NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary from** Bristol-Myers Squibb Pharmaceuticals Ltd

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Action Bladder Cancer UK
   b. Fight Bladder Cancer

4. **Evidence Review Group report** prepared by ScHARR

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**
   a. Technical engagement response form
   b. Technical engagement response to additional questions 1
   c. Technical engagement response to additional questions 2

7. **Technical engagement responses and statements from experts:**
   a. James Catto – clinical expert, nominated by Bristol-Myers Squibb Pharmaceuticals
   b. Syed A Hussain – clinical expert, nominated by Bristol-Myers Squibb Pharmaceuticals
   c. Kevin Gorman – patient expert, nominated by Action Bladder Cancer UK
   d. Lydia Makaroff – patient expert, nominated by Fight Bladder Cancer

8. **Technical engagement responses from consultees and commentators:**
   a. NCRI-ACP-RCP-RCR

9. **Evidence Review Group critique of company response to technical engagement** prepared by ScHARR

Post change in licence documents

10. Company updated submission – overview

11. Company updated survival analysis for PD-L1 subgroup

12. Company updated CE analysis for PD-L1 subgroup

13. Company updated ITC for PD-L1 subgroup

14. Evidence Review Group – response to technical engagement updated for change in licence

15. Evidence Review Group – addendum (PD-L1 ITC response)

16. Evidence Review Group corrected cost-effectiveness analysis

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for treating resected high-risk invasive urothelial cancer

ID2694

Document A

Company evidence submission summary for committee

Bristol Myers Squibb Pharmaceuticals Ltd confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

June 2021

File name	Version	Contains confidential information	Date
	1	**Yes**	**27 April 2021**
Revised submission	**2**	**Yes**	**30 June 2021**

Contents

Tables and figures

List of tables

List of figures

Abbreviations

AE	adverse event
BSC	best supportive care
CI	confidence intervals
CrCl	creatinine clearance
CSR	clinical study report
DBL	database lock
DFS	disease-free survival
DMFS	distant metastasis-free survival
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
LRDFS	locoregional disease-free survival
LYG	life years gained
MIBC	muscle invasive bladder cancer
MIUC	muscle invasive urothelial carcinoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NUTRFS	non-urothelial tract recurrence-free survival
OS	overall survival
PAS	patient access scheme
PD-1	programmed death-1
PFS2	progression-free survival on next line systemic therapy
QALY	quality-adjusted life year
RC	radical cystectomy
UTUC	upper urinary tract urothelial carcinoma

Submission summary

A.1 Health condition

Urothelial carcinoma is cancer of the cells of the inner lining of the bladder and upper urinary tract.[1,2] There were 8,686 new bladder cancer diagnoses in England in 2017[3] and 1,288 of upper urinary tract urothelial carcinoma (UTUC).[4]

Muscle invasive urothelial cancer (MIUC) encompasses muscle invasive bladder cancer (MIBC) and UTUC. Around 50% of bladder cancer patients present with muscle invasive (Stage II to IV) disease, of which around 24% undergo radical resection with curative intent.[5] However, without perioperative (neoadjuvant or adjuvant) therapy, approximately half will experience recurrence.[6] For UTUC, reported 3-year disease-free survival (DFS) for UK patients after radical surgery is 46% with routine surveillance and 71% with adjuvant chemotherapy.[7]

High risk of recurrence is indicated by factors including lymph node involvement; residual T2 disease; T3 disease; and non-receipt of neoadjuvant therapy.[8-11]

Recurrence, particularly outside of the urothelial tract, is associated with poor prognosis, and prevention of recurrence is therefore critical in improving survival. Disease-specific survival after recurrence is approximately 14-22 months.[12] The great majority of recurrences occur in the first 3 years after surgery[12-14] and late recurrences are uncommon.[12]

Cisplatin-based neoadjuvant chemotherapy is standard of care for cisplatin-eligible patients,[8,15] but is not suitable for less fit patients. There is currently no alternative active adjuvant treatment to reduce recurrence, except in the small proportion of patients who are cisplatin-eligible and did not receive neoadjuvant cisplatin. There is therefore a high unmet need for new adjuvant treatment options for patients with MIUC who are at high risk of recurrence.

A.2 Clinical pathway of care

The treatment pathway for MIBC is presented in Figure 1, adapted from the National Institute for Health and Care Excellence (NICE) Guideline NG2.[8,15] NICE guidelines state that neoadjuvant cisplatin-based chemotherapy should be offered to eligible

patients before radical cystectomy (RC). however, many patients cannot receive neoadjuvant chemotherapy because they either refuse cisplatin-based therapy or are cisplatin-ineligible.

Eligibility for cisplatin is based on fitness and comorbidities. MIUC is predominantly a disease of older people, and many patients are considered ineligible; common reasons include poor Eastern Cooperative Oncology Group (ECOG) performance status, creatinine clearance (CrCl) <60 mL/min, presence of significant hearing loss or peripheral neuropathy, and heart failure.

Adjuvant treatment options are limited to routine surveillance, or adjuvant cisplatin for those patients who did not receive neoadjuvant cisplatin and are fit and willing to receive cisplatin-based therapy after RC. Thus, cisplatin-ineligible patients currently have no options for perioperative therapy. In addition, a number of studies report no significant improvement in overall survival (OS)[14,16] or DFS[17] with adjuvant cisplatin chemotherapy, highlighting the need for new adjuvant treatment options regardless of eligibility for cisplatin.

