-time point, the LYG with observed data could

be estimated at 0.04 meaning that the benefit from the observed data contributed to only 3% of the total benefit (1.25 LYG), while 97% of the incremental life-expectancy comes from survival extrapolations. Using the 22 month-time point, the LYG with observed data could be estimated at 0.19 meaning that the benefit from observed data contributed to only 16% of the total benefit (1.25 LYG) while 84% of the incremental life-expectancy comes from survival extrapolations.

Should pembrolizumab be recommended by NICE for routine use within the NHS, the fact that most of the incremental benefit in terms of LYG comes from extrapolated data advocates for a review of this STA within a short period of time using longer follow-up data from KEYNOTE-045.

Table 55: Proportion of LYG based on the observed and extrapolated data

Time-point	LYG		Incremental LYG	Proportion of LYG from observed data	Proportion of LYG from extrapolated survival
	UK SOC	Pembrolizumab			
10 months	0.60	0.56	0.04	3%	97%
22 months	0.98	0.78	0.20	16%	84%

Additionally, we have explored in a scenario analysis the impact of using the ERG's preferred assumptions (including the 24-week cut-off), and using different parametric distributions and at different time horizons.

In Table 56, Table 57 and Table 58 we present results for the ERG's base-case, based on analyses undertaken at a 2-year, 10-year and 35-year time horizon, respectively. Results based on a 2-year time horizon showed that the expected mean incremental costs and mean effects (LYG/QALYs) are similar, irrespective of the parametric distribution.

Table 56: Using the ERG's preferred base-case, with results based on a 2-year time-horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£14,445	0.80	0.55	-	-	-	-
Pembrolizumab	£46,483	1.02	0.70	£32,038	0.22	0.15	£209,686
Weibull							
UK SOC	£14,521	0.79	0.55	-	-	-	-
Pembrolizumab	£46,369	1.02	0.71	£31,848	0.23	0.16	£195,312
Gompertz							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£14,285	0.82	0.56	-	-	-	-
Pembrolizumab	£46,157	1.04	0.72	£31,872	0.22	0.15	£207,614
Log-logistic							
UK SOC	£14,342	0.80	0.55	-	-	-	-
Pembrolizumab	£46,250	1.03	0.71	£31,908	0.23	0.16	£196,744
Log-normal							
UK SOC	£14,342	0.81	0.56	-	-	-	-
Pembrolizumab	£46,152	1.04	0.72	£31,810	0.23	0.16	£195,344
Generalised gamma							
UK SOC	£14,185	0.83	0.71	-	-	-	-
Pembrolizumab	£46,271	1.03	0.57	£32,086	0.20	0.14	£225,655

Results based on the 10-year time-horizon showed that the expected mean LYG and QALYs ranged from 0.33 to 1.30, and 0.23 to 0.84, respectively, while expected mean incremental costs were all above £35,000 but less than £40,000. These results showed that at a 10-year time horizon, extrapolations based on a Gompertz parametric distribution, added to the observed 24-week Kaplan-Meier data, gave the most favourable ICER (approximately £47,400 per QALY gained) compared to using a generalised gamma distribution (£146,000 per QALY gained).

Table 57: Using the ERG's preferred base-case, with results at a 10-year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£15,782	0.89	0.61	-	-	-	-
Pembrolizumab	£50,529	1.35	0.92	£37,747	0.46	0.31	£111,336
Weibull							
UK SOC	£15,476	0.85	0.58	-	-	-	-
Pembrolizumab	£51,424	1.48	1.00	£35,949	0.63	0.43	£84,555
Gompertz							
UK SOC	£17,991	1.25	0.83	-	-	-	-
Pembrolizumab	£57,751	2.55	1.67	£39,760	1.30	0.84	£47,408
Log-logistic							
UK SOC	£16,725	1.04	0.70	-	-	-	-
Pembrolizumab	£54,172	1.93	0.70	£37,448	0.89	0.58	£64,021
Log-normal							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£16,735	1.04	0.70	-	-	-	-
Pembrolizumab	£55,548	2.15	1.42	£38,814	1.11	0.72	£53,682
Generalised gamma							
UK SOC	£19,178	1.43	0.94	-	-	-	-
Pembrolizumab	£53,164	1.76	1.18	£33,985	0.33	0.23	£145,980

Results based on the 35-year time-horizon showed that the expected mean LYG and QALYs ranged from 0.10 to 2.38, and 0.11 to 1.45, respectively, while the expected mean incremental costs were all greater than £32,000 but less than £50,000. These results showed that at a 35-year time horizon, extrapolations based on a Gompertz parametric distribution, added to the observed 24-week Kaplan-Meier data, gave the most favourable ICER (approximately £33,200 per QALY gained) compared to using a generalised gamma distribution (approximately £298,800 per QALY gained).

Table 58: Using the ERG's preferred base-case, with results at a 35-year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£15,782	0.89	0.61	-	-	-	-
Pembrolizumab	£50,545	1.35	0.92	£34,763	0.46	0.31	£111,108
Weibull							
UK SOC	£15,476	0.85	0.58	-	-	-	-
Pembrolizumab	£51,518	1.49	1.01	£36,043	0.64	0.43	£83,713
Gompertz							
UK SOC	£20,361	1.56	1.01	-	-	-	-
Pembrolizumab	£68,322	3.94	2.45	£47,961	2.38	1.45	£33,179
Log-logistic							
UK SOC	£17,174	1.09	0.73	-	-	-	-
Pembrolizumab	£57,307	2.34	1.51	£40,132	1.25	0.78	£51,405
Log-normal							
UK SOC	£16,945	1.06	0.71	-	-	-	-
Pembrolizumab	£59,876	2.71	1.74	£42,931	1.65	1.02	£41,933
Generalised gamma							
UK SOC	£21,866	1.78	1.14	-	-	-	-
Pembrolizumab	£54,223	1.88	1.25	£32,357	0.10	0.11	£297,821

These results offer some insight on the impact of using different parametric distributions and time horizons. As expected, at the 2-year time horizon, the choice of parametric distributions has no impact on the expected mean costs and benefits, as they are all similar. This is a consequence of the results being heavily dependent on the observed data and not the extrapolations. Also the ICERs increase, and this is a result of the model not capturing all costs and benefits over this short duration. Conversely, at the 10-year time horizon, the economic model utilizes more information from the parametric distributions in the form of the estimated overall difference in survival time. It can be seen that there is some variation in the incremental costs, but more so in the incremental effects (LYG/QALYs) and this is reflected in the range of ICERs derived. Similarly, at the 35-year time horizon, the model depends heavily on the parametric distributions in order to inform on the cost-effectiveness. These results show that there is some variation in the incremental costs and effects, and this is reflected in the ICERs.

These analyses highlight that the results are dependent on the time horizon and the choice of parametric distribution used for estimating the overall survival. It should be noted that the economic model only allows the same parametric distribution to be used for estimating the overall difference in mean survival time between pembrolizumab and UK SOC. It would have been informative to choose parametric distributions based on goodness-of-fit measures (also informed by clinical opinion), whereby allowing the different functional forms to be used in order to estimate mean overall survival.

5.4 Conclusions of the cost effectiveness section

The company submission is based around pembrolizumab versus UK SOC. The company used a partitioned survival model to assess the cost-effectiveness of pembrolizumab compared to UK SOC (docetaxel/paclitaxel), in people with advanced or metastatic urothelial cancer. The model defined health states of pre-progression, post-progression and death, and the cost-effectiveness was analysed over a 35-year time horizon. Clinical effectiveness inputs to the model relied solely on the KEYNOTE-045 trial. Key costs included in the model were the cost of pembrolizumab and the cost of UK SOC. A PAS was provided for pembrolizumab. The model appeared to have captured the key features of people with advanced or metastatic urothelial cancer.

The model submitted by the company provided a deterministic ICER of approximately £45,800 per QALY gained, and at a willingness-to-pay threshold of £50,000 (see section 7), the

company's probabilistic analysis yielded a 0.57 probability of pembrolizumab being cost-effective when compared to UK SOC. The probabilistic ICERs are in relative agreement.

Other than two easily fixed errors (application of maximum time on treatment and estimation of QALYs), which the company corrected and provided an updated model, there were no discrepancies found between the models reported in the company submission and the copy of the model given to the ERG.

However, there are several areas of uncertainty that may impact on the cost-effectiveness results, as the model was most sensitive to changes made to the overall survival:

- The cut-off time point used for the overall survival model; and
- The choice of parametric function for the overall survival model

The ERG considers the two-phase piecewise model to be feasible in order to model overall survival. However, it would have been more appropriate to use an extrapolation based on a log-logistic parametric distribution, added to the observed 24-week Kaplan-Meier data instead of a log-normal distribution, added to 40-week observed data. It should be noted that there is uncertainty in the overall survival, especially beyond the trial time horizon and this will invariably have an impact on the life years gained and hence, the cost-effectiveness results.

Furthermore, the CS compared the extrapolated OS for people in the UK SOC with that reported by Cancer Research UK for patients with stage IV bladder cancer. The ERG however, have concerns regarding the comparability of people in the KEYNOTE-045 trial with those from Cancer Research UK.

The CS model incorporates utility scores based on time to death, which results in a relatively unusual method to estimate life years (based on death incidence) and subsequent QALYs. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC arms relative to life years based on progression status. The ERG believes that using utility scores based on progression status is a more appropriate method to estimate life years and subsequent QALYs.

The base-case analysis included data for patients receiving vinflunine in the estimation of utility values, which is currently not recommended in England. The ERG believes that such patients should have been excluded from the analysis.

The age-related utility decrements are estimated from an outdated study that does not allow for the incorporation of decrements for patients aged more than 75 years old. The ERG believes that this is a limitation that possibly overestimates QALYs in both treatment arms.

Furthermore, the ERG removed the adverse events that did not meet the company's own inclusion criteria (pneumonia, hyphosphataemia and fatigue) and associated costs and prevalence were set to zero.

In the base-case analysis, pembrolizumab was compared to UK SOC based on the distribution of the regimens observed in KEYNOTE-045. The ERG believes that cost of UK SOC should be based on the UK market share of docetaxel and paclitaxel.

The ERG presented a preferred base-case analysis taking into account all issues raised in his chapter. Our preferred analysis increased the ICER to £51,405 per QALY.

When interpreting these results, it is important to consider the impact of these key sources of uncertainty in the ICER, and the impact any alternative assumptions would make.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Alterations to the base-case assumptions were made by the ERG as identified in Chapter 5. Details of the alterations can be found in Appendix 11.1. The impact on each change individually on the base-case analysis is shown in Table 59.

Table 59: ERG re-estimation of cost-effectiveness

	ΔC	**ΔQALY**	**ΔC/QALY**	**Ratio[+]**
Pembrolizumab vs UK SOC				
CS base-case model	£39,115	0.85	£45,833	-
ERG models				
Exclusion of vinflunine patients from estimation of utility values	£39,115	0.86	£45,712	0.997
Use utility values based on progression status	£39,115	0.72	£54,665	1.193
Estimation of age-related utility decrements based on Ara and Brazier (2010)	£39,115	0.84	£46,673	1.018
Averse event prevalence and costs related to pneumonia, hypophosphatemia and fatigue are set to zero	£39,230	0.85	£45,984	1.003
Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel	£39,239	0.85	£45,978	1.003
Use a log-logistic distribution for OS modelling	£37,029	0.62	£59,246	1.293
Use a cut-off point of 24 weeks for OS modelling	£42,693	1.25	£34,168	0.745
ERG preferred base-case analysis	**£40,132**	**0.78**	**£51,405**	**1.122**

7 END OF LIFE

On page 170 of the main CS, the company have presented a table (Table 61) regarding end-of-life criteria. There are three main criteria to fulfil for the appraisal of end of life treatments:[43]

1. the treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
2. 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; and
3. the treatment is licensed or otherwise indicated, for small patient populations.

Regarding criterion 1, the company has indicated the median OS is lower than 24 months in patients with advanced/metastatic urothelial cancer following platinum based chemotherapy. The statement was supported by two references that were not included in the background section and for which no details were provided of the estimates of life expectancy in these two studies. In the clarification response document, the company has responded that the estimated life expectancy of patients with advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy is estimated to be between 6.5 and 9 months based on the references provided.[44, 45]

In KEYNOTE-045, the median OS was 7.4 months in the SOC arm and between [redacted] and [redacted] months in the UK SOC arm after adjustment for treatment switching. In terms of life expectancy, survival extrapolations for the UK SOC arm indicate a life expectancy of 1.59 years with the company's base-case model and 1.09 years with the ERG's preferred base-case model. Therefore, the ERG agree that pembrolizumab fulfils criterion 1 for end-of-life treatment.

Regarding end-of-life criterion 2, the company indicated that pembrolizumab offers an extension of life of at least 3 months compared to UK SOC both in terms of median OS (10.3 months vs. 6.9 months for pembrolizumab and UK SOC respectively) and months of life gained (32.5 months vs. 19 months for pembrolizumab and UK SOC respectively). The 3.4 months median OS gain is based on the median OS for the UK SOC after adjustment for treatment switching using the 2-stage model. With other adjustment methods, the median OS gain would fluctuate between [redacted] and [redacted] months. As previously indicated, the results comparing pembrolizumab and UK SOC must be viewed with caution since they correspond to a post-hoc analyses. The most robust estimate of the median OS gain should be taken from the entire population from KEYNOTE-045 (+2.9 months) although the ERG appreciates that one of the treatments of the

SOC arm (vinflunine) is not currently available within the NHS. In terms of life-year gained, the company's estimate is 13.5 months while the ERG's estimate is 15 months. Overall, the ERG agree that pembrolizumab fulfils criterion 2 for end-of-life treatment.

The company has not described how pembrolizumab fulfils criterion 3. However, the company reports that the number of patients estimated to be eligible for pembrolizumab will be 502 (CS p234). The ERG clinical advisor also confirms that the patient population relevant to the decision problem would be small.

8 INNOVATION

On page 31 of the CS, the company have presented a statement on how pembrolizumab could represent a step-change in the management of people with advanced/metastatic urothelial cancer after progression or recurrence following platinum-based chemotherapy. Unlike conventional chemotherapies, pembrolizumab belongs to an emerging class of immunotherapy drugs whose mechanism of action consists of increasing the ability of the immune system to kill cancer cells. There is a growing number of immunotherapies which are being evaluated in many cancer types, both in solid tumours and in hematologic malignancies. Some of these, like pembrolizumab, atezolizumab, avelumab, or nivolumab, are already licensed in cancers other than urothelial cancers.

In the innovation section, the company have emphasised the high unmet need for patients with advanced/metastatic urothelial cancer after platinum-based regimen, and indicated that pembrolizumab has demonstrated significant survival benefit and improved tolerability profile compared to conventional chemotherapy. The ERG agree with the company's statement on the high unmet need within the scoped population. The ERG also agree on the significant survival benefit with pembrolizumab although longer-term survival confirmatory analyses will be needed to more accurately evaluate the benefit on life expectancy. The ERG also appreciate the fact that pembrolizumab has a better safety profile compared to conventional cytotoxic chemotherapy.

9 OVERALL CONCLUSION

9.1 Clinical effectiveness evidence

Regarding clinical effectiveness, pembrolizumab used as single agent was evaluated against SOC (either paclitaxel, docetaxel, or vinflunine) in the KEYNOTE-045 trial. This phase 3 trial was of good quality, with a low risk of bias in most domains except for the blinding of participants and personnel since the study was open-label (high-risk of bias).

There were two co-primary endpoints that were assessed in three groups: the entire population, the population positive for PD-L1 expression, and the population strongly-positive for PD-L1 expression.

Regarding PFS, the risk of progression or death was similar between pembrolizumab and SOC in the three populations although the proportion of patients free from progression at 1 year was higher for pembrolizumab.

Regarding OS, the risk of death was reduced with pembrolizumab compared to SOC in the three populations.

The results of PFS and OS in the numerous subgroups showed consistency with the overall findings for the entire population.

The evaluations of quality of life were presented as exploratory objectives. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results.

The safety profile of pembrolizumab was more favourable compared to SOC with no treatment-related events of grade ≥3 with an incidence of ≥5% observed in the pembrolizumab group.

As of April, 2017, pembrolizumab is not licensed for urothelial cancers and a submission aimed to extend the marketing authorisation is currently being assessed with the CHMP. Based on the results of KEYNOTE-045 presenting the clinical effectiveness and safety profile of pembrolizumab in advanced/metastatic urothelial cancers after failure to platinum-based therapy,

the ERG believes it's likely that the CHMP will consider the balance between benefits and risks of pembrolizumab is positive.

No indirect comparisons were presented by the company. There is no data comparing pembrolizumab to BSC which is a relevant comparator in people with poor performance status.

9.2 Cost-effectiveness evidence

The model constructed by the company appears to be logical and methodologically sound. Its main shortcomings relate to the utility values and the overall survival modelling methods.

With regard to the utility values, the ERG believe that utilities should be expressed based on progression status, since this is common practice in previous immunotherapy appraisals and follows the model structure. Furthermore, the time to death based method of estimating utilities overestimates life years gained for both treatment arms. In addition, age-related utility decrements were estimated based on the algorithm in Ara and Brazier (2010)[32] by the ERG; since to the best of our knowledge this is the most recent and coherent source.

With regard to overall survival modelling, the ERG considers the two-phase piecewise model to be suitable for modelling overall survival. However, it would have been more appropriate to use an extrapolation based on a log-logistic parametric distribution, added to the observed 24-week Kaplan-Meier data instead of a log-normal distribution, added to 40-week observed data.

The ERG have presented a scenario with a preferred base-case analysis; this preferred base-case increases the ICER slightly compared with the CS submission.

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11 APPENDICES

11.1 Log of all changes made to the CS base-case model

Reference	Changes made in each analysis	Changes in excel spreadsheet
Table 44: Excluding vinflunine patients when estimating utility values in the pooled analysis	Time to death utilities Progression based utilities	"Settings sheet" – change utility measure tab to 2 "Settings sheet" – change utility measure tab to 2 & approach of evaluating utility tab to 1
Table 45: Excluding vinflunine patients when estimating utility values specific for each treatment arm	Time to death utilities Progression based utilities	"Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2 "Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2 & approach of evaluating utility tab to 1
Table 46: Progression-based utilities (inc. vinflunine patients)	Progression based utilities	"Settings sheet" – change approach of evaluating utility tab to 1
Table 47: Utility values from TA272 (pooled utility values excluding vinflunine)	Use progression based utility values: 0.65 for progression-free and 0.25 for progressed	"Settings sheet" – change utility measure tab to 2 & approach of evaluating utility tab to 1

		"Utility sheet" – change cells F114 to 0.65 and F115 to 0.25
Table 48: Applying age-related utility decrements based on values from Ara and Brazier (2010)	Inclusion of proportion of males Estimate utility values for general population based on algorithm in Ara and Brazier [32] Estimate utility decrements relative to baseline age	"GenInputs" sheet – cell F23 "Utility" sheet – cells D162 to D243 "Utility" sheet – cells E162 to E243 and G162 to G217 and leave cell J162 blank
Table 49: Adverse event utility values excluding vinflunine patients in the pooled analysis	Time to death utilities Progression based utilities	"Settings sheet" – change utility measure tab to 2 "Utility sheet" – change cells D24 and E24 to 0.137 "Settings sheet" – change utility measure tab to 2 & approach of evaluating utility tab to 1 "Utility sheet" – change cells D24 and E24 to 0.137
Table 50: Adverse event utility values excluding vinflunine patients for each specific treatment arm	Time to death utilities	"Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2

	Progression based utilities	"Utility sheet" – change cells D25 to 0.1950 and E25 to 0.058 "Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2 & approach of evaluating utility tab to 1 "Utility sheet" – change cells D25 to 0.1950 and E25 to 0.058
Table 51: Adverse event costs	Removal of unjustified AE costs - set prevalence and cost for pneumonia, fatigue and hyphosphataemia to zero in both treatment arms Using AE costs as provided in Table 34 of ERG report.	CostInputs" sheet – cells F34, F37 & F38 set to 0. "RxInputs" sheet – cells E39, E42, E43, Q39, Q42 & Q43 set to 0. "CostInputs" sheet change cells: F31 → 7352.54; F32 →1733.22; F33 →119.40 & F34 →2233.40
Table 52: Estimation of cost of UK SOC based on UK market share of docetaxel and paclitaxel	Source of distribution of patients in paclitaxel and docetaxel arm	"Settings sheet" – change source of distribution of patients in paclitaxel and docetaxel arm tab to 2
Table 53: Changing overall survival functions	Choice of parametric function for OS curve fitted to KNO45 data:	

	Log-logistic model 24 week cut-off	"Settings sheet" – change OS of pembrolizumab and OS of control arm to Log logistic (tab 4) "Settings sheet" – change cut-off time point to week 24 (tab 2)
Table 54: ERG preferred base-case analysis	Exclusion of vinflunine patients Progression based utilities Age-related decrements: 1. Inclusion of proportion of males 2. Estimate utility values for general population based on algorithm in Ara and Brazier [32] 3. Estimate utility decrements relative to baseline age Removal of unjustified AE costs - set prevalence and cost for pneumonia,	"Settings sheet" – change utility measure tab to 2 "Settings sheet" – change approach of evaluating utility tab to 1 1. "GenInputs" sheet – cell F23 2. "Utility" sheet – cells D162 to D243 3. "Utility" sheet – cells E162 to E243 and G162 to G217 and leave cell J162 blank CostInputs" sheet – cells F34, F37 & F38 set to 0. "RxInputs" sheet – cells E39, E42, E43, Q39, Q42 & Q43 set to 0.

	fatigue and hyphosphataemia to zero in both treatment arms	
	Source of distribution of patients in paclitaxel and docetaxel arm	"Settings sheet" – change source of distribution of patients in paclitaxel and docetaxel arm tab to 2
	Log-logistic model	"Settings sheet" – change OS of pembrolizumab and OS of control arm to Log logistic (tab 4)
	24 week cut-off	"Settings sheet" – change cut-off time point to week 24 (tab 2)

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Appendix: Exploratory survival analyses undertaken by the ERG

Produced by: Warwick Evidence

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Date completed: 28th April 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/108/19.