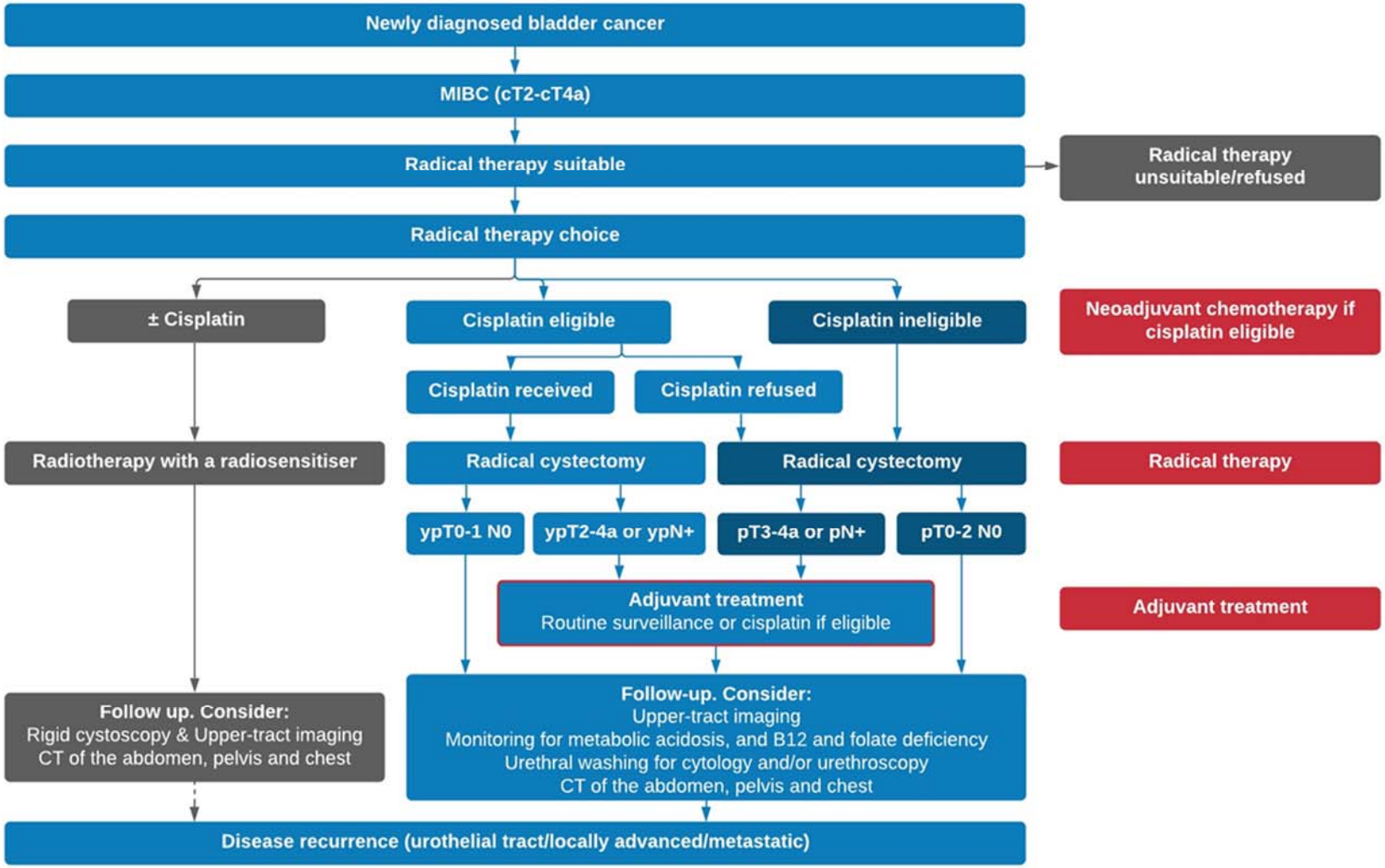


Figure 1. Detailed treatment pathway for muscle invasive bladder cancer in the UK

Nivolumab is indicated in the adjuvant setting for high-risk patients. Adapted from NICE Guideline NG2, with additional input from UK expert clinician[8,15]

There are no specific UK guidelines for the treatment of UTUC. Guidelines for the treatment of high-risk non-metastatic UTUC are available from the European Association of Urology (EAU), summarised in Figure 2. Localised adjuvant chemotherapy (instillation into the bladder) is recommended.[2] UK clinical experts reported that adjuvant chemotherapy would be offered to cisplatin-eligible high-risk UTUC patients following the results of the UK-based POUT trial, which found that adjuvant cisplatin-based chemotherapy in UTUC patients significantly improved DFS compared with surveillance.[7] Some patients in this trial received carboplatin-based treatment, but this was not associated with a significant increase in DFS.

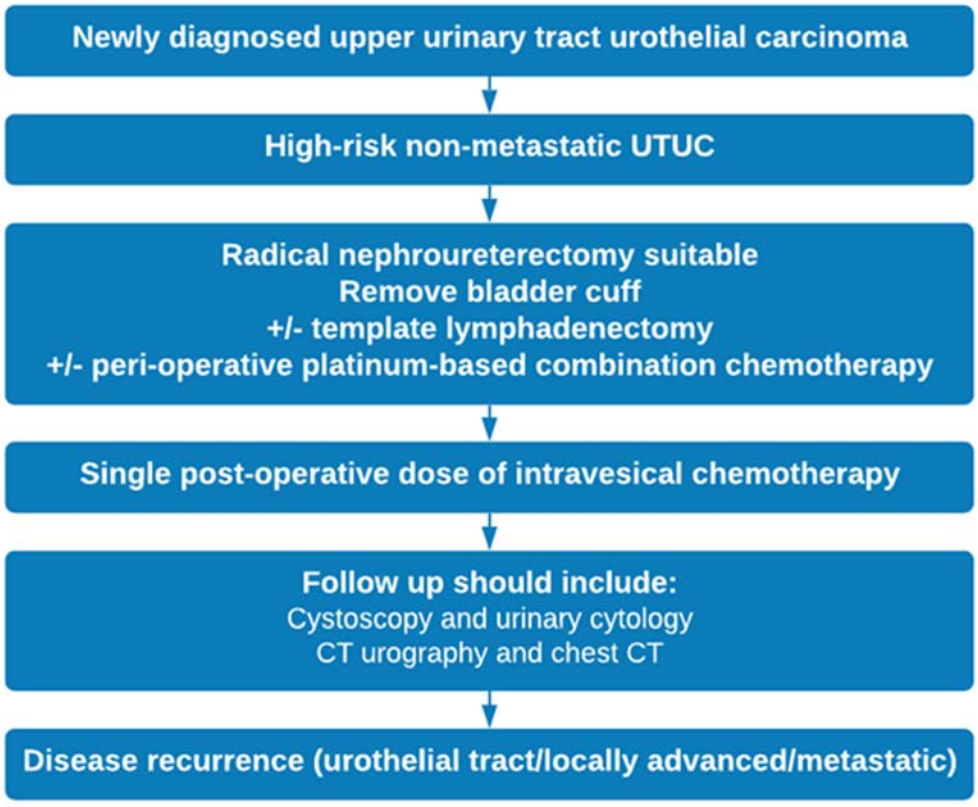


Figure 2. Summary of EAU guidelines for the surgical management of high-risk non-metastatic upper urinary tract urothelial carcinoma

Adapted from Roupret et al., 2016[2]

A.3 The technology

Table 1. Technology being appraised – B.1.2 (page 14)

UK approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Nivolumab is a human immunoglobulin G4 monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[18] In the adjuvant setting nivolumab acts by enhancing the patients' own immune system to recognise and destroy individual tumour cells at an early stage. Further details are provided in Section B.1.3.6.1.
Marketing authorisation/CE mark status	A regulatory submission was made to the EMA on the [redacted]. The earliest anticipated CHMP opinion is expected in [redacted] and anticipated approval in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The proposed indication for nivolumab for the treatment of urothelial cancer is as follows: *"Opdivo monotherapy is indicated for the treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of IUC"* Nivolumab is licensed for the following indications: • as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy • as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

	• in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation • as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults • in combination with carboplatin for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma • as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults • in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma • in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma. • as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin • as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy • as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy
Method of administration and dosage	240 mg IV every 2 weeks over 30 minutes for a maximum of 12 months[18]
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	**List price:** £2,633.00 per 240 mg (24 mL) vial; £1,097.00 per 100 mg (10 mL) vial; £439.00 per 40 mg (4 mL) vial.[19] Average cost/dose: £2,633.00 **With patient access scheme (PAS):** [redacted] per 240 mg (24 mL) vial; [redacted] per 100 mg (10 mL) vial; [redacted] per 40 mg (4 mL) vial. Average cost/dose with PAS: [redacted]
PAS (if applicable)	A confidential simple discount PAS for nivolumab of [redacted] is applied.
CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; PAS: patient access scheme; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2	

A.4 Decision problem and NICE reference case

The submission covers the technology's full marketing authorisation for this indication. The company submission is consistent with the final NICE scope and the NICE reference case, with the exception of one comparator and the analysis of subgroups (see table for differences and rationale).

Table 2. The decision problem – B.1.1 (page 12)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with invasive urothelial cancer who are at high-risk of recurrence following radical surgical resection	People with invasive urothelial cancer who are at high-risk of recurrence following radical surgical resection	As NICE scope
Intervention	Nivolumab	Nivolumab	As NICE scope
Comparator(s)	• Adjuvant chemotherapy (e.g. cisplatin-based regimen) • Best supportive care (monitoring and further treatment at recurrence)	• Best supportive care (monitoring and further treatment at recurrence)	Clinical experts suggest that best supportive care (BSC) is the predominant strategy in the adjuvant setting, as the great majority of cisplatin-eligible patients will receive neoadjuvant cisplatin and are not therefore eligible for further cisplatin. Patients may also be ineligible for cisplatin-based adjuvant therapy due to comorbidities or poor performance status. A small proportion of patients are eligible for cisplatin therapy in the adjuvant setting, of which a proportion would refuse it. Hence, cisplatin-based chemotherapy is considered of limited relevance and not a relevant comparator for the base case analysis. As chemotherapy was not a comparator in the trial, use of an indirect treatment comparison (ITC) of

			nivolumab vs chemotherapy was considered. An ITC was undertaken but important limitations in the evidence base (study heterogeneity and small sample sizes) meant that the results were subject to considerable uncertainty and were not considered suitable to inform decision-making (Section B.2.9).
Outcomes	The outcome measures to be considered include: • disease-free survival • overall survival • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • disease-free survival • overall survival (modelled) • adverse effects of treatment • health-related quality of life	Analysis of OS data (Kaplan-Meier estimates and hazard ratios) from the trial was not available at the time of submission as the number of deaths required to inform the first OS interim analysis was not reached at the time of the August 2020 database lock. OS is estimated in the model via time spent in the DFS and post-recurrence health states.
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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Aligned with NICE reference case and NICE scope.	As per NICE scope