Declared competing interests of the authors

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OncoGenex. She also received reimbursement for attending a symposium and/or speaker fees from Bayer, MSD, Janssen, Astellas, Sanofi, Pierre Fabre, GSK and funds for research from Pierre Fabre. [redacted]Dr Jo Cresswell is employed by South Tees NHS Trust Hospital. South Tees is part of the Imvigor clinical trial which is a commercially funded RCT. The research costs are met by Roche. Dr Cresswell has not received any personal funding from Roche.

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Word count: 1,157

Please note that: Sections highlighted in [redacted] are redacted.

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In this Appendix, the ERG explored fitting various parametric curves to the UK SOC data using the 24-week cut-off to project an estimate of overall survival.

The company has kindly provided the ERG with individual patient data (IPD) for the UK SOC arm based on the intention-to-treat analysis. Using this data, the ERG has developed the Kaplan-Meier plot for the UK SOC.

As stated in section 5.2.6.1 of the ERG report, the ERG considers that at a 24-week cut-off, the trend follows an internally consistent pattern of cumulative hazard (see Figure 6 of the ERG report) and this time-point would provide sufficient data in order to extrapolate overall survival. The ERG has therefore explored in a scenario analysis the impact of using this cut-off, by fitting various parametric models to these data. In Figure 1 and Figure 2, we present the Kaplan-Meier plots using data beyond 24-weeks, with parametric models used to extrapolate overall survival.

Figure 1: UK SOC Kaplan-Meier plots of data beyond the 24-week cut-off with parametric models

Figure 2: UK SOC Kaplan-Meier plots with two-phase piecewise models

Figure 2 shows an estimate of overall survival for UK SOC, using the two-phase piecewise approach. Figure 2 demonstrates the impact of using different parametric distributions, when added to the 24-week Kaplan-Meier data in order to estimate overall survival. Based on visual inspection, these extrapolations all fit well to the Kaplan-Meier data up to 14 months, but does not fit well with the flat tail as seen in the data. An extrapolation based on the Weibull distribution is lower than an extrapolation based on the generalised gamma to estimate overall survival.

Table 1 shows the goodness-of-fit measures according to information criteria (AIC/BIC) for UK SOC based on a 24-week cut-off. These results show that there was no clear best statistical fit for UK SOC, as these points were very close. If we were to choose based on the lowest AIC/BIC then the log-normal would have been the most appropriate model for UK SOC. However, consideration of model fits should also be judged in terms of clinical plausibility.

Table 1: Goodness-of-fit measures for overall survival based on the 24-week cut-off

Model	**UK SOC**	
	AIC	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

Results in Table 2 show that the 5-year overall survival for UK SOC is overestimated when using all extrapolations except the exponential, whereby survival is underestimated. Our clinical expert suggests that 5-year overall survival to be approximately 3-4%.

Table 2: 5-year survival for overall survival for UK SOC based on the 40-week cut-off (company's analysis)

Model	Overall survival
Exponential	[redacted]
Weibull	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Generalised Gamma	[redacted]

In Table 3, we compared the ERG's and the company's 5-year overall survival for UK SOC. In summary, comparisons based on the intention-to-treat analyses were comparable. Based on clinical input, extrapolations based on the log-normal or log-logistic parametric models provided reasonable estimates of overall survival. It should be noted that in the ERG's economic base-case, using the two-stage approach in addition to the 24-week cut-off, similar parametric distributions provided reasonable estimates of overall survival.

Table 3: 5-year survival for overall survival for UK SOC based on the 24-week cut-off

Model	UK SOC (ITT)	
	Company	ERG
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

The ERG would have liked to undertaken a similar exercise using the pembrolizumab IPD. However, we were only provided with IPD for UK SOC. Another approach the ERG could have been undertaken would have been to digitize the Kaplan-Meier plot for pembrolizumab then re-constructing the IPD to compare the estimated overall survival. However, time constraints precluded the ERG from fully undertaking these analyses.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Appendix: Additional analyses as requested by NICE undertaken by the ERG

Produced by: Warwick Evidence

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Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/108/19.

Declared competing interests of the authors

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Word count: 1,023

Please note that: Sections highlighted in [redacted] are redacted.

List of Tables

Table 1: ERG preferred base-case analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
deterministic						
UK SOC	£17,439	1.09	0.73	-	-	-
Pembrolizumab	£57,457	2.34	1.51	£40,017	0.78	£51,235
probabilistic						
UK SOC	£17,689	1.12	0.75	-	-	-
Pembrolizumab	£57,986	2.38	1.54	£40,298	0.79	£50,902

Table 1 shows the deterministic and probabilistic results using the ERG preferred base-case analysis. Although pembrolizumab was more expensive than the UK SOC, it generated more QALYs. The deterministic and probabilistic ICERs were of similar magnitudes - deterministic ICER: £51,235 per QALY and probabilistic ICER: £50,902 per QALY.

Table 2: Cost-effectiveness analyses using the ERG preferred base-case analysis for the histology groups (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
patients with predominately transitional cell urothelial carcinoma						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
patients with pure transitional cell urothelial cancer						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Using the ERG preferred base-case analysis for patients with predominantly transitional cell urothelial carcinoma when no adjustment was made the deterministic ICER was [redacted] and for patients with pure transitional cell urothelial carcinoma when no adjustment was made the deterministic ICER was [redacted] - see Table 2.

Table 3: Cost-effectiveness analyses using the ERG preferred base-case analysis for patients whose tumours express positive PD-L1 (CPS≥1%) (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
crossover adjustment: IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Using the ERG preferred base-case analysis, for patients whose tumours express positive PD-L1 (CPS≥1%), the deterministic ICERs were [redacted] the £50,000/QALY threshold (see Table 3). Whereas for patients whose tumours express positive PD-L1 (CPS≥10%), the deterministic ICER was [redacted] the £50,000/QALY threshold when no adjustment was made; however, when using the RPSFT adjustment, the deterministic ICER was [redacted] (see Table 4).

Table 4: Cost-effectiveness analyses using the ERG preferred base-case analysis for patients whose tumours express strongly positive PD-L1 (CPS≥10%) (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Cost-effectiveness analyses using the ERG preferred base-case analysis for patients with CPS<1% (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Using the ERG preferred base-case analysis, for patients who were negative for PD-L1 (CPS<1%), it is clearly evident that cost-effectiveness results depend on whether or not patient crossover is accounted in the estimation. The deterministic results showed an ICER of [redacted] per QALY for the ITT population and when the RPSFT method of crossover adjustment was made pembrolizumab was [redacted] (see Table 5).

It is unclear why the total LYG in the UK SOC group is [redacted]. [redacted]. Similarly, the ERG has noted that the total costs in the pembrolizumab group are much [redacted] in the CPS<1% subgroup compared to other populations (around [redacted] vs. around [redacted] to [redacted] respectively). There is also no obvious reason to explain this. Overall, the ERG believes that the reliability of the cost-effectiveness results in the CPS<1% subgroup is questionable.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019] – Addendum 1

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Date completed: 24th May 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/108/19.

Declared competing interests of the authors
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the report, and reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses.

Word count: 41,506

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

In Tables 1 and 2 we include the overall survival estimates based on the fully-fitted parametric curves for UK SOC and pembrolizumab, respectively.

Table 1: UK SOC overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using 0-week cut-off (fully-fitted parametric curves)						
5-year	0.003	0.000	0.019	0.024	0.000	0.01

Table 2: Pembrolizumab overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using 0-week cut-off (fully-fitted parametric curves)						
5-year	0.02	0.033	0.119	0.116	0.183	0.146

In tables 3 to 5, we have presented results, based on analyses undertaken at a 2-year, 10-year and 35 year time horizon, using the 0-week cut-off (fully-fitted curves to the overall survival Kaplan-Meier data) for each parametric curve.

Table 3: Using the ERG's preferred base-case, with results based on a 2-year time-horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£14,641	0.80	0.55	-	-	-	-
Pembrolizumab	£46,845	1.01	0.70	£32,203	0.21	0.15	£209,945
Weibull							
UK SOC	£14,871	0.77	0.53	-	-	-	-
Pembrolizumab	£46,707	1.02	0.70	£31,835	0.24	0.17	£184,485
Gompertz							
UK SOC	£14,788	0.78	0.54	-	-	-	-
Pembrolizumab	£46,349	1.03	0.71	£31,560	0.25	0.18	£179,062
Log-logistic							
UK SOC	£14,587	0.79	0.54	-	-	-	-
Pembrolizumab	£46,433	1.02	0.71	£31,846	0.23	0.16	£193,465
Log-normal							
UK SOC	£14,642	0.81	0.56	-	-	-	-
Pembrolizumab	£46,391	1.03	0.71	£31,748	0.22	0.16	£204,404
Generalised gamma							
UK SOC	£14,690	0.80	0.55	-	-	-	-
Pembrolizumab	£46,310	1.03	0.71	£31,620	0.23	0.16	£190,486

Table 4: Using the ERG's preferred base-case, with results at a 10-year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£15,932	0.88	0.60	-	-	-	-
Pembrolizumab	£50,069	1.26	0.86	£34,137	0.37	0.26	£131,104
Weibull							
UK SOC	£15,382	0.80	0.55	-	-	-	-
Pembrolizumab	£50,575	1.33	0.91	£35,193	0.54	0.36	£96,576
Gompertz							
UK SOC	£15,456	0.81	0.56	-	-	-	-
Pembrolizumab	£56,331	2.30	1.51	£40,875	1.48	0.95	£42,924
Log-logistic							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£16,577	0.98	0.66	-	-	-	-
Pembrolizumab	£53,561	1.81	1.21	£36,985	0.83	0.55	£67,401
Log-normal							
UK SOC	£16,594	0.98	0.66	-	-	-	-
Pembrolizumab	£53,711	1.83	1.22	£37,117	0.85	0.56	£66,343
Generalised gamma							
UK SOC	£16,147	0.91	0.62	-	-	-	-
Pembrolizumab	£54,775	2.01	1.33	£38,629	1.10	0.71	£54,285

Table 5: Using the ERG's preferred base-case, with results at a 35-year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£15,932	0.88	0.60	-	-	-	-
Pembrolizumab	£50,074	1.26	0.86	£34,142	0.37	0.26	£131,018
Weibull							
UK SOC	£15,382	0.80	0.55	-	-	-	-
Pembrolizumab	£50,595	1.33	0.91	£35,213	0.54	0.37	£96,353
Gompertz							
UK SOC	£15,456	0.81	0.56	-	-	-	-
Pembrolizumab	£64,669	3.39	2.13	£49,213	2.58	1.57	£31,360
Log-logistic							
UK SOC	£16,829	1.01	0.68	-	-	-	-
Pembrolizumab	£55,971	2.12	1.38	£39,142	1.11	0.70	£55,486
Log-normal							
UK SOC	£16,661	0.99	0.67	-	-	-	-
Pembrolizumab	£55,617	2.07	1.36	£38,956	1.08	0.69	£56,366
Generalised gamma							
UK SOC	£16,159	0.91	0.62	-	-	-	-
Pembrolizumab	£58,062	2.43	1.57	£41,903	1.52	0.95	£44,147

Verification of NICE ICERs, using the ERG preferred assumptions (slide 1)

Scenario	**Pembrolizumab vs UK SOC**					
	5-year OS UK SOC	**Incr. costs**	**Incr. LYG**	**Incr. QALYs**	**ICER**	**D ICER**
ERG base case	3.2%	£40,017	1.25	0.78	£51,235	
Model using the ERG preferred assumptions with a 40 week time-point (as in the Company submission)						
Exponential	0.3%	£35,028	0.51	0.35	£100,765	+£49,530
Weibull	2.9%	£35,006	0.51	0.34	£101,593	+£50,358
Gompertz	24.3%	£39,432	1.15	0.72	£55,118	+£3,883
Log-logistic	7.1%	£37,153	0.82	0.53	£70,304	+£19,069
Log-normal	7.8%	£39,239	1.12	0.71	£55,407	+4,172
G. Gamma	17%	£38,116	0.96	0.61	£62,809	+11,574
Model using the ERG preferred assumptions with a 24 week time-point						
Exponential	0.4%	£34,648	0.46	0.31	£110,621	+£59,386
Weibull	0.1%	£35,928	0.64	0.43	£83,381	+£32,146
Gompertz	5.9%	£47,846	2.38	1.45	£33,092	-£18,143
Log-logistic	3.2%	£40,017	1.25	0.78	£51,235	£0
Log-normal	2.9%	£42,816	1.65	1.02	£41,807	-£9,428
G. Gamma	8.9%	£32,242	0.10	0.11	£295,841	£244,606
Source: ERG model						

Verification of NICE ICERs, using the ERG preferred assumptions (slide 2) – **please note this also refers to Table 5 of Addendum 1**

Scenario	**Pembrolizumab vs UK SOC**					
	5-year OS UK SOC	**Incr. costs**	**Incr. LYG**	**Incr. QALYs**	**ICER**	**D ICER**
ERG base case	3.2%	£40,017	1.25	0.78	£51,235	-
Model using the ERG preferred assumptions with a 0 week time-point						
Exponential	0.34%	£34,142	0.37	0.26	£131,018	+£79,783
Weibull	0.01%	£35,213	0.54	0.37	£96,353	+£45,118
Gompertz	0.00%	£49,213	2.58	1.57	£31,360	-£19,875
Log-logistic	2.38%	£39,142	1.11	0.71	£55,486	+£4,251
Log-normal	1.87%	£38,956	1.08	0.69	£56,366	+£5,131
G. Gamma	0.98%	£41,903	1.52	0.95	£44,147	-£7,088
Source: ERG model						

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

You are asked to check the ERG report from Warwick to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Wednesday 10 May 2017** 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 Background information

Description of problem	Description of proposed amendment	Justification for amendment

Page 26 of the ERG report states:
 	
"The company report that, according to Leal et al.,[4] informal care constitutes 18% of costs, productivity losses due to mortality and morbidity 23% (misquoted by company as 29%) and healthcare costs 59% (misquoted by company as 53%) of the total costs of bladder cancer in the European Union (EU) (CS, p36)."
	Proposed revision to the existing text, as follows
	
	"The company report that, according to Leal et al.,[4] informal care constitutes 18% of costs, productivity losses due to mortality and morbidity 29% and healthcare costs 53% of the total costs of bladder cancer in the European Union (EU) (CS, p36)."
		The values were calculated from Table 2 of the publication by Leal et al. The values were estimated as follows:
		
		Costs of bladder cancer in 2012, UK:
		• Total costs: £543,630
		• Health care costs: £286,380 (53%)
		• Productivity losses:
		  ○ Mortality: £126,204 (23%)
		  ○ Morbidity: £29,754 (6%)

		• Informal care costs: £101,291 (18%)
Page 27 of the ERG report discusses the use of Sangar et al.	No amendment	For clarification purposes, the costs reported by Sangar et al. were intended as a representation of the potential cost impact of the population under question in this submission as there is no available information on the cost impact of urothelial cancer in the UK.

Issue 2 Risk of bias

Description of problem	Description of proposed amendment	Justification for amendment
Page 17 of the ERG report states: "The KEYNOTE-045 trial was of good quality, with a low risk of bias in most domains except for the blinding of participants and personnel since the study was open-label (high-risk of bias). Given the presence of a key-domain rated as high-risk of bias, the ERG concludes that the KEYNOTE-045 as a whole is at high risk of bias".	We request the ERG reconsider their assessment that "KEYNOTE-045 as a whole is at high risk of bias"	Please note that blinded independent central review of PFS and ORR endpoints occurred, and therefore an element of blinding was in place in the KEYNOTE-045 study.
Page 68 of the ERG report states: "This phase 3 trial was of good quality, with a low risk of bias in most domains except for the blinding of participants and personnel since the study was open-label thus considered to be at high-risk of bias"	As per above, we request the ERG reconsider their assessment that, due to the open-label design of the study, KEYNOTE-045 was "considered to be at high-risk of bias".	

Issue 3 Exclusion of two scoped comparators (BSC and retreatment with a platinum-based regimen)

Description of problem	Description of proposed amendment	Justification for amendment
Page 18 of the ERG report states: "The ERG has concerns regarding the exclusion of two scoped comparators, BSC and retreatment with a platinum-based regimen, from the decision problem"	Proposed revision to the existing text, as follows: "The ERG has concerns regarding the exclusion of two scoped comparators, BSC and retreatment with a platinum-based regimen, from the decision problem, **although the company provided justification for their decision in the CS** "	In our CS, MSD had not stated that retreatment with platinum-based chemotherapy was an "irrelevant comparator" as stated in the ERG report. Instead we had explained in Table 1 of the CS that as no evidence exists for a comparison between pembrolizumab and retreatment with 1st line platinum-based chemotherapy; consequently, the latter had not been considered as a comparator in our CS. We had also further explained in Table 1 of the CS that although re-treatment with platinum-based chemotherapy is included in the NICE clinical guideline on bladder cancer, some of these treatment regimens are used off-label and there is limited evidence on the value of their use in this setting. The ERG have stated in their report that BSC would only be considered in patients with poor PS (>2). As all patients in KEYNOTE-045 had PS 0-2, it did not include a population that would be considered for BSC in this line of therapy. Specifically, page 18 of the ERG report acknowledges this with the sentence "*In people with poorer PS (>2), BSC is a valid option within the NHS. Since KEYNOTE-045 only included patients with PS≤2, the CS includes no evidence on the clinical effectiveness of pembrolizumab in people who would otherwise be offered BSC*."
Page 18 of the ERG report states: "The company justified the exclusion of a retreatment with platinum-based chemotherapy since there is no evidence to compare with pembrolizumab. The ERG agrees there is no evidence but disagrees that this makes a treatment with platinum-based chemotherapy an irrelevant comparator."	MSD requests the ERG re-consider the wording of this sentence, given the justification provided – i.e. MSD had not stated that retreatment with platinum-based chemotherapy was an "irrelevant comparator".	
Page 34 of the ERG report states: "With regards to retreatment with a platinum-based chemotherapy, the company indicated that no evidence exists for a comparison between pembrolizumab and retreatment with platinum-based chemotherapy, thus the latter was excluded. The ERG believes this is not a valid reason to exclude retreatment with platinum-based chemotherapy"	Proposed revision to the existing text, as follows: "With regards to retreatment with a platinum-based chemotherapy, the company indicated that no evidence exists for a comparison between pembrolizumab and retreatment with platinum-based chemotherapy, thus **it was not possible for them to consider retreatment with platinum based chemotherapy as a comparator** ~~the latter was excluded~~. The ERG believes this is not a valid reason to exclude retreatment with platinum-based chemotherapy"	

Issue 4 Taxane regimens considered as standard care

Description of problem	Description of proposed amendment	Justification for amendment
Page 27-28 of the ERG report states: "…platinum-based chemotherapies and taxane regimens are, according to the company, standard treatment (CS, p31). However, the use of taxane regimens is not regulated by National Institute for Health and Care Excellence (NICE) guidelines[6] and does not have Medicines and Healthcare Products Regulatory Agency (MHRA) marketing authorisation in the UK for bladder or urothelial cancer…."	Proposed revision to the existing text, as follows: : "…platinum-based chemotherapies and taxane regimens are, **according to the final scope for this appraisal and subsequently the company in their submission,** standard treatment (CS, p31). However, the use of taxane regimens is not regulated by National Institute for Health and Care Excellence (NICE) guidelines[6] and does not have Medicines and Healthcare Products Regulatory Agency (MHRA) marketing authorisation in the UK for bladder or urothelial cancer…."	Please note that this stance was taken in our company submission to reflect the information issued by NICE in the Final Scope for this appraisal.
Page 30 of the ERG report states: "The NICE guideline for bladder cancer (NG2)[7] does not recommend a 3rd line treatment, but the final scope for pembrolizumab suggests, as does the company, that patients receive docetaxel or paclitaxel after two lines of chemotherapy."	Proposed revision to the existing text, as follows: "The NICE guideline for bladder cancer (NG2)[7] does not recommend a 3rd line treatment, but the final scope for pembrolizumab suggests ~~, as does the company,~~ that patients receive docetaxel or paclitaxel after two lines of chemotherapy. **This positioning has been reflected in the CS**"	

Issue 5 Positioning of pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment
Page 28 of the ERG report states: "The company positions pembrolizumab as 2nd line treatment for locally advanced or metastatic MIBC."	Proposed revision to the existing text, as follows: "The company positions pembrolizumab as 2nd **or 3rd** line treatment for locally advanced or metastatic MIBC."	Please refer to CS page 38, Figure 4 (Treatment algorithm for locally advanced or metastatic urothelial bladder cancer with proposed positioning of pembrolizumab)

Issue 6 PD-1 / PD-L1 terminology

Description of problem	Description of proposed amendment	Justification for amendment
Page 32 of the ERG report states: "Pembrolizumab is not the only PD-1 inhibitor that has been evaluated within the scope of urothelial cancers. Atezolizumab	Proposed revision to the existing text, as follows: "Pembrolizumab is not the only PD-1**/PD-L1** inhibitor that **is being** ~~has been~~ evaluated within the scope of urothelial	Atezolizumab is not a PD-1 inhibitor. It is a PD-L1 inhibitor and therefore the sentence as it currently stands is factually inaccurate.

is one of these and is currently subject to an ongoing appraisal (ID939). Nivolumab and durvalumab should also emerge in the coming months"	cancers. Atezolizumab is one of these and is currently subject to an ongoing appraisal (ID939). Nivolumab and durvalumab should also emerge in the coming months"	

Issue 7 Treatment duration

Description of problem	Description of proposed amendment	Justification for amendment
Page 33 of the ERG report states: "The anticipated licensed dosing regimen is 200mg every 3 weeks with a treatment continuing until disease progression or unacceptable toxicity, whichever occurs first."	Proposed revision to the existing text, as follows: "The anticipated licensed dosing regimen is 200mg every 3 weeks with a treatment continuing until disease progression or unacceptable toxicity, whichever occurs first. **It should be noted that in the CS, the economic modelling is based on a maximum treatment duration for pembrolizumab of 2 years, in line with study design of KEYNOTE-045.**"	In the CS, a maximum treatment duration of 24 months has been assumed in all economic modelling, in line with the duration of pembrolizumab treatment in KEYNOTE-045. Although this represents a potential divergence from the anticipated licenced treatment duration (i.e. until disease progression or unacceptable toxicity), such an approach has previously been accepted for pembrolizumab in NSCLC – see NICE TA428 Ref: NICE (2017) Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (https://www.nice.org.uk/guidance/ta428) .

Issue 8 Studies identified during the systematic search

Description of problem	Description of proposed amendment	Justification for amendment
Page 36 of the ERG report states: "The ERG's targeted independent searches for systematic reviews and longer term survival data identified two additional relevant studies.[13, 15, 16]''	Please remove this sentence.	The two studies mentioned in the ERG report as "additional relevant studies" identified by the ERG's targeted independent searches were already identified by MSD during our systematic search, as detailed in our CS and associated appendices. We consider it factually inaccurate to detail these in the ERG report as "additional relevant studies". : Ref 13 in ERG report: Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L,

		Daugaard G, 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. http://dx.doi.org/10.1200/JCO.2008.20.5534 - Please note that this study was identified in our systematic search as detailed in Appendix 3 of the CS, Table 1: List of included studies; potential indirect evidence (NCT00315237) Ref 15 in ERG report: von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18:3068-77. http://dx.doi.org/10.1200/jco.2000.18.17.3068 Ref 16 in ERG report: von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602-8. http://dx.doi.org/10.1200/jco.2005.07.757 - Please note both the above references concern a study that was also identified in our systematic search but excluded based on population, given that this was a first-line population. Please refer to Appendix 3 of the CS, Table 2: List of studies excluded following full text review.

Issue 9 Blinding

Description of problem	Description of proposed amendment	Justification for amendment
Page 43, Table 2: Question 4 – ERG box states "The statement in Appendix 7 (p85) mentioned above in the CS: "No blinding of outcome assessment according to protocol" is unclear or an error."	Proposed revision to the existing text, as follows: "The statement in Appendix 7 (p84) mentioned above in the CS: "No blinding of outcome assessment according to protocol" **has been confirmed by the company to have been included in error** ~~is unclear or an error~~."	We can confirm that the statement in Appendix 7 (p85) of the CS ("No blinding of outcome assessment according to protocol") was included in error. In KEYNOTE-045, because the treatment assignment was unblinded, images were read by blinded independent central reviewers, without knowledge of the treatment assignment, to minimise bias in the response assessments. The correct information regarding blinding was provided on pages 50 -51 of the CS, which stated : "*Although the trial was open label, analyses or summaries generated by randomised treatment assignment, actual treatment received, and/or PD-L1 biomarker status was limited and documented. Access to the allocation schedule for summaries or analyses was restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who had no other responsibilities associated with the study.* *In addition, imaging data for the primary analysis were centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment, in order to minimise bias in the response assessments*."

Issue 10 Objectives

Description of problem	Description of proposed amendment	Justification for amendment
Page 46 of the ERG report states: "For the primary objective, PFS was assessed according to RECIST 1.1 based on blinded independent central radiologic (BICR) review"	Proposed revision to the existing text, as follows: "For the **co-primary** objective of PFS, assessment was conducted according to RECIST 1.1 based on blinded independent central radiologic (BICR) review "	Please refer to the CS page 57 (section 4.3.1) which confirms that PFS was a co-primary endpoint alongside OS.

Page 46 of the ERG report states: "The KEYNOTE-045 trial had several exploratory objectives which were mainly PFS assessed by RECIST 1.1 by investigator review along with the assessment of changes in HRQoL from baseline using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire"	Proposed revision to the existing text, as follows: "The KEYNOTE-045 trial had several exploratory objectives which were mainly PFS assessed by RECIST 1.1 by investigator review along with the assessment of changes in HRQoL from baseline using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire **and to characterise utilities in previously-treated subjects with recurrent/progressive metastatic urothelial cancer using the EuroQol EQ-5D"**	Please refer to the exploratory objectives listed in the CS page 60 (section 4.3.1)

Issue 11 Effectiveness in further subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment
Page 57-58, Table 9	Please mark the values in the following columns as confidential: - Control - Number of Events (%) - Pembrolizumab - Number of Events (%)	This information has not been published and is taken directly from CSR
Page 60-61, Table 10	Please mark the values in the following columns as confidential: - Control - Number of Events (%) - Pembrolizumab - Number of Events (%)	This information has not been published and is taken directly from CSR
Page 62-65, Table 11	Please mark the values in the following columns as confidential: - Control - Number of Responses (ORR %)	This information has not been published and is taken directly from CSR

	- Pembrolizumab - Number of Responses (ORR %) - Pembrolizumab vs Control Rate Difference (95% CI)	

Issue 12 Safety: adverse events

Description of problem	Description of proposed amendment	Justification for amendment
Page 66 of the ERG report states: "Adverse events considered by the investigator to be "possibly," "probably," or "definitely" related to the study treatment were combined into the category drug-related AEs."	Please delete this sentence or amend in line with the response MSD previously provided to Clarification question A13: i.e. "Adverse events considered by the investigator to have a reasonable possibility of being related to the sponsor's product were classified as drug-related AEs."	As explained previously in MSD's response to clarification question A13, The sentence stating that 'adverse events considered by the investigator to be "possibly," "probably," or "definitely" related to the study treatment were combined into the category drug-related AEs' had been included in the CS in error. The criteria, considered by investigators when assessing the relationship between the AEs and the study drug, were clarified in our response to clarification question A13.
Page 66-67 of the ERG report states: The only AEOSI of grade 3, 4, or 5 severity that were observed in two or more patients who were treated with pembrolizumab were pneumonitis (2.3% of the patients), colitis (1.1%), and nephritis (0.8%); there was only one grade 5 event (0.4%), which was pneumonitis.[10]	Proposed revision to the existing text, as follows: "The only AEOSI of grade 3, 4, or 5 severity **(regardless of whether they were attributed to study treatment by the investigator)** that were observed in two or more patients who were treated with pembrolizumab were pneumonitis (2.3% of the patients), colitis (1.1%), and nephritis (0.8%); there was only one grade 5 event (0.4%), which was pneumonitis.[10]"	For clarification purposes and for consistency with the details in the study publication, an amendment to the current text is proposed.

Issue 13 Conclusions of the clinical effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment
Page 69 of the ERG report states: "The safety profile of pembrolizumab was more favourable than that of SOC. There was no treatment-related ≥3 event occurring with a frequency of ≥5% incidence in the pembrolizumab group."	Proposed revision to the existing text, as follows: "The safety profile of pembrolizumab was more favourable than that of SOC. There were no treatment-related **events of grade ≥ 3 severity that occurred with an incidence of ≥5%** in the pembrolizumab group"	For consistency with the clearer wording which has been used on page 16 of the ERG report, an amendment to the current text is proposed.

Issue 14 End of life criteria

Description of problem	Description of proposed amendment	Justification for amendment
Page 140 of the ERG report states: "On page 170 of the main CS, the company have presented a table (Table 61) regarding end-of-life criteria. There are three main criteria to fulfil for the appraisal of end of life treatments:43 1. the treatment is indicated for patients with a short life expectancy, normally less than 24 months; and 2. 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; and 3. the treatment is licensed or otherwise indicated, for small patient populations."	Proposed revision to the existing text, as follows: "On page 170 of the main CS, the company have presented a table (Table 61) regarding end-of-life criteria. There are **two** main criteria to fulfil for the appraisal of end of life treatments: 1. the treatment is indicated for patients with a short life expectancy, normally less than 24 months; and 2. 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~~; and~~ ~~3. the treatment is licensed or otherwise indicated, for small patient populations."~~	Criterion 3 is no longer relevant – in our CS we had stated (and referenced) that according to the new CDF TA process, the criterion of small patient population no longer applies. Please refer to the updated User Guide for Evidence Submissions published by NICE in January 2015. Ref: NICE (2015) Single technology appraisal: User guide for company evidence submission template. Available at: https://www.nice.org.uk/guidance/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333
Page 141 of the ERG report states: "The company has not described how pembrolizumab fulfils criterion 3. However, the company reports that the number of patients estimated to be eligible for pembrolizumab will be 502 (CS p234). The ERG clinical advisor also confirms that the patient population relevant to the decision problem would be small."	Please remove this text in line with the justification provided.	As per the justification provided above, criterion 3 is no longer relevant according to the updated User Guide for Evidence Submissions published by NICE in January 2015.

Issue 15 Innovation

Description of problem	Description of proposed amendment	Justification for amendment
Page 142 of the ERG report states: "There is a growing number of immunotherapies which are being evaluated in many cancer types, both in solid tumours and in hematologic malignancies. Some of these,	Suggested revision to the existing text, as follows: There **are** a growing number of immunotherapies which are being evaluated in many cancer types, both in solid tumours and in hematologic malignancies. Some of these, like	For clarification purposes, pembrolizumab and nivolumab are the only drugs of those listed in the existing text, which have licenses in the UK at the present time. Therefore we suggest that reference to atezolizumab and

like pembrolizumab, atezolizumab, avelumab, or nivolumab, are already licensed in cancers other than urothelial cancers."	pembrolizumab **~~, atezolizumab, avelumab, or~~ and** nivolumab, are already licensed **in the UK** in cancers other than urothelial cancers.	avelumab should be deleted from this paragraph.

Issue 16 References to excluded studies

Description of problem	Description of proposed amendment	Justification for amendment
Page 71 of the ERG report states: "The company provided an excel document titled "ID1019 Economic SLR" which included references to the excluded studies."	Suggested revision to the existing text, as follows: "The company provided an excel document titled "ID1019 Economic SLR" which included references to the excluded studies **and reasons for exclusion**."	In the same paragraph it is stated: "The ERG requested at the clarification stage details of the 126 papers which were evaluated in full, including references and reasons why studies were excluded." For completeness and as requested, MSD has provided both the references of excluded studies and reasons for exclusion.

Issue 17 Studies independently assessed

Description of problem	Description of proposed amendment	Justification for amendment
Page 71 of the ERG report states: "The CS did not state whether the studies were independently assessed by two reviewers."	Please remove this text in line with the justification provided.	Please refer to section 5.1.1 of the CS where it states: "All retrieved studies were reviewed by two independent researchers and assessed against the eligibility criteria set out in the final protocol and presented in Table 62 below."

Issue 18 NICE reference case checklist

Description of problem	Description of proposed amendment	Justification for amendment
Page 72 of the ERG report states: "Patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy."	Suggested revision to the existing text, as follows: **"Yes.** Patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy."	For clarification purposes and in line with the rest of the table when the reference case or TA methods guidance is met.
Page 72 of the ERG report states: "Cost-effectiveness analysis (Cost per quality-	Suggested revision to the existing text, as follows: **"Yes.** Cost-effectiveness analysis (Cost per quality-adjusted	

adjusted life year (QALY))"	life year (QALY))"	
Page 72 of the ERG report states: "The standard UK EQ-5D tariff is used, which is based upon time-trade off."	Suggested revision to the existing text, as follows: **"Yes.** The standard UK EQ-5D tariff is used, which is based upon time-trade off."	

Issue 19 Model structure

Description of problem	Description of proposed amendment	Justification for amendment
Page 73 of the ERG report states: "The partitioned survival approach uses an "area under the curve" approach, where the number of patients in the two health states: PFS and OS, is taken directly from survival curves fitted to the clinical data."	Suggested revision to the existing text, as follows: "The partitioned survival approach uses an "area under the curve" approach, where the number of patients in the two health states: **pre-progression and death ~~PFS and OS~~**, is taken directly from survival curves fitted to the clinical data"	Please note that the model structure consists of three health states: pre-progression, post-progression and death.
Page 73 of the ERG report states: "Patients in the pre-progression health state, stay in that health state until disease progression"	Suggested revision to the existing text, as follows: "Patients in the pre-progression health state, stay in that health state until disease progression **or death**."	For clarification purposes and in order to clearly reflect the model structure.

Issue 20 Subgroups

Description of problem	Description of proposed amendment	Justification for amendment
Page 74 of the ERG report states: "The company also presented results for the following subgroups of patients in the CS Appendix: 1. patients with advanced or metastatic urothelial cancer of predominantly transitional cell histology. 2. patients with advanced or metastatic urothelial cancer of pure transitional cell histology. 3. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥1%) urothelial cancer. 4. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥10%)	Suggested revision to the existing text, as follows: "The company also presented results for the following subgroups of patients in the CS Appendix: 1. patients with advanced or metastatic urothelial cancer of predominantly transitional cell histology. 2. patients with advanced or metastatic urothelial cancer of pure transitional cell histology. 3. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥1%) urothelial cancer. 4. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥10%) urothelial cancer. **5. patients with advanced or metastatic urothelial cancer by individual comparator regimen i.e., pembrolizumab vs. docetaxel and pembrolizumab vs. paclitaxel"**	In the CS, subgroup analyses were presented by individual comparator regimens, by histology and by level of PD-L1 expression.

urothelial cancer."		
Tables 25-28 and figures 14-17 presented in pages 97-101 of the ERG report	If the subgroups presented in this section refer to UK SOC, please update the tables and include the respective confidentiality marking.	Please note that these tables refer to the overall SOC of the KEYNOTE-045 trial. However, it seems more appropriate to include tables referring to the UK SOC, which were presented in Appendix 11 of the CS.

Issue 21 Updated economic model

Description of problem	Description of proposed amendment	Justification for amendment
Page 76 of the ERG report states: "The ERG found an error in the application of maximum treatment duration of UK SOC in the model. That is, the duration of paclitaxel or docetaxel treatment continued beyond 18 weeks (6 cycles) and reached a maximum of 58 weeks. However, upon clarification the company provided the ERG with a new updated economic model correcting for this error."	Suggested revision to the existing text, as follows: "The ERG found an error in the application of maximum treatment duration of UK SOC in the model. That is, the duration of paclitaxel or docetaxel treatment continued beyond 18 weeks (6 cycles) and reached a maximum of 58 weeks. However, ~~**upon clarification**~~ the company **had also identified the error and** provided the ERG with a new updated economic model correcting for this error."	Please note that we are uncertain whether the ERG identified the error prior to MSD identifying the error in the model; nevertheless MSD took the opportunity to correct and present an updated version of the model to the ERG when submitting responses to clarification questions.

Issue 22 Adjusting for treatment switching

Description of problem	Description of proposed amendment	Justification for amendment
Page 78 of the ERG report states: "Three statistical techniques were used to adjust for treatment switching in the UK SOC arm, as some patients in this group received PD-L1 treatments following disease progression."	Suggested revision to the existing text, as follows: "Three statistical techniques were used to adjust for treatment switching in the UK SOC arm, as some patients in this group received **PD-1/**PD-L1 treatments following disease progression."	Please refer to page 133 of CS. Patients in the control arm may have received PD-L1 or PD-1 treatment following disease progression.
Page 78 of the ERG report states: "There were 33 patients who switched from the control arm to other treatments; however, only 22 of these were actually eligible to switch with 11 patients appearing to switch prior to disease progression."	Suggested revision to the existing text, as follows: "There were ~~**33**~~ **22** patients who switched from the control arm to other treatments; however, only ~~**22**~~ **14** of these were actually eligible to switch with ~~**11**~~ **8** patients appearing to switch prior to disease progression."	Please refer to page 162 of Appendix 10 of the CS. Thirty three patients have switched from the entire control arm, whereas 22 patients have switched from the 182 of control patients who were pre-assigned to paclitaxel or docetaxel by the investigator prior to randomisation. From these, only 14 patients were eligible for switching,
Page 78 of the ERG report states: "However, there were 11 subjects who	Please remove this text in line with the justification provided.	Please note that patients, who did not meet the eligibility criteria for switchover (8 in the

switched without meeting the planned requirements, which will confound the analysis slightly.		UK SOC arm), were not included in the analysis.

Issue 23 Cut-off point for extrapolation

Description of problem	Description of proposed amendment	Justification for amendment
Page 83 of the ERG report states: "The company suggested that the 40-week cut-off point is more appropriate than a 24-week cut-off to extrapolate beyond the observed data, because there is greater change in the slope before 40 weeks."	Suggested revision to the existing text, as follows: "The company suggested that the 40-week cut-off point is more appropriate than a 24-week cut-off to extrapolate beyond the observed data, because there is ~~**greater**~~ **a clearer** change in the slope ~~**before**~~ **after** 40 weeks"	For clarification purposes and in order to reflect the wording used in the CS.

Issue 24 Parametric approach for extrapolation of OS

Description of problem	Description of proposed amendment	Justification for amendment
Page 93 of the ERG report states: "Based on the AIC/BIC, the log-logistic compared to using the log-normal distribution provided a better fit to the pembrolizumab data."	Suggested revision to the existing text, as follows: "Based on the AIC/BIC, the log-logistic compared to using the log-normal distribution provided a better fit to the pembrolizumab data, **whereas the log-normal distribution provided the best fit to the UK SOC data based on the AIC/BIC**."	For clarification purposes and for completeness.

Issue 25 Extrapolation of PFS

Description of problem	Description of proposed amendment	Justification for amendment
Page 94 of the ERG report states: "The company further suggested that the proportional hazard assumption did hold because the Kaplan-Meier plots crossed, therefore separate parametric models were fitted to project progression-free survival."	Suggested revision to the existing text, as follows: "The company further suggested that the proportional hazard assumption did **not** hold because the Kaplan-Meier plots crossed, therefore separate parametric models were fitted to project progression-free survival."	Please refer to section 5.3.3 of the CS, where it is stated that the PH assumption for PFS did not hold.
Page 96 of the ERG report states: "As suggested by the company, there was no clear best parametric fit for pembrolizumab or UK SOC, as all the distributions were very similar. This was seen in the parametric fits (Figure 11 and Figure 12)	Suggested revision to the existing text, as follows: "As suggested by the company, **an exponential distribution was the best fit to the pembrolizumab PFS data, while** there was no clear best parametric fit for ~~**pembrolizumab or**~~ the UK SOC, as all the distributions were very similar. This was seen in the parametric fits (~~**Figure 11 and**~~ Figure 12) and	Please refer to section 5.3.3 of the CS, where the rational for selecting the appropriate parametric distribution for extrapolation of PFS data.

and AIC/BIC (Table 24).In the base case, the company has chosen the exponential model to extrapolate PFS for the UK SOC and for consistency, used the exponential model for pembrolizumab."	AIC/BIC (Table 24).In the base case, the company has chosen the exponential model to extrapolate PFS for ~~**the UK SOC**~~ **pembrolizumab** and for consistency, used the exponential model for ~~**pembrolizumab**~~ **the UK SOC**."	

Issue 26 Time on Treatment data

Description of problem	Description of proposed amendment	Justification for amendment
Page 102 of the ERG report states: "It should be noted that in the Kaplan-Meier plot of pembrolizumab (Figure 18), the data appears to have been truncated, whilst in the electronic model it suggested that people received treatment beyond 70 weeks (approximately). As a result, it is unclear to the ERG whether a) the parametric curves have been fitted to all the data or b) the parametric curves have been fitted to truncated data."	Please remove this text in line with the justification provided.	Survival curves were fitted to all data, not truncated data. MSD requests to remove the text as it suggests that clinical trial data were not used appropriately.
Page 104 of the ERG report states: "In the base case, it was assumed that people received pembrolizumab for a maximum of 35 cycles (24 months) (based on anticipated licence) and a maximum of six cycles (18 weeks) treatment with UK SOC, which is in line with clinical practice in England."	Suggested revision to the existing text, as follows: "In the base case, it was assumed that people received pembrolizumab for a maximum of 35 cycles (24 months) (~~**based on anticipated licence**~~ **in line with the KEYNOTE-045 protocol**) and a maximum of six cycles (18 weeks) treatment with UK SOC, which is in line with clinical practice in England."	Please refer to section 5.5.5 of the CS, where the number of administrations required for pembrolizumab and the UK SOC is described.

Issue 27 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment
Page 105 of the ERG report states: "This approach in the CS model may have under-estimated costs and over-estimated benefits associated with the two treatment arms."	Suggested revision to the existing text, as follows: **"Given the toxicity profile of the comparator**, this approach in the CS model may have under-estimated costs and over-estimated benefits associated with the ~~**two**~~ **UK SOC** treatment arm~~**s**~~."	Given the toxicity profile of the treatment regimens included in the cost-effectiveness analysis, MSD believes that this is a conservative approach.
Page 112 of the ERG report states: "However, the ERG noted that data related to fatigue, pneumonia and	Please remove the text in the identified pages in line with the justification provided.	Please note that fatigue has an incidence rate of 5.95% which is above the >5% threshold. For clarification, it should be noted that the

hypophosphataemia were included in the utility calculations despite these adverse events not meeting these criteria and no other justification for their inclusions was provided.“ Page 129 of the ERG report states:”Table 51 shows the sensitivity analysis performed when removing the adverse events that did not meet the company’s own inclusion criteria (pneumonia, hyphosphataemia and fatigue) – costs and prevalence were set to 0.” Page 137 of the ERG report states: “Furthermore, the ERG removed the adverse events that did not meet the company’s own inclusion criteria (pneumonia, hyphosphataemia and fatigue) and associated costs and prevalence were set to zero.” Page 151 of the ERG report states: “Removal of unjustified AE costs - set prevalence and cost for pneumonia, fatigue and hyphosphataemia to zero in both treatment arms.” Page 152 of the ERG report states: “Removal of unjustified AE costs - set prevalence and cost for pneumonia, fatigue and hyphosphataemia to zero in both treatment arms.”		incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on consideration of the specific AE occurring at any-grade of severity. This is explained in section 5.3.5 of the CS.
Page 112 and 113 of the ERG report states: “The ERG also has some concerns over the methods used to determine which adverse events were drug related, which may possibly create bias in favour of pembrolizumab. Unit costs and incidence of additional adverse events that cancer patients typically exhibit, such as dyspnoea, hypertension, and abdominal pain were not considered in the CS model.	Please remove this text in line with the justification provided.	Please refer to MSD’s response to clarification question A13 for the methods used to selection of drug related adverse events. Please note that in the economic analysis any AE was included and not only drug related AEs. Also, please refer to section 5.3.5 of the CS where it is stated that the method for selection the AE to be included in the cost-effectiveness analysis, has been validated by

		clinical experts.