Subgroups to be considered	PD-L1 status of the resected tumour	None	The primary endpoint of CheckMate 274 was analysed in two primary populations: all randomised patients and patients with tumour cell PD-L1 expression level ≥ 1%. The submission presents the clinical evidence from both populations, but economic modelling was only carried out in the all randomised patients population.
Perspective for outcomes	All direct health effects, whether for patients or, where relevant, carers	Patient perspective (i.e. clinical outcomes)	
Perspective for costs	NHS and personal social services (PSS)	In line with NICE reference case	In line with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime (40 years)	In line with NICE reference case
Synthesis of evidence on health effects	Not applicable – direct evidence vs the comparator specified in the scope available from a randomised controlled trial		
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	In line with NICE reference case	In line with NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Disease free health state utility is informed by data from CheckMate 274. Recurred disease health state utility is informed by utility values from CheckMate 274.	In line with NICE reference case
Source of preference data for valuation of changes in health-	Representative sample of the UK population	UK preference set	In line with the NICE reference case

related quality of life			
Equity considerations	None specified.	As per NICE scope	As per NICE scope
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	NHS reference costs, Healthcare costing standards for England, electronic market information tool (eMIT), clinician advice	In line with NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	3.5% on costs and benefits	In line with NICE reference case

A.5 Clinical effectiveness evidence

Evidence to support the effectiveness of nivolumab monotherapy for the treatment of patients with MIUC who are at high risk of recurrence after undergoing radical resection is derived from CheckMate 274, a phase 3, randomised, double-blind, multi-centre study of adjuvant nivolumab versus placebo.[20] Information is taken from the study publication, Bajorin et al.,[21] a conference presentation by Bajorin et al.,[22] the clinical study report (CSR; database lock [DBL] 27 August 2020),[23] and an [redacted].[24] A summary is provided in Table 3 and the trial is described in Section B.2.3.

Table 3. Clinical effectiveness evidence

Study title	**CheckMate 274**
Study design	Phase 3, randomised, double-blind, multi-centre study of adjuvant nivolumab versus placebo
Population	Adult patients who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC) in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence.
Intervention(s)	Nivolumab monotherapy at a dose of 240mg administered intravenously over 30 minutes at 2-week intervals until recurrence, unacceptable toxicity or discontinuation from study for a maximum of 1 year.
Comparator(s)	Placebo administered intravenously over 30 minutes at 2-week intervals until recurrence, unacceptable toxicity or discontinuation from study for a maximum of 1 year.
Outcomes specified in the decision problem	**Disease-free survival** **Adverse effects of treatment** **Health-related quality of life** Note: analysis of overall survival data is not available at the time of submission as unblinding of OS is event-driven and the data have not reached sufficient maturity. Thus, the company remains blinded to the OS analyses.
Reference to section in submission	B.2.2, B.2.6.1, B.2.6.4, and B.2.10

A.6 Key results of the clinical effectiveness evidence

The pivotal study informing the clinical efficacy of nivolumab in this indication is CheckMate 274. The study methodology is described in Section B.2.3–B.2.4 and the results are available in Sections B.2.6 (all randomised patients), B.2.7 (subgroups) and B.2.10 (adverse reactions). At the DBL, August 2020, median follow-up was 20.9

months and 19.5 months for all randomised patients in the nivolumab (N = 353) and placebo arms (N = 356), respectively, with a minimum follow-up time of 5.9 months.[21] Results are presented for the all randomised patients population and DFS is presented for the co-primary population (all randomised patients with tumour cell PD-L1 expression level ≥ 1%), all results were consistent with those in all randomised subjects.

DFS was the primary endpoint and considered the most appropriate endpoint in the adjuvant setting. Additionally, OS analysis (i.e. Kaplan-Meier OS curve per treatment arm and hazard ratios) was not available at the time of submission as data were not mature enough to unblind the analyses.

A.6.1 *Disease-free survival (DFS)*

Patients treated with nivolumab had a statistically significant and clinically relevant improvement in DFS compared to placebo (20.8 vs 10.8 months, hazard ration [HR] 0.70 [98.22% CI: 0.55, 0.90]; p < 0.001), with Kaplan-Meier curves separating after 3 months favouring nivolumab.[21] DFS rates at 6 months (74.9% [95% CI: 69.9, 79.2] vs 60.3% [95% CI: 54.9, 65.3]) and 12 month (62.8% [95% CI: 57.3, 67.8] vs 46.6 [95% CI: 41.1, 51.9]) were also markedly higher in the nivolumab arm than with placebo.[21] The primary DFS results are shown in Table 4 and Figure 3.

Rates of locoregional disease-free survival and distant metastasis-free survival were assessed as exploratory endpoints and are described in Section A.6.4 .

Table 4. DFS results, all randomised patients

Endpoint	Nivolumab (N = 353)	Placebo (N = 356)
DFS (Primary definition)*		
Events, n (%)	170 (48.2)	204 (57.3)
Median, months (95% CI)	20.8 (16.5, 27.6)	10.8 (8.3, 13.9)
Hazard Ratio (% CI)	0.70 (98.22% CI: 0.55, 0.90)	
6 months, % (95% CI)	74.9 (69.9, 79.2)	60.3 (54.9, 65.3)
12 months, % (95% CI)	62.8 (57.3, 67.8)	46.6 (41.1, 51.9)
*primary definition of DFS accounts for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer. Abbreviations: CI: confidence interval, DFS: disease-free survival. Source: Bajorin, 2021[21]		