Issue 28 Utility values

Description of problem	Description of proposed amendment	Justification for amendment
Page 107 of the ERG report states: "The company points out that, due to the timing of the questionnaires, it is unlikely that the utility score captured the expected decline of health prior to death."	Suggested revision to the existing text, as follows: "The company points out that, due to the timing of the questionnaires **(administered until drug discontinuation or at the 30-day-safety follow-up visit**), it is unlikely that the utility score **after progression** captured the expected decline of health prior to death. **Therefore, this led to an overestimation of the utilities in post-progression health state."**	For clarification purposes, and according to section 5.4.1. of the CS, this statement refers to utility values based on progression status, and more specifically on the post-progression utility values.
Page 107 of the ERG report states: "The company found no significant differences in EQ-5D at baseline, and so decided to use pooled utility values for both arms. The ERG notes that statistically significant differences were observed in the progression based values (see CS table 75), and borderline statistically significant differences in the survival based utility values (see CS table 74)."	Suggested revision to the existing text, as follows: "The company found no significant **or clinically meaningful** differences in EQ-5D **scores per treatment arm ~~at baseline~~**, and so decided to use pooled utility values for both arms. The ERG notes that statistically significant differences were observed in the progression based values (see CS table 75)**~~, and borderline statistically significant differences in the survival based utility values (see CS table 74)~~**."	Please refer to section 5.4.1. of the CS where it is stated: "There were no statistically significant or clinically meaningful differences in EQ-5D scores by treatment arm; therefore, the scores from the pooled treatment group were used.". Please note that there are statistically significant differences in progression-based but this is not the case for the utilities by time-to-death.
Page 107 of the ERG report states:"Furthermore, the ERG noted that treatment-specific utility values are lower for pembrolizumab compared to UK SOC when measured based on time to death, except for the (180 to 360) and (30 to 90) categories. However, patients in such categories only account for about 13% of all patients in the model. And, in fact, utility values were reported as considerably higher for pembrolizumab compared to UK SOC when measured based on progression status. Such findings appear to be counter-intuitive, as using one method of valuation of HRQoL over the other should not result in higher utility estimates for a particular treatment."	Suggested revision to the existing text, as follows: "Furthermore, the ERG noted that treatment-specific utility values are lower for pembrolizumab compared to UK SOC when measured based on time to death, except for the **~~(~~[**180 to 360) and **~~(~~[**30 to 90) categories. However, patients in such categories only account for about 13% of **~~all~~ pembrolizumab** patients in the model. And, in fact, utility values were reported as considerably higher for pembrolizumab compared to UK SOC when measured based on progression status." **~~Such findings appear to be counter-intuitive, as using one method of valuation of HRQoL over the other should not result in higher utility estimates for a particular treatment."~~** Please remove the text in page 23 and 110 in line with the justification provided.	Please note that patients in those categories account for 12% of pembrolizumab arm in the cost-effectiveness model. Utility values estimated by time-to-death approach, do not indicate that any of the treatment arms have an overall better HRQoL. Thus it is inappropriate to compare the utility values based on progression status to the utility values based on the time-to-death approach, as the methodology employed is different.

Page 23 of the ERG report states: "Counter-intuitive utility estimates were obtained when reported separately for each treatment arm. That is, when estimating utilities based on time to death patients receiving UK SOC reported higher estimates, whereas when estimating utilities based on progression status patients receiving pembrolizumab reported higher estimates." Page 110 of the ERG report states: "The ERG has reservations about using separate utilities for each treatment arm, due to counter-intuitive estimates."		
Page 107-108 of the ERG report states:"To the best of the ERG's knowledge, this approach is not common in practice, and has only been used for previous studies investigating melanoma treatments."	Please remove this text in line with the justification provided.	Please refer to section 5.4.1 of the CS where references have been provided for the estimation of time-to-death utilities in patients with melanoma, as well as in patients with NSCLC.
Page 108 of the ERG report states: "The ERG has concerns over the reliability of the survival based utility estimates, with a large amount of missing data. The pembrolizumab arm has a median ToT of 15 weeks, meaning all patients should have completed on average four EQ-5D questionnaires whilst on treatment, excluding baseline, plus two follow-up questionnaires giving a total of six responses per person. It is likely that the subgroup of patients living beyond 360 days actually has a higher median ToT meaning six responses is an underestimate. However, examination of Table 74 of the CS concludes that the ≥ 360 day survival pembrolizumab group averaged 3.4 responses per person, suggesting almost half of their possible data is missing for this subgroup. The CS fails to mention how missing EQ-5D data was managed. Similarly, patients surviving < 30 days should only have completed one EQ-5D questionnaire, so the ERG is	Please remove this text in line with the justification provided.	Please refer to section 5.4.1 of the CS. As stated in our CS, EQ-5D scores collected within each time category were used. The time categories are the time from EQ-5D measurement to the end of overall survival. Therefore, EQ-5D questionnaires administered to the same patient may contribute to more than one time category. For example, if a patients had EQ-5D scores measured on days 20 and 40 before the end of overall survival, he/she would contribute to the calculation in the <30 AND [30, 90] rows. Additionally, please note that missing data were excluded from the analyses of the EQ-5D scores. Please refer to footnotes of Tables 74 and 75 of the CS were it is stated that the number of patients and records of non-missing EQ-5D values have only been included. Finally, please note that the estimates are pooled across all non-missing EQ-5D scores (regardless whether they are from the same

unsure how there can be more responses than people in these subgroups for both treatment arms. Additionally, despite the fact that these survival-time based groups are mutually exclusive, they appear to contain more members than were in the trial, with a total 596 subjects obtained from Table 74 when only 542 were recruited. The ERG would expect the total to be below 542 when accounting for patients who were censored prior to 360 days. It is also unknown how the company obtained their average estimates for each group, and whether they calculated an average per person, and averaged this, or whether they averaged across all questionnaire responses."		patient or not), which is (the sum of all non-missing EQ-5D scores in the specified period)/(the total number of non-missing EQ-5D scores in the specified period).
Page 108 of the ERG report states: "A previous TA[17] reported related utilities for comparison which are shown in Table 31, though they were not specific to bladder cancer. The lower values seen in Table 31 (despite the CS stating the utility values in KEYNOTE-045 are comparable with these in TA272) support the view that the post-progression score is overestimated by the CS data."	Suggested revision to the existing text, as follows: "A previous TA[17] reported related utilities for comparison which are shown in Table 31, though they were not specific to ~~**bladder**~~ **urothelial** cancer. The lower values seen in Table 31(despite the CS stating the utility values in KEYNOTE-045 are ~~**comparable**~~ **in line** with these in TA272) support the view that the post-progression score is overestimated by the CS data."	Please note that this appraisal refers to urothelial cancer. Also, please refer to section 5.4.5 of the CS where it is stated that the progression based utility values from KEYNOTE-045 were considered in line with the utility values presented in TA272 as the post-progression utility values are lower than the pre-progression values.
Page 108 of the ERG report states: "Furthermore, the value for progressed health state for the pembrolizumab and UKSOC pooled arm is 0.647 (see CS clarification section B Table 3); however, the ERG believe that this value should be lower than 0.641 (pembrolizumab and control pooled). The ERG were unsure whether this was a typo or some confusion in their analysis (see Table 31).	Please remove this text in line with the justification provided.	Please note that the pooled utility values are not weighted by the number of patients but by the number of records. Therefore, there is not an error in the analyses performed.

Issue 29 Model validation with clinical trial data

Description of problem	Description of proposed amendment	Justification for amendment
Page 124 of the ERG report states: "The second reason relates to the fact that model predictions beyond 1 year were not validated, as OS and PFS estimates from KEYNOTE were not presented for a time point beyond 1 year in the CS. This is the case despite having follow up trial data beyond 1 year. Upon inspection of OS outcomes at 14.5 months, model outcomes were slightly higher compared to trial outcomes in the pembrolizumab arm (40.2% vs 39.3%) and slightly lower in the UK SOC arm (24.6% vs 25.7%). The same is true at 16.1 months (pembrolizumab: 37.8% vs 36.8%; UK SOC: 22.5% vs 25.7%). If we compare OS outcomes at 20 months, model outcomes are lower compared to trial outcomes in both pembrolizumab (33.3% vs 36.8%) and UK SOC (18.9% vs 25.7%). Despite that, the underestimation of OS is more profound in the UK SOC arm.	Please remove this text in line with the justification provided.	12.5 months is the last available time point at which data is available based on the KM data for the UK SOC arm from KEYNOTE-045. However, the ERG appears to have assumed that the OS data for the UK SOC arm at 12.5 months (25.7%) remains the same at later time points, i.e. at 14.5, 16.1 and 20 months. Additionally, for pembrolizumab, the 39.3%,36.8% and 36.8% quoted in the ERG report refers to data collected at 14.4, 16 and 20.5 months, respectively and not for the 14.5, 16.1 and 20 months.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019] - Erratum

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Date completed: 27th April 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/108/19.

Declared competing interests of the authors
Dr Maria De Santis received consultancy fees within the last 5 years from MSD, Merck, Pfizer, Roche, AstraZeneca, Pierre Fabre, Sanofi, BMS**,** Amgen, Astellas, Bayer, Celgene, Eisai, ESSA,

Ferring, GSK, Ipsen, Janssen, Novartis, Dendreon, Seattle Genetics, Shionogi, Synthon, Teva and OncoGenex. She also received reimbursement for attending a symposium and/or speaker fees from Bayer, MSD, Janssen, Astellas, Sanofi, Pierre Fabre, GSK and funds for research from Pierre Fabre.

Dr Jo Cresswell is employed by South Tees NHS Trust Hospital. South Tees is part of the Imvigor clinical trial which is a commercially funded RCT. The research costs are met by Roche. Dr Cresswell has not received any personal funding from Roche.

Acknowledgements

We would like to thank Dr Emma Loveman for providing advice and comments during the two week clarification period and Dr Martin Connock for providing advice and comments on the survival analysis. Professor Aileen Clarke read the report and provided advice.

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.

This report should be referenced as follows

Pembrolizumab for previously treated advanced or metastatic urothelial cancer: A Single Technology Appraisal. Warwick Evidence, 2017.

Contributions of authors

Xavier Armoiry (Senior Research Fellow) helped co-ordinate the project and the report, and conducted, reviewed and critiqued the clinical effectiveness evidence; Theodoros Mantopoulos (Research Associate) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Daniel Gallacher (Research Associate) conducted, reviewed and critiqued the survival analysis and cost-effectiveness evidence; Peter Auguste (Research Fellow) conducted, reviewed and critiqued the survival analysis and undertook additional analyses; Jacoby Patterson (Independent Research Consultant) conducted, reviewed and critiqued the clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional analyses; Karoline Munro (Research Project Administrator) conducted, reviewed and critiqued the background section; Maria De Santis (Associate Clinical Professor) provided expert clinical advice; Joanne Cresswell (Consultant Urological Surgeon) provided expert clinical advice; Hema Mistry (Assistant Professor) co-ordinated the project and

the report, and reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses.

Word count: 41,506

Please note that: Sections highlighted in [redacted] are redacted.

The ERG noted several issues with the submitted clinical evidence.

- The ERG has concerns regarding the exclusion of two scoped comparators, BSC and retreatment with a platinum-based regimen, from the decision problem.
- The company justified the exclusion of BSC stating that alternative treatments are available (e.g. docetaxel and paclitaxel). While the statement is true, these drugs are offered only in people with good performance status, which is the population included in KEYNOTE-045. In people with poorer PS (>2), BSC is a valid option within the NHS. Since KEYNOTE-045 only included patients with PS≤2, the CS includes no evidence on the clinical effectiveness of pembrolizumab in people who would otherwise be offered BSC.
- The company stated that "No evidence exists for a comparison between pembrolizumab and retreatment with 1st line platinum-based chemotherapy; therefore the latter has not been considered as a comparator in this submission." The ERG agrees there is no evidence for this comparison. However, the ERG feels this should not have been excluded from consideration, but included, and any lack of evidence base then reported.
- The anticipated label indication of pembrolizumab is broader than the population in KEYNOTE-045. If the label indication does not restrict the use of pembrolizumab to patients who previously received a platinum-based regimen, the label indication cannot be supported by clinical evidence since 100% of people in KEYNOTE-045 had a prior platinum-based regimen. Some evidence on the effectiveness of pembrolizumab in people ineligible for cisplatin will be provided by the full results of KEYNOTE-052 that is a single-arm study that enrolled 370 patients.
- Assuming pembrolizumab obtains a label indication in patients with urothelial cancers regardless of the PD-L1 expression, this means that patients who are negative for PD-L1 expression could also be offered pembrolizumab which is a drug that specifically acts on the PD-L1 pathway. As previously stated, the ERG believes that the results in people with negative PD-L1 expression are inconclusive.
- The evaluation of the quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results.

- Owing to open-label design of KEYNOTE-045, the results on quality of life should be treated with caution.
- There was uncertainty in the effectiveness of the methods used to adjust for treatment switching in the UK SOC.
- There was uncertainty in the extrapolation of overall survival estimates from the trial to the duration of the economic model, with cost-effectiveness results being sensitive to the methods used to extrapolate. The ERG has reservations regarding the choice of the cut-off point used for the piecewise modelling approach and the choice of parametric distribution used to model long-term overall survival.
- Health-related quality of life estimates included those for patients receiving vinflunine, which is not recommended in England. Using utilities by time to death is an unusual method of estimating life years and subsequent QALYs and resulted in slight overestimation of life years in both treatment arms compared to estimates based on progression status.
- Estimation of age-related utility decrements was based on an outdated study that did not incorporate a decrement for patients aged more than 75 years old, resulting in overestimation of QALYs.
- Unexpected utility estimates were obtained when reported separately for each treatment arm. That is, when estimating utilities based on time to death patients receiving UK SOC reported higher estimates, whereas when estimating utilities based on progression status patients receiving pembrolizumab reported higher estimates.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of modifications to the model assumptions made by the company.

Overall changes:

- Excluding vinflunine patients from the estimation of utility values.
- Using utility values based on progression status rather than time to death.
- Using pooled utility and adverse event disutility values.
- Changing source of estimating age-related utility decrements.

- Estimating the cost of UK SOC based on the UK market share of docetaxel and paclitaxel.
- Use a cut-off point of 24 weeks for the overall survival modelling approach.
- Use a log-logistic distribution for overall survival modelling for pembrolizumab and UK SOC.

The ERG have presented a scenario with a preferred base-case analysis for pembrolizumab versus UK SOC. The ICER has increased slightly compared with the CS submission, resulting in a deterministic ICER of £51,235 per QALY including apatient access scheme (PAS).

The ERG carried out some exploratory analyses using the ERG preferred base-case, and noted that the vast majority (84% to 97%) of benefits in terms of life years gained was from the extrapolated data rather than the observed data.

and the low ability to detect the cancer at an early stage. The company also highlights that there is a lack of advances in the development of therapies (CS, p35).

The company indicates that staging of urothelial carcinoma is undertaken according to the Tumour, Node and Metastases (TNM) classification which provides staging information as 0, I, II, III or IV. The Evidence Review Group's (ERG) clinical advisors have confirmed the use of the TNM staging system.

On page 34, the company states that around 75% of newly diagnosed urothelial bladder cancers are non-muscle invasive (also called NMIBC), which have a high rate of recurrence (70%) and progression into muscle invasive disease (10-25%). The statement is misleading since it is high-risk NMIBC has a recurrence rate of 70% over 5 years and high-risk forms only represent 10% of all NMIBC. Low-risk NMIBC has low recurrence and progression is very rare.

The company states that patients with muscle invasive urothelial cancer will be offered radical surgical treatments, e.g. full cystectomy. The ERG's clinical experts commented that patients can also be treated with radical radiotherapy, ideally with chemo-radiotherapy. The ERG's clinical experts also commented that the correct terminology for the surgical procedure is radical cystectomy and overall that the phraseology used in the CS implies an unfamiliarity with United Kingdom (UK) bladder cancer practice.

The company states that surgery is followed by difficult lifestyle adjustments for patients and carers due to decreased urinary and sexual function. This reduces the quality of life "consistently and significantly" (CS, p36). This again can be supported by advice given by Cancer Research UK.

The ERG however found a discrepancy between the annual cost estimates that the company quoted. The company quotes estimates given by Leal et al.[4] for costs of bladder cancer in 2012 and Sangar et al.[5] for cost estimates in 2001-2. The company report that, according to Leal et al.,[4] informal care constitutes 18% of costs, productivity losses due to mortality and morbidity 29% and healthcare costs 53% of the total costs of bladder cancer in the European Union (EU) (CS, p36). According to Leal et al.,[4] the total healthcare costs were €286 million, the total costs including productivity loss and

the UK for bladder or urothelial cancer; notwithstanding our clinical advisors tell us that taxanes are used in UK practice.

The company states that pembrolizumab has been granted a Breakthrough Therapy Designation for advanced melanoma, for advanced (metastatic) non-small cell lung cancer (NSCLC) and advanced NSCLC whose tumours express PD-L1 and for locally advanced or metastatic urothelial cancer with progression on or after platinum containing chemotherapy by the Food and Drug Administration (FDA). In the UK, pembrolizumab is recognised under the MHRA's Early Access to Medicines Scheme for unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care, and has received Promising Innovative Medicines (PIM) designation for treatment of metastatic NSCLC under certain circumstances (CS, p31).

The treatment pathway is, as the company states, determined by the performance status of the patient and the level of renal function. According to the NICE guideline[6] it also takes the recurrence history, size and number of cancers, histological type, grade and stage, risk category of the cancer and the predicted risk of recurrence into account. The company positions pembrolizumab as 2nd or 3rd line treatment for locally advanced or metastatic MIBC. The current treatment pathway is a chemotherapy regimen for 2nd line and no regulated treatment for 3rd line, although the NICE scope suggests docetaxel and paclitaxel (see Figure 1).

3.2 Intervention

The intervention in the decision problem is pembrolizumab as monotherapy, which matches the final scope. The company provides a description of the technology and the mechanism of action of pembrolizumab (CS p27) which the ERG's clinical advisors have confirmed is an accurate description. Pembrolizumab is an intravenously administered medication that has been authorised for use in indications other than this current appraisal including:

- treatment of advanced (unresectable or metastatic) melanoma in adults;
- first-line treatment of metastatic NSCLC in adults whose tumours express programmed cell death 1 ligand 1 (PD-L1) with a ≥50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations; and
- treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

With regards to the present submission, pembrolizumab is currently unlicensed in people with urothelial cancers, which means the benefit/risk balance has not been assessed by the European regulatory authority. In this report, the ERG will present the main clinical effectiveness and safety outcomes of pembrolizumab in adults with locally advanced/metastatic urothelial cancers. Based on this evidence, the ERG believes it is likely that the Committee for Medicinal Products for Human Use (CHMP) will conclude that the benefits of pembrolizumab outweighs the risks.

Pembrolizumab is a highly selective humanised monoclonal antibody against programmed death-1 (PD-1). It exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and programmed cell death 1 ligand 2 (PD-L2), on antigen presenting tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab activates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates antitumour immunity.

Pembrolizumab is part of a new class of immunotherapies which comprises drugs like nivolumab and atezolizumab. Pembrolizumab is not the only PD-1/PD-L1 inhibitor that has been evaluated within the scope of urothelial cancers. Atezolizumab is one of these and is currently subject to an ongoing appraisal (ID939). Nivolumab and durvalumab should also emerge in the coming months.

given the relatively favourable safety profile of the drug. However, this would have to be supported by clinical effectiveness data in this subgroup.

With regards to retreatment with a platinum-based chemotherapy, the company indicated that no evidence exists for a comparison between pembrolizumab and retreatment with platinum-based chemotherapy, thus the latter was not considered as a comparator in this submission. The ERG believes this is not a valid reason to exclude retreatment with platinum-based chemotherapy. Our clinical advisors indicated that retreatment with platinum-based chemotherapy can be considered within the NHS depending on the time to recurrence/progression after platinum therapy. In cases of early recurrence/progression (<12 months), which corresponds to the vast majority of patients, retreatment with platinum-based chemotherapy would in general not be considered while it could be considered in the rare cases of late recurrence (> 12 months). In case of relapse after 6-12 months, a carboplatin-gemcitabine therapy can be occasionally offered in second line (after first line platinum regimen) of locally advanced/metastatic urothelial cancers but only in patients with good PS.

With regards to the comparators, the ERG would like to highlight that neither the NICE scope nor the company submission have included other PD-L1 inhibitors such as atezolizumab, nivolumab, or durvalumab; although all these drugs are anticipated to have the same positioning should they be recommended by NICE within the NHS.

3.4 Outcomes

The outcome measures to be considered in the NICE scope have been reported in the decision problem. They are overall survival (OS), progression-free survival (PFS), response rates (RR), adverse effects (AE) and health-related quality of life (HRQoL).

sources, including bibliographic databases, trials registers, conference proceedings and the company's own records. Database searches were limited to English language, but were not limited by date. Most search terms and lines were combined appropriately.

There are some issues that may have resulted in some records being missed: a) line 22 of the Embase cisplatin+gemcitabine / MVAC search misses out line 17; b) the use of 'NOT' combined with many study type terms in all the bibliographic database searches; and c) not hand searching the reference lists of relevant reviews or articles. However, the use of other search terms in the database searches and searching in other sources mean that overall the clinical effectiveness searches appear to be reasonably comprehensive. At the clarification stage, the ERG requested an update of the first set of searches and the company responded "it was not possible to run the updated search in the short timeline provided. However, we do not anticipate any new studies, given the limited clinical advancements in this area." The ERG's targeted independent searches for systematic reviews and longer term survival data did not identify any additional studies. However, the ERG believe that two of the studies that were identified in these independent searches, which were also listed in the CS as either potential indirect evidence (NCT00315237),[13] or excluded[15, 16]), were relevant to survival extrapolations (Section 5.2.6.2).

4.3 Inclusion / exclusion criteria used in the study selection

The eligibility criteria are listed in CS Table 6, CS page 44. The eligible population includes adults with advanced/metastatic urothelial carcinoma recurring or progressing follow platinum-based regimen. The intervention of interest for this single technology appraisal (STA) is pembrolizumab, which is stated in the Population Intervention Comparator Outcome Study Design (PICOS) table along with six different comparators (paclitaxel/gemcitabine; carboplatin/paclitaxel; cisplatin+gemcitabine; MVAC; docetaxel; and paclitaxel). The company indicated that the listed comparators were selected consistent with practice relevant to the UK setting. Therefore, vinflunine was not mentioned since this drug was issued with a negative recommendation by NICE in 2013.[17] The company has not listed BSC (see Section 3.3).

For the purpose of indirect and mixed treatment comparisons, the company included any RCTs with comparisons between any of the interventions of interest. This is why the vinflunine pivotal RCT [13] was included although vinflunine is not listed. To improve the quality of the reporting, the ERG believes that it would have been clearer to list all the potential comparators in the PICOS

table (CS table 6, page 44) while identifying those of relevance to the UK setting. The company's eligibility criteria for the systematic review state that trials with outcome measures

OS was defined as the time from randomisation to death from any cause and PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression or death due to any cause, whichever occurred first.

For the co-primary objective, PFS was assessed according to RECIST 1.1 based on blinded independent central radiologic (BICR) review. Tumour imaging was scheduled for week 9 followed by every 6 weeks during the first year and every 12 weeks thereafter. RECIST 1.1[23] corresponds to a revised guideline on response evaluation criteria in solid tumours (RECIST). These criteria are often used in clinical trials for anti-cancer therapies with the aim to assess tumour shrinkage (objective response) and disease progression. The RECIST 1.1 guideline defines key criteria on measurability of tumour at baseline (definition, methods of measurements), and tumour response evaluation (assessment of tumour burden and measurable disease, response criteria: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (StD)).

As part of the secondary endpoints, PFS was also assessed per RECIST 1.1 from randomisation to specific time points (6 and 12 months), and per modified RECIST (mRECIST) 1.1 based on BICR review. The mRECIST 1.1 corresponds to the RECIST 1.1 criteria with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1.

Other pre-specified secondary endpoints included ORR according to RECIST 1.1 and mRECIST 1.1 both based on BICR review, response duration according to RECIST 1.1 by BICR review, and occurrence of adverse events. ORR was defined as the proportion of patients who had either a CR or PR.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

The KEYNOTE-045 trial had several exploratory objectives which were mainly PFS assessed by RECIST 1.1 by investigator review along with the assessment of changes in HRQoL from baseline using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.

Primary outcomes

Analyses of OS by subgroup showed consistency of survival benefit favouring pembrolizumab across subgroups (CSR p116), with consistent point estimates for the HR in important subgroups such as ECOG-PS, liver metastasis, haemoglobin, time from prior chemotherapy, prior platinum (cisplatin versus carboplatin), investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine), and Bellmunt risk scores (see Table 9). Few exceptions were noted (e.g., 'non-White,' 'East Asia,' and 'never smoker'). The small numbers of events in some subgroups result in wide CIs and preclude an accurate interpretation of treatment effect.

Table 9: Overall survival by subgroup factors

	Control		Pembrolizumab		Hazard Ratio (95% CI)†
	N	Number of Events (%)	N	Number of Events (%)	
Overall	272	[redacted]	270	[redacted]	0.73(0.59,0.91)
<65 years	125	[redacted]	105	[redacted]	0.75(0.53,1.05)
≥65 years	147	[redacted]	165	[redacted]	0.76(0.56,1.02)
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	0.89(0.66,1.20)
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	0.61(0.43,0.86)
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	0.80(0.61,1.05)
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	0.57(0.37,0.88)
Female	70	[redacted]	70	[redacted]	0.78(0.49,1.24)
Male	202	[redacted]	200	[redacted]	0.73(0.56,0.94)
White	201	[redacted]	188	[redacted]	0.65(0.50,0.84)
Non-White	63	[redacted]	70	[redacted]	1.12(0.70,1.79)
ECOG 0/1	264	[redacted]	262	[redacted]	0.74(0.59,0.92)
ECOG 2	4	[redacted]	2	[redacted]	0.43(0.04,4.20)
ECOG 0	106	[redacted]	119	[redacted]	0.99(0.66,1.47)
ECOG 1/2	162	[redacted]	145	[redacted]	0.66(0.50,0.87)
East-Asia	48	[redacted]	58	[redacted]	1.25(0.72,2.18)
Non-East Asia	224	[redacted]	212	[redacted]	0.66(0.52,0.85)
EU	117	[redacted]	106	[redacted]	0.59(0.42,0.84)
Non-EU	155	[redacted]	164	[redacted]	0.79(0.60,1.06)
US	59	[redacted]	47	[redacted]	0.83(0.48,1.41)
Non-US	213	[redacted]	223	[redacted]	0.71(0.56,0.91)
Never Smoker	83	[redacted]	104	[redacted]	1.06(0.72,1.55)
Former Smoker	148	[redacted]	136	[redacted]	0.71(0.52,0.97)
Current Smoker	38	[redacted]	29	[redacted]	0.32(0.15,0.68)
Cisplatin	213	[redacted]	198	[redacted]	0.73(0.56,0.94)
Carboplatin	56	[redacted]	70	[redacted]	0.74(0.47,1.18)
Most Recent Prior Therapy:		[redacted]		[redacted]	
Neo Adjuvant	22	[redacted]	19	[redacted]	0.53(0.20,1.41)
Adjuvant	31	[redacted]	12	[redacted]	0.53(0.18,1.57)
1L Metastatic	157	[redacted]	183	[redacted]	0.72(0.54,0.95)
2L Metastatic	60	[redacted]	55	[redacted]	0.83(0.52,1.33)
Liver Metastases at Baseline:		[redacted]		[redacted]	
Presence	95	[redacted]	91	[redacted]	0.85(0.61,1.20)
Absence	176	[redacted]	179	[redacted]	0.67(0.50,0.89)

Hb ≥10 g/dL	223	[redacted]	219	[redacted]	0.71(0.55,0.91)
Hb <10 g/dL	44	[redacted]	43	[redacted]	0.75(0.46,1.22)
Time from Most Recent Chemo Therapy:		[redacted]		[redacted]	
≥3 Months	167	[redacted]	166	[redacted]	0.66(0.49,0.89)
<3 Months	104	[redacted]	103	[redacted]	0.82(0.58,1.15)
Transitional Cell	197	[redacted]	186	[redacted]	0.80(0.62,1.04)
Mixed Transitional/ nontransitional histology	73	[redacted]	82	[redacted]	0.58(0.37,0.89)
Prior Brain Metastasis	5	[redacted]	2	[redacted]	NA(NA,NA)
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	0.73(0.58,0.91)
Paclitaxel	84	[redacted]	266	[redacted]	0.76(0.55,1.04)
Docetaxel	84	[redacted]	266	[redacted]	0.76(0.55,1.05)
Vinflunine	87	[redacted]	266	[redacted]	0.69(0.51,0.94)
Burden of Disease on Baseline Tumour Volume:		[redacted]		[redacted]	
< Median	117	[redacted]	132	[redacted]	0.54(0.38,0.78)
≥ Median	135	[redacted]	115	[redacted]	0.91(0.68,1.23)
Risk Scores: 0	44	[redacted]	54	[redacted]	0.82(0.42,1.62)
1	97	[redacted]	96	[redacted]	0.73(0.49,1.08)
2	80	[redacted]	66	[redacted]	0.84(0.56,1.24)
3 or 4	45	[redacted]	45	[redacted]	0.76(0.47,1.24)
Site of Primary Tumour:		[redacted]		[redacted]	
Upper Tract	37	[redacted]	38	[redacted]	0.53(0.28,1.01)
Lower Tract	234	[redacted]	232	[redacted]	0.77(0.60,0.97)
Lymph Node Only	38	[redacted]	29	[redacted]	0.46(0.18,1.21)
Visceral Disease	233	[redacted]	240	[redacted]	0.75(0.60,0.95)

† Based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Score (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (Hb) (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
N = sample size
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

In the clarification questions, the ERG asked the company to provide further explanations of the cut-offs used to determine PD-L1 expression. In their response, the company commented that the OS benefit of pembrolizumab versus chemotherapy was observed across all PD-L1 CPS expression levels (page 8, clarification document). The ERG agree with this comment with respect to patients positive and strongly positive for PD-L1 expression. However, the ERG disagree with this statement pertaining to the group of patients negative for PD-L1 expression since the HR for death is 0.89 (95% CI 0.66, 1.20). Indeed, since the study was not designed to test the superiority of pembrolizumab in this subpopulation, the sample size may have been

Table 10: Progression-Free Survival Based on RECIST 1.1 per Central Radiology Assessment (Primary Censoring Rule) by Subgroup Factors

	Control		Pembrolizumab		Hazard Ratio (95% CI)†
	N	Number of Events (%)	N	Number of Events (%)	
Overall	272	[redacted]	270	[redacted]	0.98(0.81,1.19)
<65 years	125	[redacted]	105	[redacted]	0.98(0.73,1.33)
≥65 years	147	[redacted]	165	[redacted]	1.08(0.83,1.40)
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	1.07(0.82,1.39)
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	0.91(0.68,1.24)
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	1.04(0.82,1.33)
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	0.89(0.61,1.28)
Female	70	[redacted]	70	[redacted]	0.96(0.63,1.44)
Male	202	[redacted]	200	[redacted]	1.01(0.81,1.28)
White	201	[redacted]	188	[redacted]	0.88(0.70,1.10)
Non-White	63	[redacted]	70	[redacted]	1.48(0.99,2.23)
ECOG 0/1	264	[redacted]	262	[redacted]	0.98(0.80,1.19)
ECOG 2	4	[redacted]	2	[redacted]	2.92(0.26,32.93)
ECOG 0	106	[redacted]	119	[redacted]	1.16(0.84,1.60)
ECOG 1/2	162	[redacted]	145	[redacted]	0.96(0.74,1.23)
East-Asia	48	[redacted]	58	[redacted]	1.68(1.05,2.67)
Non-East Asia	224	[redacted]	212	[redacted]	0.86(0.69,1.06)
EU	117	[redacted]	106	[redacted]	0.90(0.66,1.24)
Non-EU	155	[redacted]	164	[redacted]	1.03(0.80,1.33)
US	59	[redacted]	47	[redacted]	0.85(0.53,1.37)
Non-US	213	[redacted]	223	[redacted]	1.03(0.83,1.28)
Never Smoker	83	[redacted]	104	[redacted]	1.13(0.80,1.60)
Former Smoker	148	[redacted]	136	[redacted]	1.05(0.79,1.38)
Current Smoker	38	[redacted]	29	[redacted]	0.47(0.25,0.88)
Cisplatin	213	[redacted]	198	[redacted]	0.99(0.79,1.24)
Carboplatin	56	[redacted]	70	[redacted]	0.97(0.64,1.48)
Most Recent Prior Therapy:		[redacted]		[redacted]	
Neo Adjuvant	22		19		0.94(0.40,2.19)
Adjuvant	31	[redacted]	12	[redacted]	0.94(0.38,2.30)
1L Metastatic	157	[redacted]	183	[redacted]	0.88(0.69,1.14)
2L Metastatic	60	[redacted]	55	[redacted]	1.43(0.93,2.20)
Liver Metastases at Baseline:		[redacted]		[redacted]	
Presence	95		91		1.13(0.81,1.56)
Absence	176	[redacted]	179	[redacted]	0.93(0.73,1.18)

Hb ≥10 g/dL	223	[redacted]	219	[redacted]	0.94(0.76,1.17)
Hb <10 g/dL	44	[redacted]	43	[redacted]	1.26(0.77,2.05)
Time from Most Recent Chemo Therapy:		[redacted]		[redacted]	
≥3 Months	167		166		0.81(0.63,1.04)
<3 Months	104	[redacted]	103	[redacted]	1.28(0.94,1.76)
Transitional Cell	197	[redacted]	186	[redacted]	1.08(0.86,1.36)
Mixed Transitional/ nontransitional		[redacted]		[redacted]	
histology	73		82		0.84(0.57,1.24)
Prior Brain Metastasis	5	[redacted]	2	[redacted]	NA(NA,NA)
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	0.97(0.80,1.18)
Paclitaxel	84	[redacted]	266	[redacted]	0.94(0.71,1.24)
Docetaxel	84	[redacted]	266	[redacted]	0.97(0.73,1.28)
Vinflunine	87	[redacted]	266	[redacted]	1.09(0.83,1.44)
Burden of Disease on Baseline Tumour Volume:		[redacted]		[redacted]	
< Median	117		132		0.76(0.57,1.02)
≥ Median	135	[redacted]	115	[redacted]	1.22(0.93,1.61)
Risk Scores:		[redacted]		[redacted]	
0	44		54		0.83(0.52,1.33)
1	97	[redacted]	96	[redacted]	0.99(0.70,1.39)
2	80	[redacted]	66	[redacted]	1.09(0.75,1.58)
3 or 4	45	[redacted]	45	[redacted]	1.36(0.84,2.18)
Site of Primary Tumour:		[redacted]		[redacted]	
Upper Tract	37		38		1.18(0.67,2.07)
Lower Tract	234	[redacted]	232	[redacted]	0.97(0.78,1.19)
Lymph Node Only	38	[redacted]	29	[redacted]	0.56(0.30,1.07)
Visceral Disease	233	[redacted]	240	[redacted]	1.04(0.85,1.28)

† Based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Score (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
N = sample size
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Secondary outcomes

The company did not comment on the ORR by subgroups data. These were presented in Table 14.2-34 of the CSR (p398).

Table 11: Objective Response Rate Based on RECIST 1.1 per Central Radiology Assessment by Subgroup Factors

	Control		Pembrolizumab		Pembrolizumab vs Control Rate Difference (95% CI)†
	N	Number of Responses (ORR%)	N	Number of Responses (ORR%)	
Overall	272	[redacted]	270	[redacted]	9.7(3.5,16.0)
<65 years	125	[redacted]	105	[redacted]	11.7(3.4,20.9)
≥65 years	147	[redacted]	165	[redacted]	7.4(-1.5,16.1)
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	4.3(-4.1,12.7)
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	15.3(6.0,25.0)
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	5.7(-2.0,13.4)
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	15.0(4.6,26.5)
Female	70	[redacted]	70	[redacted]	11.4(-0.7,23.9)
Male	202	[redacted]	200	[redacted]	9.1(1.9,16.4)
White	201	[redacted]	188	[redacted]	10.4(3.0,17.9)
Non-White	63	[redacted]	70	[redacted]	3.0(-9.5,15.2)
ECOG 0/1	264	[redacted]	262	[redacted]	9.6(3.3,16.0)
ECOG 2	4	[redacted]	2	[redacted]	0.0(-53.5,69.7)
ECOG 0	106	[redacted]	119	[redacted]	11.2(0.9,21.3)
ECOG 1/2	162	[redacted]	145	[redacted]	8.1(0.3,16.3)
East-Asia	48	[redacted]	58	[redacted]	-1.1(-16.2,13.1)
Non-East Asia	224	[redacted]	212	[redacted]	12.4(5.5,19.4)
EU	117	[redacted]	106	[redacted]	6.4(-4.0,17.0)
Non-EU	155	[redacted]	164	[redacted]	12.4(4.9,20.1)
US	59	[redacted]	47	[redacted]	16.2(3.8,30.6)
Non-US	213	[redacted]	223	[redacted]	7.9(0.9,15.0)
Never Smoker	83	[redacted]	104	[redacted]	9.1(-0.4,18.5)
Former Smoker	148	[redacted]	136	[redacted]	6.4(-2.4,15.4)
Current Smoker	38	[redacted]	29	[redacted]	30.9(10.3,50.7)
Cisplatin	213	[redacted]	198	[redacted]	12.0(4.7,19.4)
Carboplatin	56	[redacted]	70	[redacted]	3.2(-9.9,15.6)
Most Recent Prior Therapy:		[redacted]		[redacted]	
Neo Adjuvant	22		19		22.5(-2.3,47.1)

Adjuvant	31	[redacted]	12	[redacted]	17.2(-9.0,47.6)
1L Metastatic	157	[redacted]	183	[redacted]	10.9(3.0,18.8)
2L Metastatic	60	[redacted]	55	[redacted]	0.9(-11.0,13.3)
Liver Metastases at Baseline:		[redacted]		[redacted]	
Presence	95		91		6.9(-2.1,16.5)
Absence	176	[redacted]	179	[redacted]	10.9(2.8,19.1)
Hb ≥10 g/dL	223	[redacted]	219	[redacted]	9.8(2.7,17.0)
Hb <10 g/dL	44	[redacted]	43	[redacted]	9.4(-3.3,23.5)
Time from Most Recent Chemo		[redacted]		[redacted]	
Therapy: ≥3 Months	167		166		12.7(4.4,21.1)
<3 Months	104	[redacted]	103	[redacted]	4.9(-4.1,14.3)
Transitional Cell	197	[redacted]	186	[redacted]	7.2(-0.2,14.7)
Mixed Transitional/ nontransitional histology	73	[redacted]	82	[redacted]	16.2(4.6,27.7)
Prior Brain Metastasis	5	[redacted]	2	[redacted]	-20.0(-65.1,56.3)
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	10.0(3.8,16.3)
Paclitaxel	84	[redacted]	266	[redacted]	9.5(-0.2,17.2)
Docetaxel	84	[redacted]	266	[redacted]	15.5(7.2,22.1)
Vinflunine	87	[redacted]	266	[redacted]	3.0(-7.4,11.8)
Burden of Disease on Baseline		[redacted]		[redacted]	
Tumour Volume: < Median	117		132		11.6(1.0,22.0)
≥ Median	135	[redacted]	115	[redacted]	6.4(-1.0,14.5)
Risk Scores:		[redacted]		[redacted]	
0	44		54		13.3(-4.3,29.8)
1	97	[redacted]	96	[redacted]	11.6(0.5,22.8)
2	80	[redacted]	66	[redacted]	3.6(-7.0,15.2)
3 or 4	45	[redacted]	45	[redacted]	8.9(-3.5,22.5)
Site of Primary Tumour:		[redacted]		[redacted]	
Upper Tract	37		38		13.1(-0.2,28.3)

Lower Tract	234	[redacted]	232	[redacted]	9.2(2.3,16.1)
Lymph Node Only	38	[redacted]	29	[redacted]	15.9(-7.3,38.2)
Visceral Disease	233	[redacted]	240	[redacted]	9.7(3.7,16.0)

† Based on Miettinen & Nurminen method
N = sample size
ORR = Objective Response Rate
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Other secondary endpoints (ORR by mRECIST, PFS by mRECIST and response duration) were not presented by subgroup.

4.10.1.5 Health-related quality of life

Quality of life was assessed by EORTC-QLQ-C30 and EQ-5D questionnaires. The patient reported outcomes were to be collected prior to cycle 1, cycle 2, cycle 3, cycle 4 and every 2 cycles thereafter (e.g., cycle 6, cycle 8, cycle 10) up to a year or end of treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit (protocol p60).

EORTC-QLQ-C30:

Baseline global health status/quality of life (QoL) scores were similar between treatment arms (CS p122). At week 9, the global health status/QoL score was stable from baseline (least squares (LS) mean = -1.37 points; 95% CI: -4.10, 1.35) in the pembrolizumab arm, and a greater worsening of -5.75 points (95% CI: -8.62, -2.87) was observed in the control arm. The difference in LS means between pembrolizumab and the control arm at week 9 was 4.38 points (95% CI: 0.59, 8.16; two-sided p=0.02, not controlled for multiplicity). At week 15, there was an even greater difference in LS means between the pembrolizumab arm and control (9.05 points; 95% CI: 4.61, 13.48; two-sided p<0.001, not controlled for multiplicity) (see Table 12).

Table 12: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at Week 9 (FAS population)

	Pembrolizumab	**Chemotherapy**
Baseline: Number of patients	260	243
Baseline: Mean (SD)	61.51 (23.107)	59.12 (22.144)
Week 9: Number of patients	200	176
Week 9: Mean (SD)	63.04 (22.964)	58.48 (21.849)
Change from baseline at week 9	-1.37 (-4.10, 1.35)	-5.75 (-8.62, -2.87)
Difference in LS Means (95% CI)	4.38 (0.59, 8.16)	
p value	0.024	
Week 15: Number of patients	157	118

The evaluation on quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, the validity of the findings is in question and conclusions may not be reliable from the quality of life results.

4.10.1.6 Safety: adverse events

Adverse events considered by the investigator to have a reasonable possibility of being related to the sponsor's product were classified as drug-related AEs.

Adverse events that were considered by the investigators to be related to treatment occurred in 60.9% of the patients treated with pembrolizumab, vs. 90.2% of those who received chemotherapy (CS p152). Treatment-related events of grade 3, 4, or 5 severity were less frequent in the pembrolizumab group than in the chemotherapy group (15.0% vs. 49.4% of patients, CS p154), as was treatment-related discontinuation of therapy (5.6% vs. 11.0%). One pembrolizumab-treated patient died from treatment-related pneumonitis. Three other deaths in the pembrolizumab group were attributed by the investigators to study treatment, including one death related to urinary tract obstruction, one death related to malignant neoplasm progression, and one death of unspecified cause. In the chemotherapy group, treatment-related deaths were related to sepsis (in two patients), septic shock (in one), and unspecified cause (in one) (see Table 14). The ERG found surprising that the urinary tract obstruction and neoplasm progression that lead to two deaths in the pembrolizumab arm were attributed to study treatment.