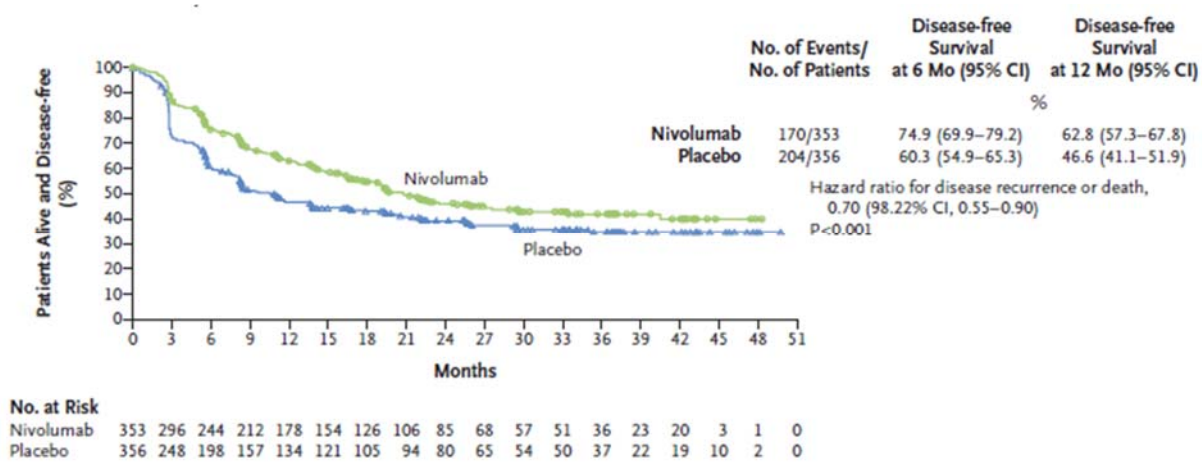


Figure 3. CheckMate 274: Kaplan-Meier plot of disease-free survival (primary definition) receiving nivolumab or placebo, all randomised patients

Source: Bajorin, 2021[21]

A.6.2 *Non-urothelial tract recurrence free survival (NUTRFS)*

Patients treated with nivolumab had a clinically meaningful improvement in NUTRFS compared to placebo (22.9 vs 13.7 months, HR = 0.72 [95% CI: 0.59, 0.89]), with the Kaplan-Meier curves separating after 3 months.[21] NUTRFS rates at 6 months (77.0% vs 62.7%) and 12 months (65.1% vs 50.4%) were also higher in the nivolumab arm than in the placebo arm, respectively.[21] The NUTRFS results are shown in Table 5 and Figure 4. This endpoint captures recurrences that are known to be associated with poor prognosis.

Table 5. NUTRFS results, all randomised patients

Endpoint	Nivolumab (N = 353)	Placebo (N = 356)
NUTRFS		
Events, n (%)	162† ([redacted]§)	190† ([redacted]§)
Median, months (95% CI)	22.9 (19.2, 33.4)†	13.7 (8.4, 20.3)†
Hazard Ratio (95% CI)	0.72 (0.59, 0.89)†	
6 months, % (95% CI)	77.0 (72.1, 81.1)†	62.7 (57.3, 67.6)†
12 months, % (95% CI)	65.1 (59.6, 70.0)†	50.4 (44.8, 55.7)†
Abbreviations: CI: confidence interval, DFS: disease-free survival, NUTRFS: non-urothelial tract recurrence-free survival. Source: §CSR [redacted][24] and †Bajorin, 2021[21]		

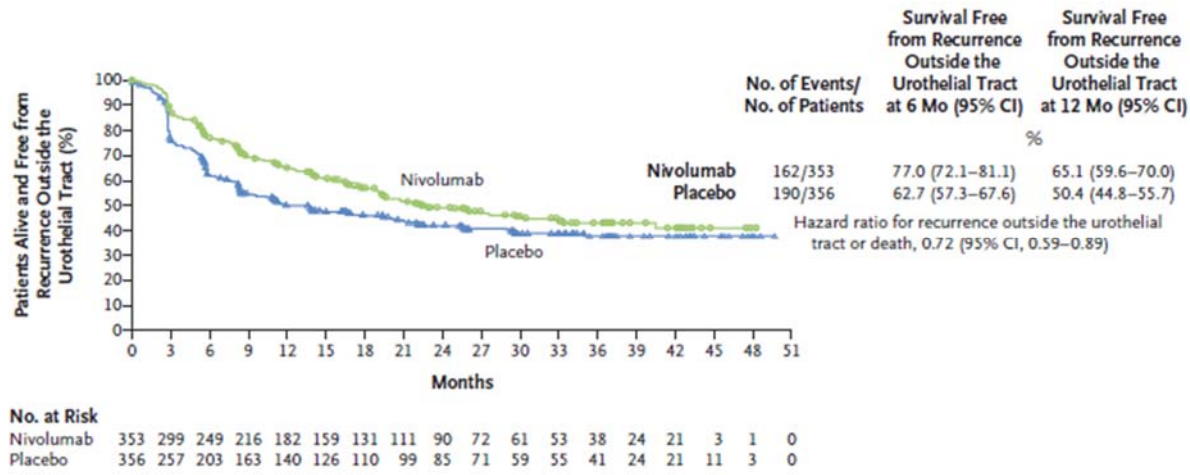


Figure 4. CheckMate 274: Kaplan-Meier plot of NUTRFS in patients receiving nivolumab or placebo, all randomised patients

Source: Bajorin, 2021[21]

A.6.3 *Health-related quality of life*

Patient reported outcomes were collected through the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), a 30-item cancer-specific instrument, and EuroQoL 5-dimensional 3-level index (EQ-5D-3L), an instrument for general health status.

EORTC QLQ-C30 baseline completion rates were [redacted], and exceeded [redacted] at all assessments through 49 weeks, in the nivolumab and placebo arms, respectively. Completion rates for follow-up visits 1 and 2 for the nivolumab and placebo arms met or exceeded [redacted], respectively. Completion rates for the EQ-5D-3L were [redacted] at baseline, and [redacted] during treatment in the nivolumab arm and placebo arm, respectively.

HRQoL as measured by EORTC QLQ-C30 remained stable in both nivolumab and placebo arms, and no mean change in score from baseline reached the minimal important difference (MID) for the patient (i.e. mean change ≥10 points) at any time point for either treatment arm, demonstrating that adjuvant nivolumab's efficacy was achieved without detriment to HRQoL. Similarly, mean EQ-5D-3L utility index and EQ-5D visual analogue scale (VAS) scores were also [redacted] between nivolumab and placebo, and [redacted] in both arms. Results are detailed in Section B.2.6.4.