The most common treatment-related adverse events of any grade were pruritus (19.5% of the patients), fatigue (13.9%), and nausea (10.9%) in the pembrolizumab group and alopecia (37.6%), fatigue (27.8%), and anaemia (24.7%) in the chemotherapy group.[10] There were no treatment-related events of grade 3, 4, or 5 severity that occurred with an incidence of 5% or more in the pembrolizumab group. In the chemotherapy group, treatment-related events of grade 3, 4, or 5 severity with an incidence of 5% or more were neutropenia (13.3%), decreased neutrophil count (12.2%), anaemia (7.8%), febrile neutropenia (7.1%), and decreased white-cell count (5.1%).

AEs of special interest (AEOSI) are immune mediated events and infusion related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab (CS p160). There were 45 (16.9%) subjects in the pembrolizumab arm with 1 or more AEOSIs. The only AEOSI of grade 3, 4, or 5 severity (regardless of whether they were attributed to study

treatment by the investigator) that were observed in two or more patients who were treated with pembrolizumab were pneumonitis (2.3% of the patients), colitis (1.1%), and nephritis (0.8%); there was only one grade 5 event (0.4%), which was pneumonitis.[10]

Table 14: Adverse Events in the As-Treated Population*

Event	Pembrolizumab Group (N = 266)		Chemotherapy Group (N = 255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	Number of patients (percent)			
Treatment-related event†				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Event occurring in ≥10% of patients in either group‡				
Pruritus	52 (19.5)	0	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhoea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anaemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0	52 (20.4)	8 (3.1)
Peripheral sensory neuropathy	2 (0.8)	0	28 (11.0)	5 (2.0)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (14.1)	31 (12.2)
Peripheral neuropathy	1 (0.4)	0	27 (10.6)	2 (0.8)
Neutropenia	0	0	39 (15.3)	34 (13.3)
Alopecia	0	0	96 (37.6)	2 (0.8)
Event of interest§				
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0

Regarding PFS, the risk of progression or death was similar between pembrolizumab and SOC in the three populations although the proportion of patients free from progression at 1 year was higher with pembrolizumab.

However, as far as OS is concerned, the risk of death was reduced with pembrolizumab compared to SOC in the three populations.

The results of PFS and OS in the numerous subgroups showed consistency with the overall findings for the entire population.

Evaluation of quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, it is difficult to draw reliable conclusions from the quality of life results.

The safety profile of pembrolizumab was more favourable than that of SOC. There were no treatment-related events of grade ≥ 3 severity that occurred with an incidence of ≥5% in the pembrolizumab group.

As of April 2017, pembrolizumab is not licensed for urothelial cancers and a submission aimed to extend the marketing authorisation is currently being assessed with the CHMP. Based on the results of KEYNOTE-045 which presents the clinical effectiveness and safety profile of pembrolizumab in advanced/metastatic urothelial cancers after failure of platinum-based therapy, the ERG believes that it's likely that the CHMP will consider the balance between benefits and risks of pembrolizumab to be positive.

No indirect comparisons were presented by the company. There is no data comparing pembrolizumab to BSC which is a relevant comparator in people with poor performance status.

The ERG requested at the clarification stage details of the 126 papers which were evaluated in full, including references and reasons why studies were excluded. For example, for the economic evaluation review in the original CS, 4 papers met the inclusion criteria from the original search but no further information or references were provided. Upon clarification the company excluded 3 of the 4 publications by stating "they should have been excluded during the secondary screening as although they provide relevant information in regards to the economic modelling, they were published prior to 2005". The company provided an excel document titled "ID1019 Economic SLR" which included references to the excluded studies and reasons for exclusion.

The flow diagrams indicated that no studies were included for the original economic evaluation and the cost and resource use reviews; however, one study was identified from the updated cost and resource use search.[17] For the original HRQoL and utility review and updated search, 24 studies were extracted from 29 publications (the reference lists, characteristics and information on utility values for these studies were included in Appendix 18).

No quality assessment was conducted by the company, as stated on p175 "as no cost-effectiveness study meeting all inclusion criteria was identified". Furthermore, the CS does not formally report whether any of the modelling attributes from the included HRQoL and utility studies were used in the development of the *de novo* economic model of pembrolizumab.

Some additional studies relevant to the population were identified by the ERG through targeted searches of the CEA Registry, NHS EED and the HTA database, but none were relevant to the decision making context.

To summarise, no cost-effectiveness studies assessing pembrolizumab for patients with advanced or metastatic urothelial cancer were identified.

5.1.4 Conclusions

The company did not provide a formal conclusion from the data available of the three systematic reviews: economic evaluation, utility and cost/resource use.

5.2 Summary and critique by the ERG of the economic evaluation submitted by the company

5.2.1 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS. Including technologies regarded as current best practice for the two populations	UK SOC i.e. physicians choice of docetaxel or paclitaxel
Patient group	As per NICE final scope	Yes. Patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes. Cost-effectiveness analysis (Cost per quality-adjusted life year (QALY))
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (lifetime duration)
Synthesis of evidence on outcomes	Systematic review	Data are drawn from one trial: KEYNOTE-045
Outcome measure	Quality-adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. Health states were evaluated using EQ-5D-3L data collected from KEYNOTE-045 trial

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
Benefit valuation	Time-trade off or standard gamble	Yes. The standard UK EQ-5D tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefits	Yes
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		A range of sensitivity and scenario analyses are presented

5.2.1 Model structure

The company presented a *de novo* cost-utility partitioned survival model with a weekly cycle length and a lifetime time horizon. The model consisted of three health states: pre-progression, post-progression, and death (Figure 2). A half-cycle correction was applied in the base-case analysis.

The partitioned survival approach uses an "area under the curve" approach, where the number of patients in the two health states: pre-progression and death, is taken directly from survival curves fitted to the clinical data. This approach did not consider post-progression survival directly. Instead, time in post-progression survival was derived from the difference in the area under the two survival health states (PFS and OS).

The model assumes all patients enter the model in the pre-progression health state. Patients in the pre-progression health state, stay in that health state until disease progression or death. Transitions to the death state could occur from either the pre-progression or post-progression health state. Costs of disease management, utilities and risks of death all differ between the pre-progression and the post-progression health states.

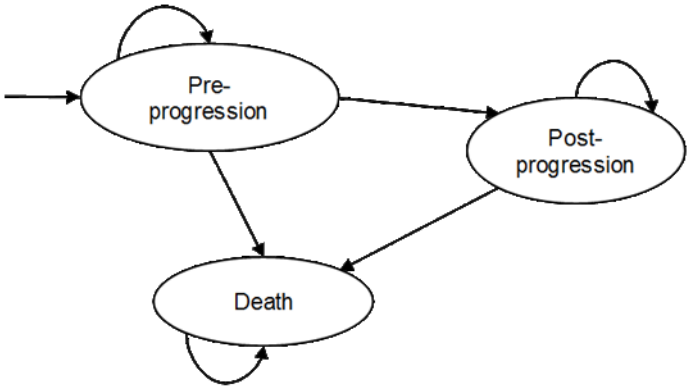


Figure 2: Model structure presented by the company

ERG summary

- Even though the model is a simple one with three health states, it is consistent with other models built in this disease area, and captures the two important clinical endpoints of OS and PFS. The cycle length of the model (1 week) should be sufficiently short to capture changes over the relevant time interval.

5.2.3 Population

The population modelled in the company's base case analysis included patients with metastatic or locally advanced/unresectable urothelial cancer which has recurred or progressed following platinum-containing chemotherapy.

The company also presented results for the following subgroups of patients in the CS Appendix:

1. patients with advanced or metastatic urothelial cancer of predominantly transitional cell histology.
2. patients with advanced or metastatic urothelial cancer of pure transitional cell histology.
3. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥1%) urothelial cancer.

4. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥10%) urothelial cancer.
5. patients with advanced or metastatic urothelial cancer by individual comparator regimen i.e., pembrolizumab vs. docetaxel and pembrolizumab vs. paclitaxel"

Data for the base-case and the subgroup analyses were based on the KEYNOTE-045 study. The study population was assumed by the company to be reasonably similar to the UK population likely to receive treatment. However, out of the 542 patients recruited in the KEYNOTE-045 study, only 4 were from the UK (see section 4.4).

Individuals in the modelled cohort had an average starting age of 65.5 years and 74.2% were male. An average body surface area (BSA) of 1.90m^2 was used to estimate the dosing of paclitaxel and docetaxel. The average BSA value was taken from the European sites of KEYNOTE-045, whereas age and gender values were taken from the overall population recruited in KEYNOTE-045 (i.e. including patients from the US and Asia).

Information on patient characteristics for the subgroup analyses were provided in Appendix 9. However, in the economic model, the ERG found that the mean values of the patient characteristics used in the base-case analysis were used in all subgroup analyses. Furthermore, the ERG found that gender was not included as a model parameter.

For all subgroup analyses presented in the Appendix, the company stated that the results should be interpreted with caution as there is uncertainty around the estimates (due to small number of patients in the subgroups). However, only deterministic cost-effectiveness results were presented in the original submission. Upon request in the clarifications the company provided the probabilistic results.

ERG summary

- In the base-case analysis patients age and gender were taken from the overall trial population, however, the use of patient characteristics from only the European sites might result in more representative patients.
- The modelled population in all subgroup analyses were based on the characteristics of patients from the overall trial population.
- The impact of gender was not included in the estimation process in the economic model.

5.2.4 Interventions and comparators

In the company's base-case analysis, pembrolizumab is compared with UK standard of care (UK SOC) i.e. investigator's choice of paclitaxel or docetaxel. Based on the KEYNOTE-045 study, among patients who received paclitaxel or docetaxel (i.e. excluding vinflunine), 48.9% received paclitaxel and 51.1% received docetaxel. A scenario analysis is presented in which the UK SOC arm is based on the UK market share of paclitaxel and docetaxel (26% and 74%, respectively).

Pembrolizumab treatment is administered at a fixed dose every 3 weeks and should continue until radiologic disease progression, toxicities leading to discontinuation, physician's decision or 24 months of uninterrupted treatment with pembrolizumab. Based on clinical expert opinion, the company assumed that a maximum of 6 cycles were administered to reflect the UK clinical practice for the treatment regimens representing UK SOC. To estimate the duration of treatment in the pembrolizumab and comparator arms, time on treatment (ToT) data from KEYNOTE-045 was used. Separate parametric curves were fitted to the patient level treatment duration data from KEYNOTE-045 to represent ToT in the economic model (see Section 5.2.6 for more detail).

As part of the subgroup analyses presented in the CS Appendix, the company presented cost-effectiveness results for the overall patient population comparing pembrolizumab with individual regimens (i.e. pembrolizumab vs paclitaxel and pembrolizumab vs docetaxel).

The appropriateness of the pooled comparator treatment was considered by the ERG. Based on the ERG's clinical experts, paclitaxel and docetaxel were regarded as appropriate comparators in the UK setting. In addition, "lumping" the two treatment options as a single treatment was considered appropriate, since paclitaxel and docetaxel treatments are considered similar in terms of clinical effectiveness.

The economic model assumed that treatment effect with pembrolizumab lasted for a lifetime (35 years). Upon clarification, the company provided further scenario analyses looking at treatment effect which lasts only for 3, 5 or 10 years.

The ERG found an error in the application of maximum treatment duration of UK SOC in the model. That is, the duration of paclitaxel or docetaxel treatment continued beyond 18 weeks (6 cycles) and reached a maximum of 58 weeks. However, the company had also identified the error and provided the ERG with a new updated economic model correcting for this error.

- Objective response rate
- Time to response
- Duration of response
- Adverse events of treatment
- Health-related quality of life

In this section we elaborate further on the co-primary endpoints: OS and PFS.

5.2.6.1 Overall survival

The estimation of long-term overall survival comprised the following methods:

1. Adjusting for treatment switching in the UK SOC arm
2. Overall survival extrapolation
3. Two-phase piecewise approach

1. Adjusting for treatment switching in the UK SOC

Three statistical techniques were used to adjust for treatment switching in the UK SOC arm, as some patients in this group received PD-1/PD-L1 treatments following disease progression. These methods included the rank-preserving structural failure time (RPSFT), the simplified 2-stage method and the inverse probability of censoring weighting (IPCW). Treatment switching was accounted for in the survival models, with three different methods investigated in addition to an ITT analysis. Details of the methods can be found in the NICE Decision Support Unit (DSU) Technical Support Document 16 by Latimer and Abrams (2014).[24] Each was implemented and considered alongside their relative assumptions in section 4.7 and Appendix 10. There were 22 patients who switched from the control arm to other treatments; however, only 14 of these were actually eligible to switch with 8 patients appearing to switch prior to disease progression.

The ERG notes that three methods were investigated for adjusting for treatment switching: IPCW, RPSFT and 2-Stage.

- RPSFT was the least suitable for two reasons. Firstly, it censors patients prior to the time point at which they switched treatments in an attempt to remove bias, however this results in a loss of information. It then generates artificial survival times for those who switch. RPSFT also assumes a common treatment effect for both switchers to the experimental arm, and those who received it for the full trial. In KEYNOTE-045, subjects were able to

- switch to a range of possible treatments, which included but were not limited to pembrolizumab. Hence, RPSFT was not a suitable choice.
- IPCW makes the assumption that there are no unobserved confounders. It relies on baseline and time dependent variables being available which predict prognosis and treatment switching. It censors patients at their point of switching, and weights the remaining patients according to their similarities to the censored patients in an attempt to remove any bias that the censoring has caused. Due to the uncertainty over the risk factors of bladder cancer and survival, it is difficult to gauge whether or not this is a suitable method in this case.
- The 2-Stage approach works when the treatment switching is linked to a particular event, e.g. disease progression, as occurred for the planned treatment switching in KEYNOTE-045. This method produces a treatment estimate for patients who switched and then shrinks their survival times accordingly to derive a survival time assuming they had not switched. However, as mentioned above, the subjects in KEYNOTE-045 did not switch to the same treatment, and so it may be incorrect to adjust their survival times by the same factor.

It is clear that none of these methods are perfect in this case. Whilst the RPSFT was the least suitable, it is difficult to decide between 2-Stage and IPCW. It is also difficult to conclude whether the methods are actually a significant improvement over the ITT analysis, or whether the adjustments go too far. The ERG would have liked to have seen further methods examined, including a simple censoring of patients at point of switch. Whilst this would have produced biased results and overestimated OS in the control arm, since it is known that switching was dependent on disease progression, it would have provided useful information in assessing the suitability of the other methods.

Table 15 and Table 16 present the treatment effect for overall survival and median overall survival, respectively. Results from the intention-to-treat (ITT) analysis (full analysis set) showed that pembrolizumab versus UK SOC had a treatment effect for overall survival of [redacted]. Treatment effectiveness results based on an adjustment method all had slightly greater treatment benefit, with hazard ratios (HR) ranging from [redacted] to [redacted]. The choice of the most appropriate adjustment method was based on the trial characteristics, the switching mechanism, the proportion of people switching, and the

	AIC	BIC	AIC	BIC
Exponential	1612.4	1616	1092.5	1095.7
Weibull	1612.9	1620.1	1085.7	1092.2
Gompertz	1608.1	1615.3	1093.5	1099.9
Log-logistic	1606.3	1613.5	1075.1	1081.5
Log-normal	1601.5	1608.7	1078.2	1084.6
Generalised Gamma	1602.8	1613.6	1079.5	1089.1

Figure 6 shows the cumulative hazard associated with death following treatment with pembrolizumab compared to paclitaxel and docetaxel. As suggested by the company, these plots do not support the proportional hazards assumption, as the difference in hazard between treatments is not constant over time. In fact, the plots cross at approximately 14 weeks. The ERG agrees with the company that there is evidence to support the use of a piecewise model to extrapolate overall survival. The company suggested that the 40-week cut-off point is more appropriate than a 24-week cut-off to extrapolate beyond the observed data, because there is a clearer change in the slope after 40 weeks. Whilst this may be plausible, the ERG considers this to be a weak justification, because using the 40-week cut-off reduces the amount of observed data that could be used to extrapolate overall survival. It would have been helpful for the company to show how the various parametric models fitted the cumulative hazard plots to support/strengthen the justification for choosing a) a suitable cut-off point and b) an appropriate parametric model to extrapolate overall survival. The ERG has explored using a 24-week cut-off because at that time point we consider that the hazards follow a predictable path.

pembrolizumab due to the larger differences that were observed. Based on the AIC/BIC, the log-logistic compared to using the log-normal distribution provided a better fit to the pembrolizumab data, whereas the log-normal distribution provided the best fit to the UK SOC data based on the AIC/BIC.

Therefore in the ERG's base-case, estimated overall survival is based on extrapolations using the log-logistic distributions, added to the observed 24-week Kaplan-Meier data. Additionally, the ERG has undertaken further analyses to show the impact of using different parametric distributions to extrapolate from the 24-week time-point on the Kaplan-Meier curve for overall survival.

Table 23: Pembrolizumab overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using a 24-week cut-off						
1-year	0.4570	0.4542	0.4487	0.4497	0.4480	0.4508
3-year	0.1235	0.1546	0.2407	0.2073	0.2542	0.1940
5-year	0.0334	0.0581	0.1691	0.1340	0.2248	0.1070
10-year	0.0013	0.0059	0.0966	0.0707	0.2174	0.0352
Using a 40-week cut-off						
1-year	0.4566	0.4520	0.4467	0.4493	0.4429	0.4416
3-year	0.1335	0.1689	0.2330	0.2065	0.3186	0.2825
5-year	0.0391	0.0708	0.1663	0.1353	0.3153	0.2394
10-year	0.0018	0.0095	0.0985	0.0731	0.3152	0.1926

5.2.6.3 Progression-free survival

In KEYNOTE-045, progression-free survival was defined as per RECIST 1.1[23] the first assessment was performed at week nine, then every six weeks. Like overall survival, projection of long-term progression-free survival was based on a two-phase piecewise model, which was derived by using Kaplan-Meier data up to week 21, then fitting parametric models to the remaining observed data. The 21-week cut-off was chosen based on the separation of the cumulative hazards for pembrolizumab and UK SOC as shown in Figure 10.

Projection of PFS was based on AIC/BIC for the second phase of the piecewise model (based on data beyond the 21-week cut-off). Table 24 shows these goodness-of-fit measures for pembrolizumab and UK SOC.

Table 24: Goodness-of-fit statistics based on the extrapolations of data beyond the 21-week cut-off, for pembrolizumab and UK SOC

Parametric model	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	339	341.4	154.1	155.4
Weibull	340.7	345.5	150.6	153.1
Gompertz	340.2	345	155.9	158.4
Log-logistic	340.2	344.9	153.6	156.1
Log-normal	339.9	344.6	153.4	155.9
Generalised Gamma	341.8	348.9	149.8	153.6

As suggested by the company, an exponential distribution was the best fit to the pembrolizumab data, while there was no clear best parametric fit for the UK SOC, as all the distributions were very similar. This was seen in the parametric fits (Figure 11 and Figure 12) and AIC/BIC (Table 24). In the base case, the company has chosen the exponential model to extrapolate PFS for pembrolizumab and for consistency, used the exponential model for the UK SOC. Figure 13 shows the two-phase piecewise approach to extrapolate PFS beyond the trial time horizon for pembrolizumab and UK SOC.

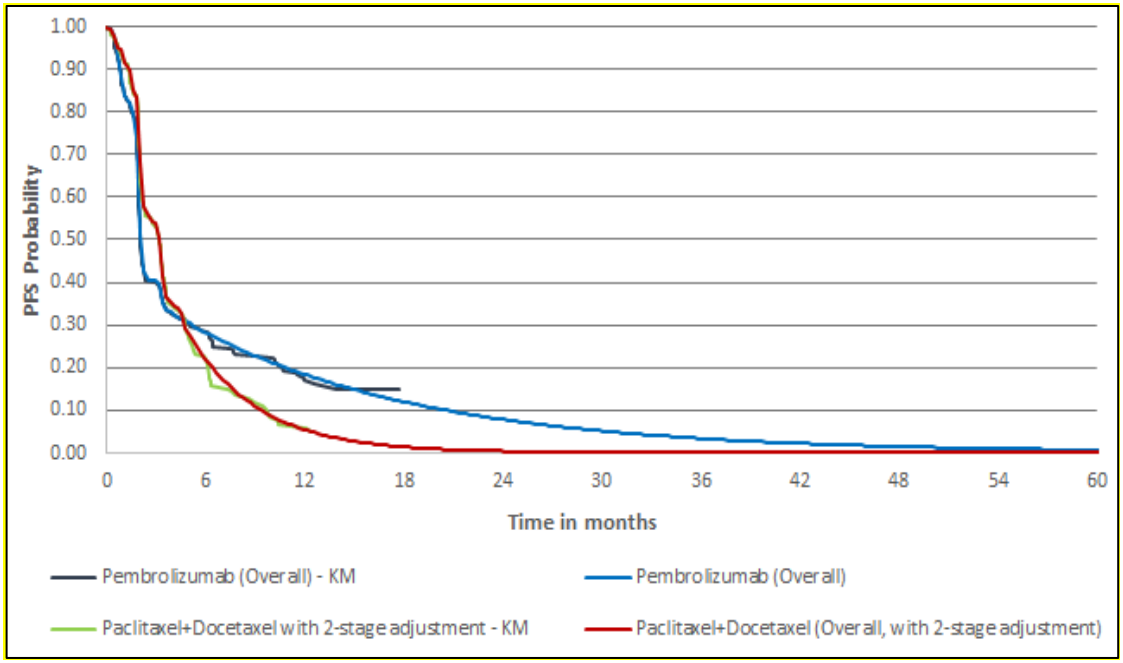


Figure 13: Kaplan-Meier plot for progression-free survival for pembrolizumab and UK SOC, with extrapolations using a 21-week cut-off point

Subgroup analysis 1: Overall survival for PD-L1 strongly positive (CPS≥ 10%)

The first subgroup that the CS considered was that of patients who were strongly PD-L1 positive (CPS≥ 10%). The key results are shown in Table 25. There were 164 patients in this group, with a total of 104 deaths observed. Pembrolizumab has a lower event rate than the control arm (59.5% vs. 66.7%) suggesting the immunotherapy is the superior treatment. Pembrolizumab also has a higher OS at both six and twelve months, but the differences are not statistically significant, likely due to power. The Kaplan Meier diagram also suggests pembrolizumab is beneficial for overall survival, as shown in Figure 14.