A.6.4 *Exploratory endpoints*

Exploratory endpoints are detailed in Section B.2.6.3.

The time to recurrence exploratory endpoint supported the findings on DFS, showing a clinically meaningful improvement in time to recurrence: median of [redacted] vs [redacted] months with nivolumab vs placebo ([redacted]; Table 6).[23]

Patients treated with nivolumab also had a clinically meaningful improvement in distant metastasis-free survival (DMFS) compared to placebo (35.0 vs 29.0 months, HR 0.74 [95% CI: 0.58, 0.93]), with Kaplan-Meier curves separating after 3 months favouring nivolumab.[22] Similarly, nivolumab was associated with clinically meaningful improvement in locoregional disease-free survival (LRDFS). DMFS and LRDFS results are shown in Table 6 and Figure 5.[21]

Progression-free survival on next line systemic therapy (PFS2) also demonstrated that nivolumab treatment resulted in [redacted] in PFS2 in all randomised patients: median of [redacted] months with nivolumab vs placebo ([redacted]).[23]

Table 6. Exploratory endpoints, all randomised patients

Endpoint	Nivolumab (N = 353)	Placebo (N = 356)
Time to recurrence		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI)	[redacted]	
6 months, % (95% CI)	[redacted]	[redacted]
DMFS (exploratory endpoint)		
Events, n (%)	132† (37.4§)	152† (42.7§)
Median, months (95% CI)	40.5 (22.4, N.A.)†	29.5 (16.7, N.A.)†
Hazard Ratio (95% CI)	0.75 (0.59, 0.94)†	
6 months, % (95% CI)	82.5 (78.0, 86.2)†	69.8 (64.5, 74.4)†
12 months, % (95% CI)	71.2 (65.8, 75.9)†	58.6 (52.8, 63.9)†
LRDFS (exploratory endpoint)		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI)	[redacted]	
LRD rate at 6 months, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DMFS: distant metastasis-free survival; LRDFS: locoregional disease-free survival. Source: CSR[23], §CSR [redacted][24], and †Bajorin, 2021[21]

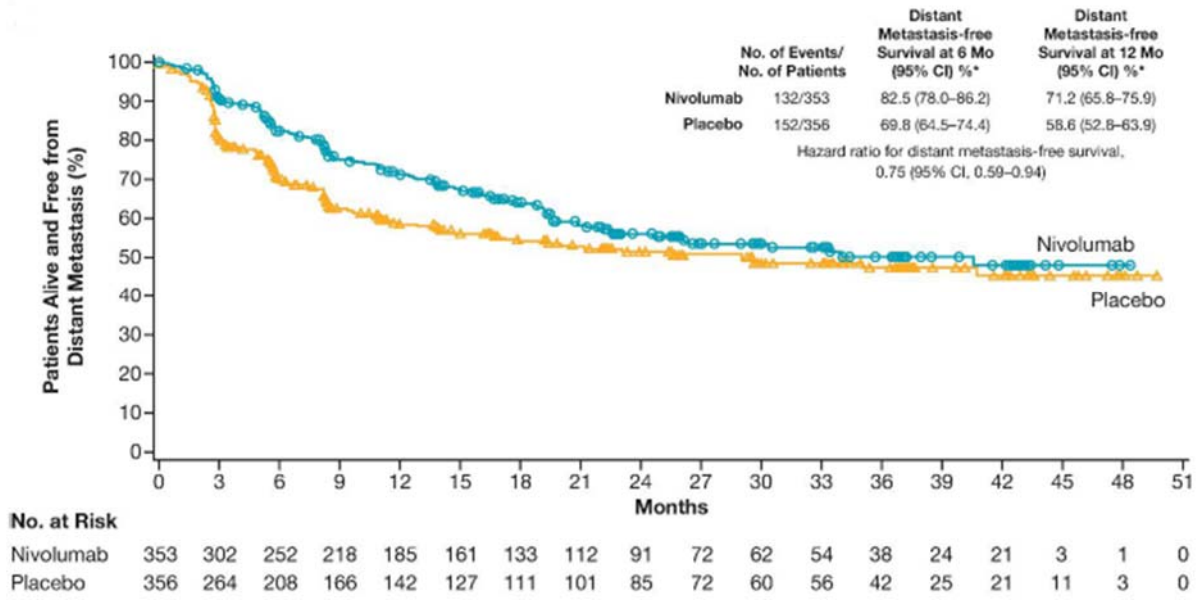


Figure 5. CheckMate 274: Kaplan-Meier plot of DMFS receiving nivolumab or placebo

Source: Bajorin, 2021[21]

A.6.5 *Tumour PD-L1 expression ≥ 1% subgroup*

Efficacy outcomes in the co-primary population all randomised patients with tumour cell PD-L1 expression level ≥ 1% were broadly consistent with all randomised subjects (Section A.6.1). Median DFS was not reached in patients with tumour cell PD-L1 expression level ≥ 1% treated with nivolumab. There was a statistically significant and clinically relevant improvement in DFS compared to placebo (HR 0.55 [98.72% CI: 0.35, 0.85]; p < 0.001; Table 7), with Kaplan-Meier curves separating after 3 months, favouring nivolumab (Figure 6).[21] Further details are shown in Section B.2.7.1.