Overall, this group has an event rate of 63.4%, which is slightly higher than of the whole population (61.6%) which could suggest the strongly positive group have a higher risk of death, however, the difference is slight. The median OS for both arms is lower in this subgroup than their relative median OS from the whole population, along with the OS at 6 and 12 months, again suggesting a worse prognosis for subjects in the strongly PD-L1 positive subgroup. The HR suggests that pembrolizumab is more effective in this subgroup with HR of 0.57 though the difference in OS suggested no change in effectiveness with a difference in median OS of 2.8 months.

Table 25: Results of PD-L1 CPS ≥ 10% Subgroup Analysis

						Pembrolizumab vs. Control
Treatment	**N**	**Number of events (%)**	**Median OS (months) (95% CI)**	**OS at 6 months in % (95% CI)**	**OS at 12 months in % (95% CI)**	**Hazard Ratio (95% CI)**
Control	90	60 (66.7)	5.2 (4.0, 7.4)	47.2 (36.0, 57.6)	26.9 (17.5, 37.2)	
Pembrolizumab	74	44 (59.5)	8.0 (5.0, 12.3)	58.5 (46.3, 68.9)	39.8 (28.0, 51.3)	0.57 (0.37, 0.88)

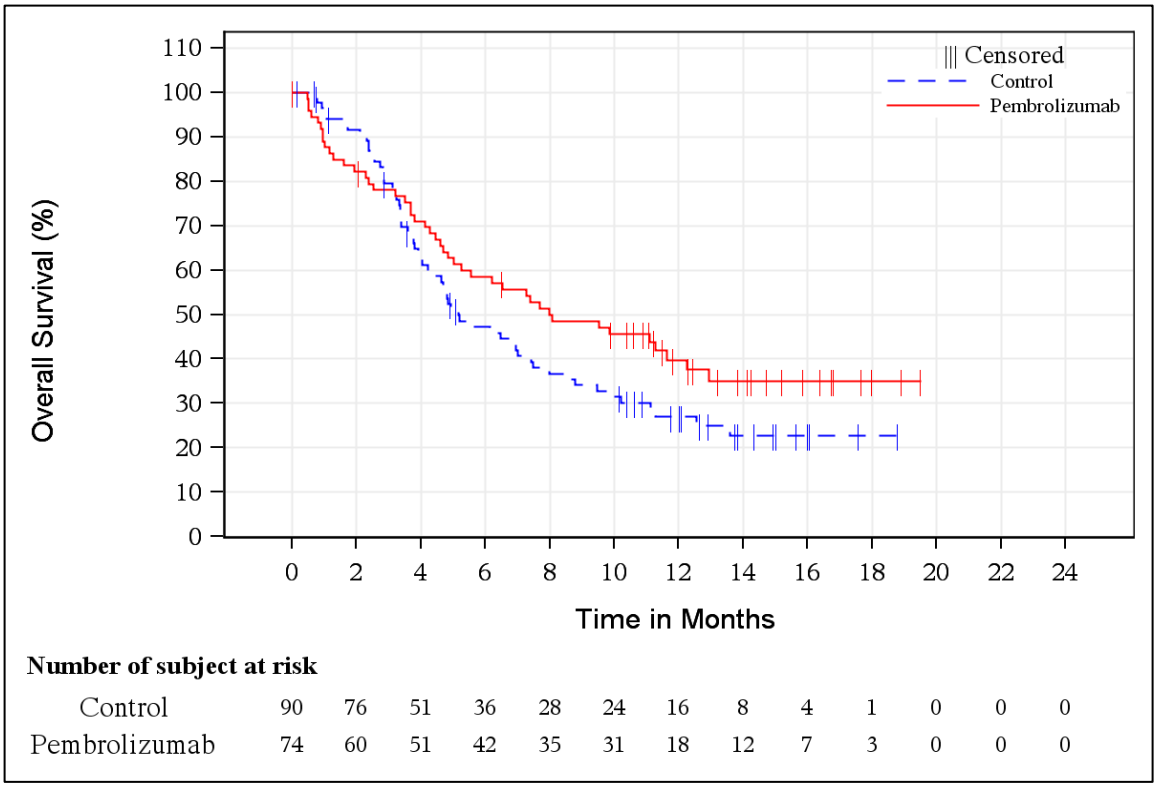


Figure 14: KM plot of PD-L1 CPS ≥ 10% Subgroup

The PD-L1 ≥ 10% subgroup was also investigated using PFS as the outcome measure. The results are shown in Table 26. There was little to distinguish between the groups, with pembrolizumab having a lower median PFS (2.1 vs 3.1 months) but a higher 6 month (24.7% vs 18.5%) and 12 month PFS (17.7% vs 3.7%). The percentage of events was almost identical, both between and arms and compared to the whole trial population, all around 80%. However, the HR has decreased to 0.89 in favour of pembrolizumab, perhaps influenced by the more noticeable difference in tails between the treatment arms, as shown in Figure 15. However, the difference was not statistically significant.

Table 26: Results of PD-L1 CPS ≥ 10% Subgroup Analysis (PFS)

Treatment	N	Number of events (%)	Median PFS (months) (95% CI)	PFS at 6 months in % (95% CI)	PFS at 12 months in % (95% CI)	Pembrolizumab vs. Control Hazard ratio (95% CI)
Control	90	72 (80.0)	3.1 2.2, 3.4)	18.5 (10.6, 28.1)	3.7 (0.7, 10.9)	
Pembrolizumab	74	59 (79.7)	2.1 (1.9, 2.1)	24.7 (15.5, 34.9)	17.7 (9.5, 27.9)	0.89 (0.61, 1.28)

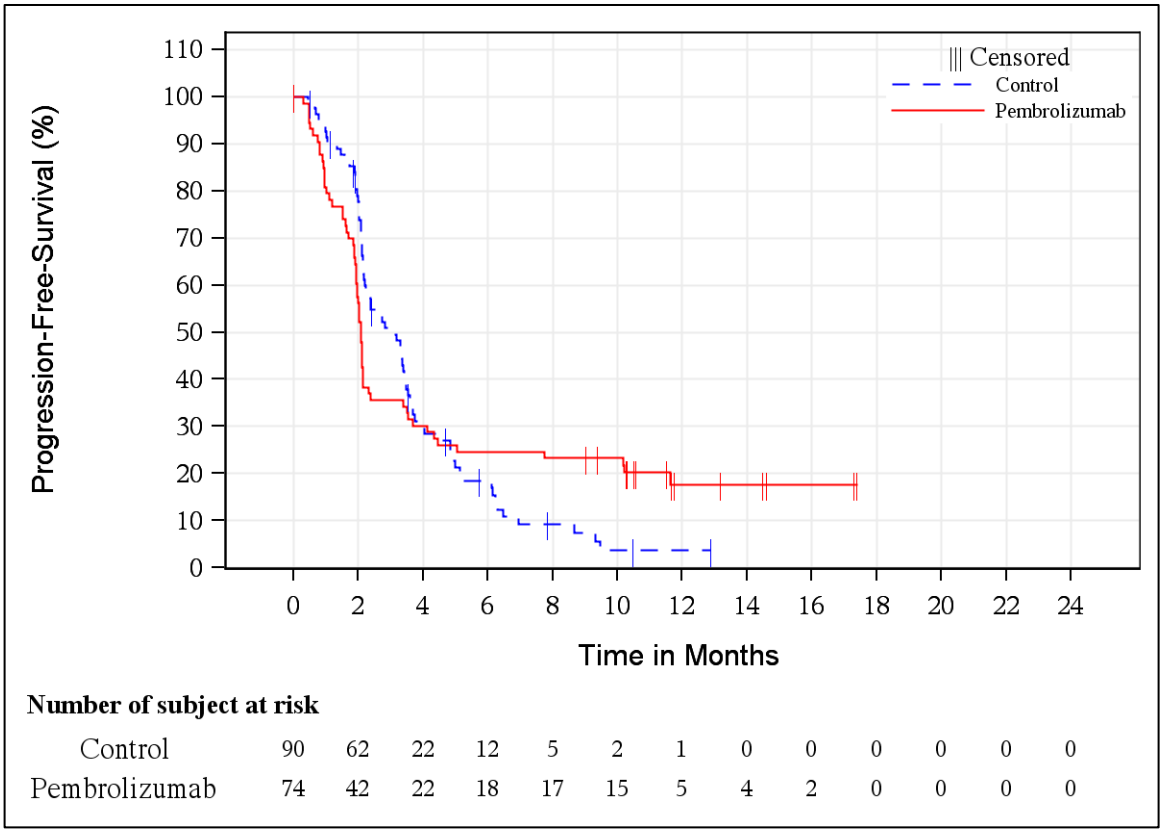


Figure 15: KM plot of PD-L1 CPS ≥ 10% Subgroup (PFS)

Subgroup analysis 2: Overall survival for PD-L1 positive (CPS≥ 1%)

The second subgroup considered by the company was that of patients who were PD-L1 positive (CPS≥1%), and the summary of results is shown in Table 27. A total of 230 patients fell into this category, 120 in the control arm, and 110 in the pembrolizumab arm. One-hundred and forty-two deaths were observed, with a higher event rate in the control arm (67.5% vs. 55.5%). This suggests pembrolizumab is superior in this subgroup, supported by a HR of 0.61, higher OS at 6 (65.9% vs 51.6%) and 12 (46.5% vs 28.8%) months and the Kaplan Meier plot is shown in Figure 16.

The combined event rate of 61.7% showed no difference to that of the whole population (61.6%). The control arm appears to have a slightly worse prognosis in this subgroup, with a lower median OS when compared to the control arm of the entire population. It also has lower OS at 6 and 12 months. In contrast, pembrolizumab appears to be more effective in this subgroup, having a higher median OS by 1 month, and increased 6 and 12 month survival rates when compared to the pembrolizumab arm of the whole trial population. However, all of these differences between the subgroup and trial population are slight and not statistically significant.

Table 27: Results of PD-L1 CPS ≥ 1% Subgroup Analysis

Treatment	N	Number of events (%)	Median OS (months) (95% CI)	OS at 6 months in % (95% CI)	OS at 12 months in % (95% CI)	Pembrolizumab vs. Control Hazard Ratio (95% CI)
Control	120	81 (67.5)	6.9 (4.7, 8.8)	51.6 (41.9, 60.4)	28.8 (20.4, 37.7)	
Pembrolizumab	110	61 (55.5)	11.3 (7.7, 16.0)	65.9 (56.1, 73.9)	46.5 (36.4, 55.8)	0.61 (0.43, 0.86)

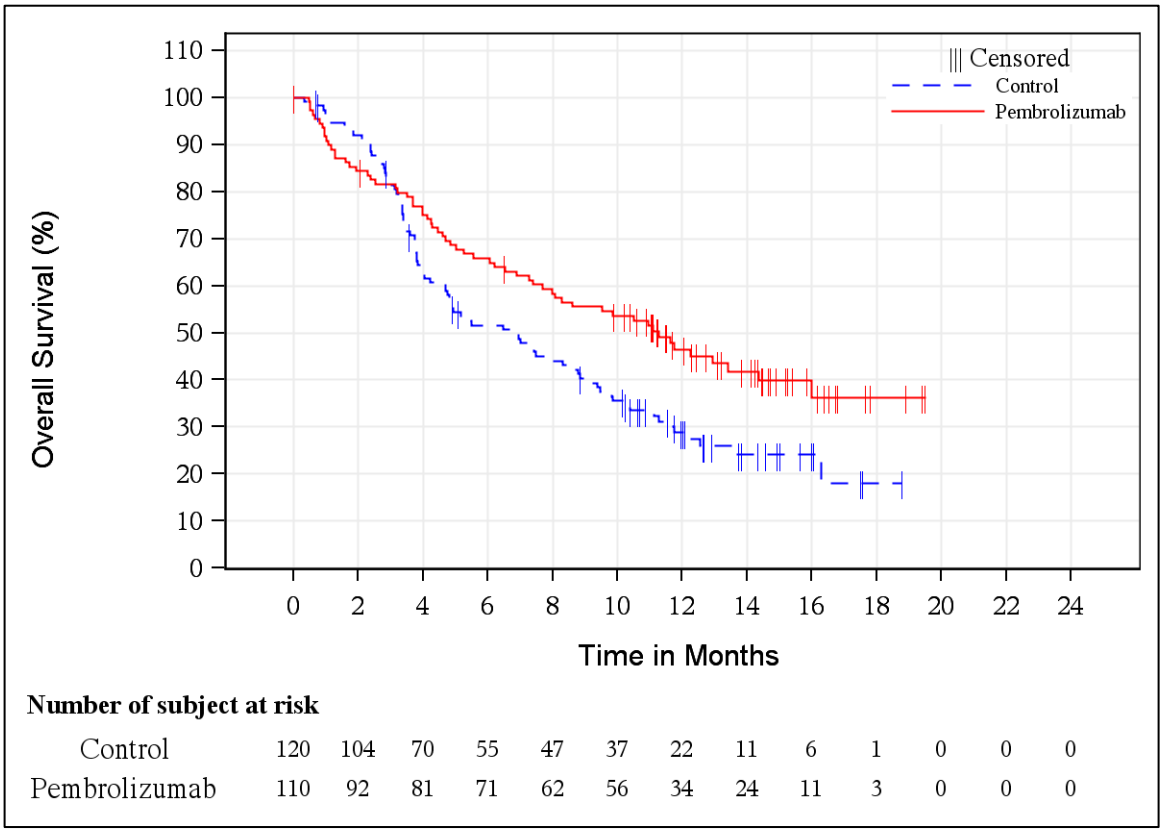
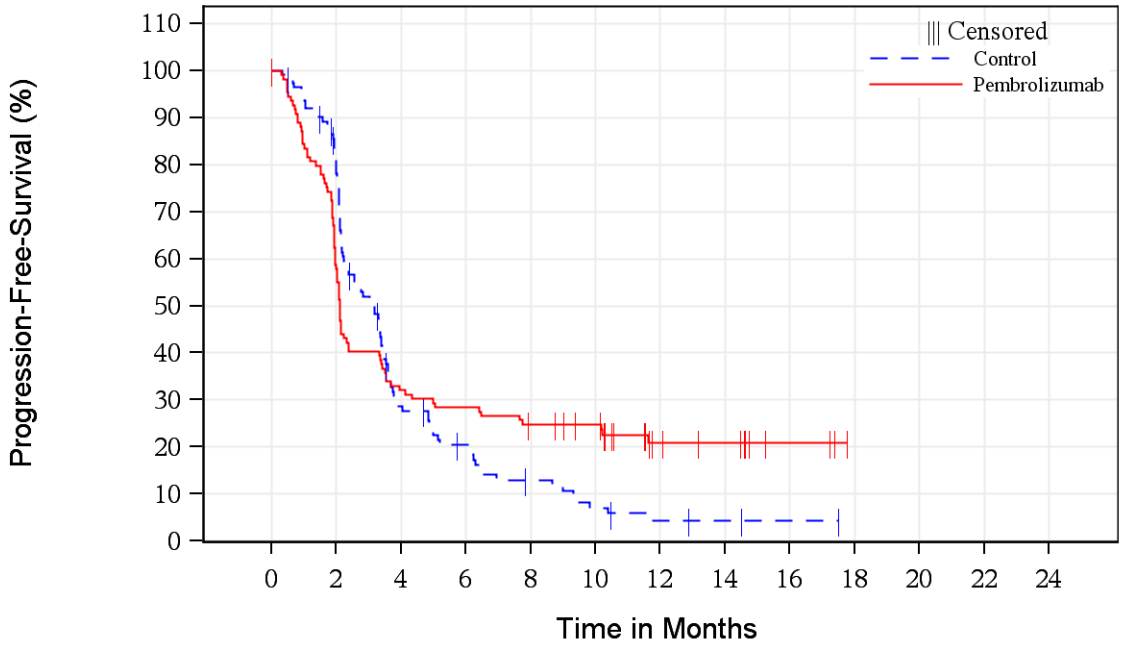


Figure 16: KM plot of PD-L1 CPS ≥ 1% Subgroup

The PFS of the PD-L1 ≥ 1% subgroup was also investigated by the company. The results are shown in Table 28. As before, there is little to distinguish this subgroup from the whole trial population, with a HR of 0.91 weakly favouring pembrolizumab. There is a difference in median PFS of 1.1 months in favour of the control arm, however pembrolizumab appears superior when comparing the 6 month (28.4% vs 20.5%) and 12 month (20.9% vs 4.4%) PFS. For completeness, the KM diagram is shown in Figure 17.

Table 28: Results of PD-L1 CPS ≥ 1% Subgroup Analysis (PFS)

Treatment	N	Number of Events (%)	Median PFS† (Months) (95% CI)	PFS at Months 6 in % (95% CI)	PFS at Months 12 in % (95% CI)	Pembrolizumab vs. Control Hazard Ratio (95% CI)
Control	120	98 (81.7)	3.2 (2.2, 3.4)	20.5 (13.3, 28.8)	4.4 (1.4, 10.4)	0.91 (0.68, 1.24)
Pembrolizumab	110	85 (77.3)	2.1 (2.0, 2.4)	28.4 (20.3, 37.1)	20.9 (13.6, 29.3)	



Number of subject at risk

Control	120	87	29	19	11	6	3	2	1	0	0	0	0
Pembrolizumab	110	64	35	31	26	23	10	8	3	0	0	0	0

Figure 17: KM plot of PD-L1 CPS ≥ 1% Subgroup (PFS)

5.2.6.4 Time on treatment

The company anticipates that the licence would indicate that people would receive treatment until disease progression. As per the KEYNOTE-045 protocol, a stopping rule was implemented whereby people could not receive pembrolizumab for longer than 24 months. Duration of treatment in pembrolizumab and UK SOC was based on time-on-treatment (ToT) data obtained from KEYNOTE-045. In addition to patients switching due to progressive disease, the time-on-treatment data was also influenced by those who discontinued treatment as a result of adverse events and other reasons listed in section 4.3.1 in the CS. The data also contained people who received additional weeks of treatment whilst their disease progression was confirmed.

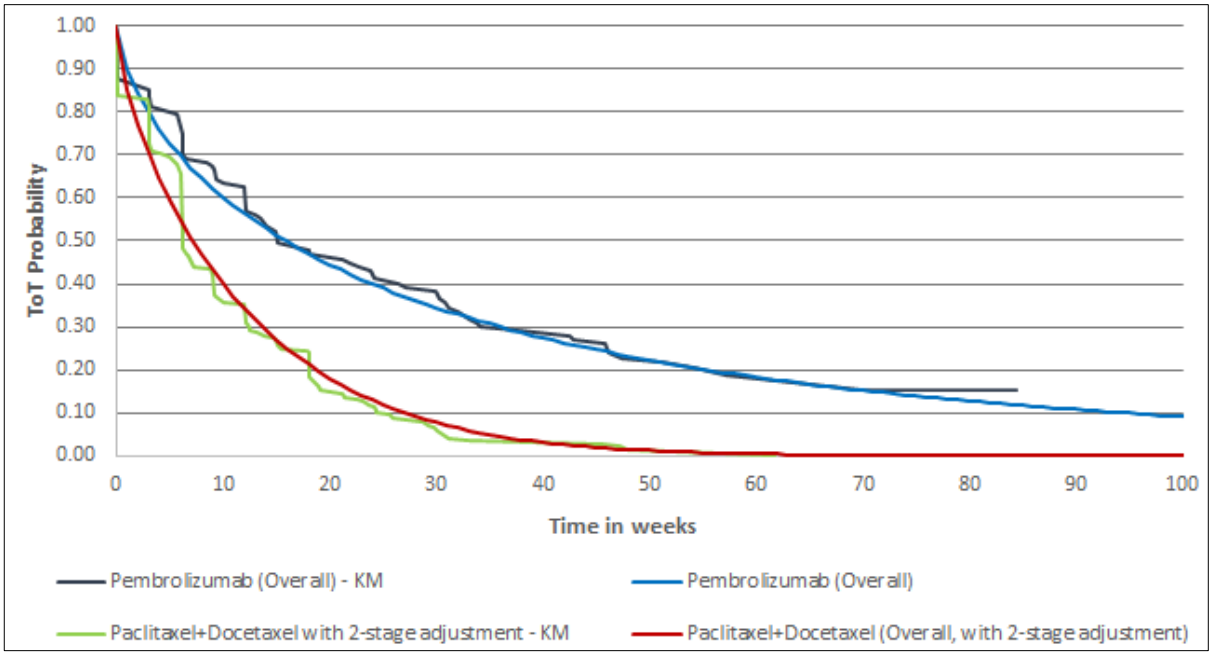


Figure 20: Kaplan-Meier plots for time-on-treatment for pembrolizumab and UK SOC (2-stage adjustment applied)

It appears that the Kaplan-Meier plot for pembrolizumab in Figure 18 is not identical to the Kaplan-Meier plot for pembrolizumab in Figure 20.

In the base case, it was assumed that people received pembrolizumab for a maximum of 35 cycles (24 months) (in line with the KEYNOTE-045 protocol) and a maximum of six cycles (18 weeks) treatment with UK SOC, which is in line with clinical practice in England. Additionally, the company stated that adjustments were made to reflect the proportion of people who received a full treatment dose within each 3-week cycle. Data on dose intensity were analysed and results showed that the average dose intensity for people treated with pembrolizumab and UK SOC was 100.42%, 102.75% (docetaxel) and 100.02% (paclitaxel), respectively. The company considered these estimates not to be realistic in clinical practice whereby dose intensity is likely to be below 100%; hence the company applied a conservative 100% dose intensity in the economic model.

5.2.7 Mortality

General population background mortality was estimated using the latest UK life tables from the Office of National Statistics.[26] In line with common practice, overall survival in the economic model was estimated as the minimum of general population survival (i.e. one minus general population mortality) and trial patients' overall survival.

5.2.7.1 Adverse events

The base-case model included adverse events graded 3+ which occurred in at least 5% of patients (at any grade) in either treatment arm, with two exceptions:

- Grade 2 diarrhoea was also included to be consistent with previous NICE appraisals.[27, 28]
- Febrile neutropenia (with a 2% incidence in the UK SOC arm) was also included as clinicians suggested that this adverse event has significant impact on quality of life and costs and is consistent with recent NICE appraisal.[27]

The incidence of adverse events was taken from the KEYNOTE-045 trial for each treatment arm (see Table 30). It is evident that patients in UK SOC arm experienced more AEs compared to patients in the pembrolizumab arm; according to the ERG's clinical advisor this is expected due to the different toxicity profiles of the drugs. The CS stated that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. However, limiting adverse events to those graded 3 or 4 in severity and affecting ≥5% patients, and without providing count data, means that multiple adverse events suffered by the same patients may be under-represented within the model. For example, a patient may experience an adverse event on multiple occasions, but this will only be modelled as a single occurrence.

For the economic model, the total number of adverse events for both pembrolizumab and UK SOC arms are all applied in the first cycle (in the first 7 days), without any further consideration of adverse events in the duration of the model. Given the toxicity profile of the comparator, this approach in the CS model may have under-estimated costs and over-estimated benefits associated with the UK SOC treatment arm.

Table 30: Grade 3+ AE rates for AEs included in the economic model based on KEYNOTE-045 data (CS Table 72)

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for UK SOC (Grade 3+)
Anaemia	8.3%	11.9%
Febrile neutropenia	0.0%	4.76%
Neutropenia	0.0%	11.9%
Diarrhoea	5.3%	5.36%
Fatigue	3.8%	5.95%
Neutrophil count decreased	0.4%	14.29%
White blood cell count decreased	0.4%	5.95%

Table 31: Mean utility values

	Pembrolizumab	Control (paclitaxel, docetaxel and vinflunine)	Pembrolizumab and control pooled (used in CS)	UKSOC (paclitaxel and docetaxel)	Pembrolizumab and UKSOC pooled	NICE TA272[17]
Time to death based (days)						
≥ 360	0.765	0.804	0.778	0.823	0.780	-
(180 to 360)	0.686	0.699	0.693	0.673	0.680	-
(90 to180)	0.566	0.612	0.590	0.595	0.578	-
(30 to 90)	0.457	0.446	0.451	0.414	0.435	-
<30	0.336	0.311	0.325	0.337	0.337	-
Progression based						
Progression-free	0.757	0.698	0.731	0.709	0.741	0.65
Progressed	0.680	0.565	0.641	0.554	0.647	0.25

The company points out that, due to the timing of the questionnaires (administered until drug discontinuation or at the 30-day-safety follow-up visit), it is unlikely that the utility score after progression captured the expected decline of health prior to death. Therefore, this led to an overestimation of the utilities in post-progression health state." The company found no significant differences in EQ-5D at baseline, and so decided to use pooled utility values for both arms. The ERG notes that statistically significant differences were observed in the progression based values (see CS table 75),that the trial was not designed with sufficient power to detect significant differences between the time-to-death based utilities. In addition, the choice of groupings of time periods was not strongly justified. (page 190 of CS). . Hence the ERG explored using un-pooled utility values in a scenario analysis.

Furthermore, the ERG noted that treatment-specific utility values are lower for pembrolizumab compared to UK SOC when measured based on time to death, except for the [180 to 360) and [30 to 90) categories. However, utility values were considerably higher for pembrolizumab compared to UK SOC when measured based on progression status. The ERG found this surprising, in particular the higher time-to-death based utility values for the UK SOC arm given its worse toxicity profile. The ERG does not have a particular explanation for such disparity, apart from the potential lack of accounting for treatment switching when estimating treatment-specific utility values and prolonged survival of unhealthy participants in the pembrolizumab arm. Due to this inconsistency, the ERG have also used pooled utility values in a scenario analysis.

In the CS base-case analysis, pooled utility values based on time to death were used. Estimated life years were based on time to death (i.e. categorising life years based on the 5 time to death points (see Table 31)) and then assigned the respective utility values in each life year category to estimate QALYs. To the best of the ERG's knowledge, this approach is not common in practice, and has only been used for previous studies investigating melanoma treatments and NSCLC.[29, 30 31]. The ERG has concerns over the effectiveness of the time-to-death based utility values due to the lack of strong justification of the categorisation of the time periods. In addition, the company clarified that the average scores were not weighted per person and were averaged across from all eligible questionnaires. The ERG feels that this could lead to overestimation of the utility values, due to a possible relationship between non-response and health status. Due to the uncertainty associated with the survival based utility estimates, the ERG chose to use progression based estimates in their scenario and base case analyses.

A literature search conducted by the company yielded 18 comparable HRQoL studies, however none presented utilities as a function of time to death and therefore were not included in any sensitivity analysis by the company. A previous TA[17] reported related utilities for comparison which are shown in Table 31, though they were not specific to urothelial cancer. The lower values seen in Table 31 (despite the CS stating the utility values in KEYNOTE-045 are in line with these in TA272) support the view that the post-progression score is overestimated by the CS data. It is also plausible that the time to death utilities are also overestimated as a result of the data collection. In a scenario analysis, the ERG will explore the impact on the incremental cost-effectiveness ratio (ICER), by using the utility values reported in TA272.

Please note that there is typo in CS Table 77, where the mean value for time to death in days ≥ 360 should be 0.778 (as used in the model and as reported in CS Table 74) as opposed to 0.761.

Disutilities for ageing and adverse events were included in the model and are shown in Table 32. The decision to assume no further decline past the age of 75 years is based on Kind et al. (1999), who did not report any change in EQ-5D utility score beyond age 75 years (i.e. utility value was constant for anyone over the age of 75 years).[32] There is the possibility that the manner in which the company derived the age disutilities may have underestimated the effect of ageing on quality of life. More recently, Ara and Brazier (2010) have provided an algorithm that estimates general population utility scores as a function of age and gender.[33] The ERG believes that using Ara and Brazier[33] to derive age-related disutilities is more appropriate as: (a) the study by Kind et al. (1999) is outdated; and (b) the algorithm can provide age-related utility decrements for people beyond the age of 75. The ERG will present updated results in the scenario analysis using updated disutility values.

Adverse event disutility values were applied only in the first cycle of the economic model and were not considered for the remaining time horizon of the model. This approach may have overestimated the resulting QALYs from both pembrolizumab and UK SOC. The ERG notes that adverse event disutilities were not accounted for in related STAs.[17]

Whilst the frequency of adverse events suggests that pembrolizumab has a favourable profile, the adverse event disutility suggests otherwise. If the adverse event disutility is broken down by arm it can be seen that adverse events have a much greater impact on quality of life in the pembrolizumab arm, as shown in Table 32. The ERG presents results based on using separate adverse event utility values for each arm in the scenario analysis.

Table 32: Disutility values

Disutility type	Inc. vinflunine patients	Exc. vinflunine patients	Details
Age	0.0045	Not applicable	Per year increase in age from 65 to 75.

Adverse event (pooled)	0.117	0.137	Average disutility of a Grade 3+ AE, with a duration of 13.9 days per event.
Adverse event pembrolizumab arm	0.195	0.195	Average disutility of a Grade 3+ AE, with unknown duration.
Adverse event control arm	0.043	0.058	Average disutility of a Grade 3+ AE, with unknown duration.

ERG summary

- Utility values used in the economic model were generated from KEYNOTE-045 trial data. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results
- The ERG has reservations about using separate utilities for each treatment arm, due to unexpected estimates.
- Estimating life years and subsequent QALYs using utility values based on time to death results is an unusual method. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC.
- The company provided utility values without vinflunine after clarification.
- Disutilities were also used for the effect of adverse effects, with the values pooled for both arms.

5.2.9 Resources and costs

5.2.9.1Intervention and comparator costs

All interventions were administered once per three week cycle. The total costs of pembrolizumab consisted of drug costs and administration costs with a single dose of 200mg typically administered intravenously over a 30 minute time period. The administration cost estimate was conservative assuming an administration period of 60 minutes (Healthcare Resource Group (HRG) code SB12Z).[34] Costs are shown in Table 33.

Table 33: Drug and administration costs

Costs	Dose per administration	Cost per mg	Cost per dose	Administration cost per dose	Total cost per dose	Source
Pembrolizumab	200mg	£26.30	£5260.00	£253.32*	£5513.32	MSD
Docetaxel	75mg/m^2	£0.13	£18.09	£253.32*	£271.41	eMIT
Paclitaxel	175mg/m^2	£0.07	£23.81	£406.63#	£430.44	eMIT
UK SOC	-	-	£20.88	£328.44	£349.32	CS

* HRG code: SB12Z – deliver simple parenteral chemotherapy at first attendance; # HRG code SB14Z – deliver complex parenteral chemotherapy at first attendance; eMIT – electronic market information tool

The estimated monitoring and disease management costs per week were £154.61 and £136.07 (not per month as the CS states on p209), respectively for the pre-progression and post-progression health states.

Adverse Events (AEs)

The costs presented for adverse events were reported in Table 84 in the CS and are replicated in Table 34. The majority of costs in the CS were obtained using NHS reference costs (2015-2016).[34] When costs were not available from the NHS reference list, costs were acquired from other sources such as NICE DSU Reports,[37] and inflated using the appropriate indices.[36] Also included in the table are costs for adverse events from other recent publications, which demonstrates the uncertainty in costs. Whilst some of this may be explained by the different health areas and the varying severity of adverse events in each study, it is likely that there is still potential for under- or over-estimation of costs.

Table 34: Adverse event unit costs

Adverse event	Costs used in CS	Costs used by other publication*
Anaemia	£1,315.94	-
Febrile neutropenia	£2,641.80	£3,538.00 [17] £7,066.63 [38] £7352.54 [39]
Neutropenia	£70.80	£1733.22 [38]
Diarrhoea	£919.84	£8.59 per day [40] £1050.76 [38]
Fatigue	£2,499.99	£2233.40 [38]
Neutrophil count decreased	£70.80	-
White blood cell count decreased	£70.80	-
Hypophosphataemia	£1,212.89	-
Pneumonia	£1,751.08	-
Rash	None	£4.30 per day [40] £109.77 [38]
Nausea/vomiting	None	£1050.76 [38]
Dyspnoea	None	£97.00 - £139.00 [40]

* These costs have not been inflated to current price year for the economic model

Only adverse events of severity grade 3 or greater with a prevalence of >5% in at least one arm were included in the economic analysis. Following a comparison of data presented in Tables 54 and 55 of the CS, the ERG noticed 26% of events in the control arm listed in both tables were

deemed unrelated to treatment, compared with 56% for pembrolizumab. Unit costs and incidence of additional adverse events that cancer patients typically exhibit, such as dyspnoea, hypertension, and abdominal pain were not considered in the CS model.

Adverse event costs were applied only in the first cycle of the economic model in the CS, without considering their impact in the remaining time horizon of the model; however, this is in line with previous STAs that the ERG have been involved with. However, this approach may underestimate adverse event costs associated with both pembrolizumab and UK SOC arms.

Terminal care costs

Terminal care costs were included in the economic model in the form of a one-off cost for all patients who transitioned to the death health state. The CS acknowledges the limited data available for terminal care in the urothelial cancer field. Estimates were calculated in line with a previous HTA report.[41]

Resource use estimates were obtained from both Marie Curie reports[42] and NICE guidance.[17, 43] Cost data was taken from a combination of the latest NHS reference costs and the PSSRU Report 2016.[34, 36] The total cost of terminal care per patient was £7252.82 for both treatment arms.

ERG Summary

- Drug dosing schedules and costs were provided by the company.
- No drug wastage costs were included.
- UK SOC treatment costs were estimated based on the KEYNOTE-045 trial docetaxel-paclitaxel administration ratio instead of the UK market administration ratio.
- Adverse event costs may have been underestimated in the economic model due to: (a) excluding some common adverse events that occur in cancer patients; (b) considering adverse events only in the first cycle of the model.

Table 50: Adverse event utility values excluding vinflunine patients for each specific treatment arm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death						
UK SOC	£20,938	1.59	1.08	-	-	-
Pembrolizumab	£60,053	2.71	1.72	£39,115	0.64	£60,714
Progression based						
UK SOC	£20,938	1.59	0.86	-	-	-
Pembrolizumab	£60,053	2.71	1.65	£39,115	0.79	£49,652

Table 51 shows the sensitivity analysis performed when using the most recent adverse event costs and again the impact of these costs were negligible (ICER decreased by £866/QALY).

Table 51: Adverse event costs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Using AE costs from alternative sources (most recent publication used where multiple options possible)*						
UK SOC	£21,638	1.59	1.10	-	-	-
Pembrolizumab	£60,014	2.71	1.95	£38,376	0.85	£44,967

***ERG unable to add costs of rash, nausea/vomiting or dyspnoea**

UK SOC	£17,563	1.09	0.72	-	-	-
Pembrolizumab	£57,457	2.34	1.67	£38,894	0.94	£42,343

ERG preferred base-case analysis

Our overall preferred ERG base-case is presented in Table 54. Changes include:

- Exclusion of vinflunine patients from estimation of utility values.
- Estimation of age-related utility decrements based on Ara and Brazier (2010).
- Use of utility values based on progression status.
- Use of pooled utility and adverse event disutility values.
- Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel.
- Use a cut-off point of 24 weeks for the overall survival modelling approach.
- Use a log-logistic distribution for overall survival modelling for pembrolizumab and UK SOC.

Table 54: ERG preferred base-case analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£17,439	1.09	0.73	-	-	-
Pembrolizumab	£57,457	2.34	1.51	£40,017	0.78	£51,235

As shown in Table 54, for the ERG preferred base-case the ICER is slightly higher at £51,235 per QALY compared to the CS base-case analysis ICER of £45,833 per QALY.

5.3.1 ERG's preferred base-case model using different parametric distributions for overall survival

Due to the paucity of published information on the long-term overall survival for people with advanced or metastatic urothelial cancer, the ERG considers there to be some uncertainty in the extrapolations. It can be seen from Figure 7, Figure 8, Table 22 and Table 23 that the three-, five- and ten-year overall survival estimates differ based on the parametric curve used, and this will have an impact on the life years gained and QALYs gained. It should be noted that the

concerns regarding the comparability of people in the KEYNOTE-045 trial with those from Cancer Research UK.

The CS model incorporates utility scores based on time to death, which results in a relatively unusual method to estimate life years (based on death incidence) and subsequent QALYs. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC arms relative to life years based on progression status. The ERG believes that using utility scores based on progression status is a more appropriate method to estimate life years and subsequent QALYs.

The base-case analysis included data for patients receiving vinflunine in the estimation of utility values, which is currently not recommended in England. The ERG believes that such patients should have been excluded from the analysis.

The age-related utility decrements are estimated from an outdated study that does not allow for the incorporation of decrements for patients aged more than 75 years old. The ERG believes that this is a limitation that possibly overestimates QALYs in both treatment arms.

In the base-case analysis, pembrolizumab was compared to UK SOC based on the distribution of the regimens observed in KEYNOTE-045. The ERG believes that cost of UK SOC should be based on the UK market share of docetaxel and paclitaxel.

The ERG presented a preferred base-case analysis taking into account all issues raised in his chapter. Our preferred analysis increased the ICER to £51,405 per QALY.

When interpreting these results, it is important to consider the impact of these key sources of uncertainty in the ICER, and the impact any alternative assumptions would make.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Alterations to the base-case assumptions were made by the ERG as identified in Chapter 5. Details of the alterations can be found in Appendix 11.1. The impact on each change individually on the base-case analysis is shown in Table 59.

Table 59: ERG re-estimation of cost-effectiveness

	ΔC	**ΔQALY**	**ΔC/QALY**	**Ratio[+]**
Pembrolizumab vs UK SOC				
CS base-case model	£39,115	0.85	£45,833	-
ERG models				
Exclusion of vinflunine patients from estimation of utility values	£39,115	0.86	£45,712	0.997
Use utility values based on progression status	£39,115	0.72	£54,665	1.193
Estimation of age-related utility decrements based on Ara and Brazier (2010)	£39,115	0.84	£46,673	1.018
Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel	£39,239	0.85	£45,978	1.003
Use a log-logistic distribution for OS modelling	£37,029	0.62	£59,246	1.293
Use a cut-off point of 24 weeks for OS modelling	£42,693	1.25	£34,168	0.745
ERG preferred base-case analysis	**£40,017**	**0.78**	**£51,235**	**1.118**

7. END OF LIFE

On page 170 of the main CS, the company have presented a table (Table 61) regarding end-of-life criteria. There are two main criteria to fulfil for the appraisal of end of life treatments:[44]

1. the treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
2. 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; and

Regarding criterion 1, the company has indicated the median OS is lower than 24 months in patients with advanced/metastatic urothelial cancer following platinum based chemotherapy. The statement was supported by two references that were not included in the background section and for which no details were provided of the estimates of life expectancy in these two studies. In the clarification response document, the company has responded that the estimated life expectancy of patients with advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy is estimated to be between 6.5 and 9 months based on the references provided.[45, 46]

In KEYNOTE-045, the median OS was 7.4 months in the SOC arm and between [redacted] and [redacted] months in the UK SOC arm after adjustment for treatment switching. In terms of life expectancy, survival extrapolations for the UK SOC arm indicate a life expectancy of 1.59 years with the company's base-case model and 1.09 years with the ERG's preferred base-case model. Therefore, the ERG agree that pembrolizumab fulfils criterion 1 for end-of-life treatment.

Regarding end-of-life criterion 2, the company indicated that pembrolizumab offers an extension of life of at least 3 months compared to UK SOC both in terms of median OS (10.3 months vs. 6.9 months for pembrolizumab and UK SOC respectively) and months of life gained (32.5 months vs. 19 months for pembrolizumab and UK SOC respectively). The 3.4 months median OS gain is based on the median OS for the UK SOC after adjustment for treatment switching using the 2-stage model. With other adjustment methods, the median OS gain would fluctuate between [redacted] and [redacted] months. As previously indicated, the results comparing pembrolizumab and UK SOC must be viewed with caution since they correspond to a post-hoc analyses. The most robust estimate of the median OS gain should be taken from the entire population from KEYNOTE-045 (+2.9 months) although the ERG appreciates that one of the treatments of the

SOC arm (vinflunine) is not currently available within the NHS. In terms of life-year gained, the company's estimate is 13.5 months while the ERG's estimate is 15 months. Overall, the ERG agree that pembrolizumab fulfils criterion 2 for end-of-life treatment.

8. INNOVATION

On page 31 of the CS, the company have presented a statement on how pembrolizumab could represent a step-change in the management of people with advanced/metastatic urothelial cancer after progression or recurrence following platinum-based chemotherapy. Unlike conventional chemotherapies, pembrolizumab belongs to an emerging class of immunotherapy drugs whose mechanism of action consists of increasing the ability of the immune system to kill cancer cells. There is a growing number of immunotherapies which are being evaluated in many cancer types, both in solid tumours and in hematologic malignancies. Some of these, like pembrolizumab, or nivolumab, are already licensed in cancers other than urothelial cancers.

In the innovation section, the company have emphasised the high unmet need for patients with advanced/metastatic urothelial cancer after platinum-based regimen, and indicated that pembrolizumab has demonstrated significant survival benefit and improved tolerability profile compared to conventional chemotherapy. The ERG agree with the company's statement on the high unmet need within the scoped population. The ERG also agree on the significant survival benefit with pembrolizumab although longer-term survival confirmatory analyses will be needed to more accurately evaluate the benefit on life expectancy. The ERG also appreciate the fact that pembrolizumab has a better safety profile compared to conventional cytotoxic chemotherapy.

	Progression based utilities	"Utility sheet" – change cells D25 to 0.1950 and E25 to 0.058 "Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2 & approach of evaluating utility tab to 1 "Utility sheet" – change cells D25 to 0.1950 and E25 to 0.058
Table 51: Adverse event costs	Using AE costs as provided in Table 34 of ERG report.	"CostInputs" sheet change cells: F31 → 7352.54; F32 →1733.22; F33 →119.40 & F34 →2233.40
Table 52: Estimation of cost of UK SOC based on UK market share of docetaxel and paclitaxel	Source of distribution of patients in paclitaxel and docetaxel arm	"Settings sheet" – change source of distribution of patients in paclitaxel and docetaxel arm tab to 2
Table 53: Changing overall survival functions	Choice of parametric function for OS curve fitted to KNO45 data: Log-logistic model 24 week cut-off	 "Settings sheet" – change OS of pembrolizumab and OS of control arm to Log logistic (tab 4) "Settings sheet" – change cut-off time point to week 24 (tab 2)

Table 54: ERG preferred base-case analsysis	Exclusion of vinflunine patients	"Settings sheet" – change utility measure tab to 2
	Progression based utilities	"Settings sheet" – change approach of evaluating utility tab to 1
	Age-related decrements: 1. Inclusion of proportion of males 2. Estimate utility values for general population based on algorithm in Ara and Brazier [33] 3. Estimate utility decrements relative to baseline age	1. "GenInputs" sheet – cell F23 2. "Utility" sheet – cells D162 to D243 3. "Utility" sheet – cells E162 to E243 and G162 to G217 and leave cell J162 blank
	Source of distribution of patients in paclitaxel and docetaxel arm	"Settings sheet" – change source of distribution of patients in paclitaxel and docetaxel arm tab to 2
	Log-logistic model	"Settings sheet" – change OS of pembrolizumab and OS of control arm to Log logistic (tab 4)
	24 week cut-off	"Settings sheet" – change cut-off time point to week 24 (tab 2)