Table 7. CheckMate 274: PD-L1 ≥ 1% efficacy results

Endpoint	Nivolumab (N = 140)	Placebo (N = 142)
DFS (Primary definition)*		
Events, n (%)	55† (39.3§)	81† (57.0§)
Median, months (95% CI)	[redacted]§	[redacted]§
Hazard Ratio (% CI)	0.55 (98.72% CI: 0.35, 0.85)†	
6 months, % (95% CI)	74.5 (66.2, 81.1)†	55.7 (46.8, 63.6)†
12 months, % (95% CI)	67.2 (58.4-74.5)†	45.9 (37.1, 54.2)†
*primary definition of DFS accounts for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer. Abbreviations: N.A.: Not available; CI: confidence interval, DFS: disease-free survival Source: §CSR [redacted][24], and †Bajorin, 2021[21]		

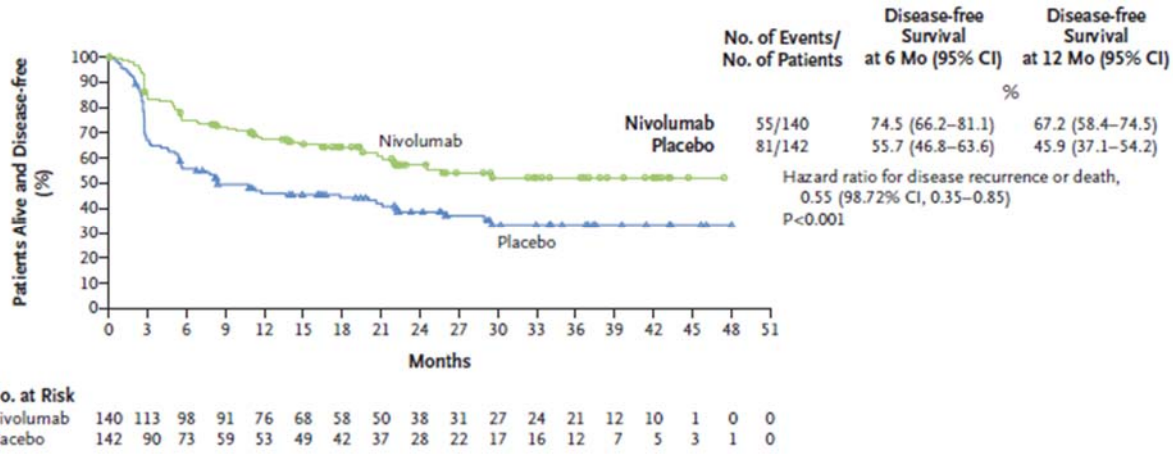


Figure 6. CheckMate 274, PD-L1 ≥1 % subgroup: Kaplan-Meier plot of disease-free survival (primary definition)

Source: Bajorin, 2021[21]

A.6.6 *Adverse reactions*

Overall, the safety profile of nivolumab in CheckMate 274 was consistent with the safety profile previously observed in other tumours studied, including in patients with metastatic urothelial carcinoma,[25,26] and no new safety concerns were identified. Nivolumab was associated with low rates of drug-related serious adverse events (AEs) and drug-related AEs leading to discontinuations, with 12.8% of patients in the nivolumab arm and 2.0% of patients in the placebo arm discontinuing treatment due to study drug toxicity.[22]

AEs seen in the CheckMate 274 study were in line with the immunotherapeutic mode of action, with most IMAEs medically manageable using established management algorithms, with resolution occurring when immune-modulating medicines (mostly corticosteroids) were administered. Most drug-related select AEs and most IMAEs with nivolumab treatment had resolved at the time of the DBL. Some endocrine IMAEs, were not considered resolved due to the continuing need for hormone replacement therapy. Safety results are detailed in Section B.2.10.

In summary, nivolumab demonstrates a favourable benefit–risk profile for the treatment of MIUC patients who have undergone resection and are at high risk of recurrence with well-established and clinically manageable safety data.

A.7 Evidence synthesis

An indirect treatment comparison (ITC) was conducted for nivolumab versus cisplatin-based adjuvant therapy for a subgroup of patients who did not receive neo-adjuvant therapy and were eligible, but actively refused, adjuvant cisplatin chemotherapy. However, the ITC was subject to significant limitations arising from heterogeneity in the evidence base and the small sample size, as detailed in Section B.2.9 and Appendix J. These limitations impact the ability of the ITC to reliably inform health technology assessment decision making for this treatment comparison. The ITC was subject to major uncertainty, lacks robustness, was exploratory in nature and was considered insufficient to be used to inform decision making. Thus, the outcomes produced from the ITC were deemed unsuitable to inform the economic model.

A.8 Key clinical issues

- Analysis of OS data was not available at time of the clinical DBL presented (27 August 2020) for the planned interim analysis of DFS, as the number of deaths required to trigger the first OS interim analysis was not reached. There is thus currently no direct evidence for nivolumab prolonging overall survival. However:
    - Lack of OS data is common in the adjuvant setting.
    - Extending DFS will result in patients accruing more survival time before moving into the next treatment line, and (provided there is no long-term harm associated with the adjuvant treatment) can therefore be expected to extend survival regardless of subsequent treatment outcomes.
    - Several studies have shown that DFS after radical treatment for UC is predictive of OS: increased DFS has been shown to predict longer overall survival.[13,14,27]
    - The great majority of recurrences under current treatment occur in the first 3 years after surgery.[12-14,27] UK clinical experts reported that after 5 years disease-free patients are assumed to be at very low risk of recurrence and are no longer followed up;[8,15] it is assumed that after 5 years of disease-free survival the patients can expect long-term remission. Therefore, nivolumab is expected to increase the proportion of patients who enter long-term remission.
- DFS as the primary endpoint: DFS is considered the most relevant endpoint in the adjuvant setting. After radical resection there is no measurable disease to follow, so DFS is the relevant outcome to measure. Furthermore, once a patient experiences recurrence, post-recurrence therapy is likely to be a significant confounder for the assessment of OS; in contrast, DFS gives a clear picture of an agent's efficacy in the adjuvant setting, regardless of subsequent treatment.
- The trial does not provide comparative evidence against adjuvant cisplatin chemotherapy. However, as described in Table 2, adjuvant cisplatin is not

considered a relevant comparator for the base case. An ITC was carried out for the subgroup patients who were eligible for adjuvant cisplatin-based chemotherapy (see Section A.7, Section B.2.9 and Appendix J) but was considered unsuitable to inform HTA decision-making due to the significant limitations described in those sections.

A.9 Overview of the economic analysis

A semi-Markov model was developed with 4 health states (Figure 7). All patients enter the model in the initial disease-free state and remain there until death, recurrence, or until they moved into the long-term disease-free state. Subsequent possible transitions in the model are illustrated by the arrows and are described in Table 8 and Section B.3.2.3.

Using a weekly cycle length, the model predicts the proportion of the population who experience a recurrence or death event. The model was designed to capture treatment benefit by demonstrating that with nivolumab, patients will potentially have a lower recurrence rate and a higher utility profile gained by more time spent in the disease-free states.

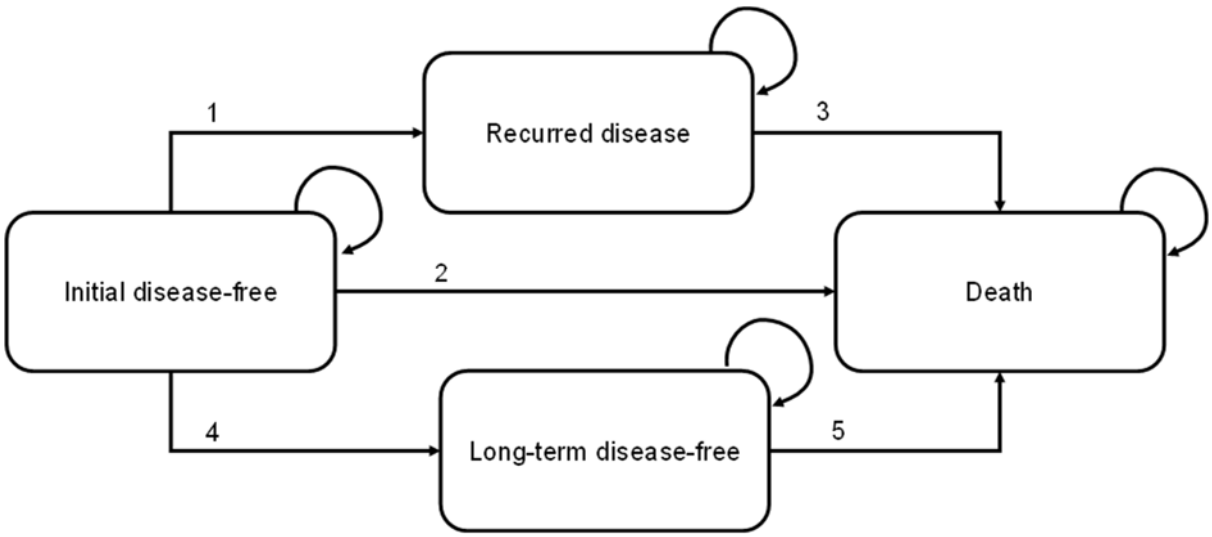


Figure 7. Model schematic

Table 8 Definition and source of transitions

Transition	Description	Source
1	Initial disease-free to recurred disease	Trial data (CM274; DFS curve)[23]
2	Initial disease-free to death	Trial data (CM274; disease-specific deaths)[23] and background mortality [28]
3	Recurred disease to death	Bellmunt et al.[29] and De Santis et al.[30] (50:50 split)
4	Initial to long-term disease free	All patients at 5 year timepoint (see Section B.3.3.2.1.3 in document B)
5	Long-term disease free to death	Background mortality [28] (see Section B.3.3.2.1.3 in document B)

CM274: CheckMate 274; DFS: disease-free survival

A.10 Incorporating clinical evidence into the model

A.10.1 *Survival analysis and extrapolation of disease-free survival*

Clinical data to inform DFS are derived from CheckMate 274[22]. Since follow-up in the clinical trial was less than the maximum time horizon of the model, extrapolation of survival data was required to inform long-term outcomes. A variety of parametric and flexible approaches to modelling DFS were developed using patient-level data from CheckMate 274 based on the 27 August 2020 DBL[22].

In the base case, a semi-parametric (piecewise) approach is used to estimate DFS outcomes in the long term. The independent models use Kaplan-Meier data to [redacted] months and [redacted] months for nivolumab and placebo respectively, followed by Weibull extrapolation.

A.10.2 *Rationale for inclusion of long-term remission*

Inspection of the DFS hazards from the trial clearly indicates a general trend towards general population mortality rates in both arms, which supports an assumption that patients who had not experienced disease recurrence by the time of maximum follow-up in the trial (around 4 years) would be at negligible ongoing risk from the disease. This finding is consistent with the literature, where it is reported that the great majority of recurrences under current treatment occur in the first 3 years after surgery.[12-14,27] UK clinical experts reported that after 5 years disease-free patients are assumed to be at very low risk of recurrence and are no longer followed up;[8,15] that is, it is assumed that after 5 years of disease-free survival the patients can expect long-term remission. Therefore, within the cost-effectiveness model, after 5 years disease-free, patients move into a long-term remission state where there is no risk of recurrence, and mortality matches age-dependent background mortality (i.e. no disease-specific mortality is applied). There are also no health state costs (i.e. no treatment or healthcare resource use) associated with this state, and quality of life within this health state matches the general population age-dependent value.

A.10.3 *Post-recurrence survival*

Analysis of OS and post-recurrence survival from the CheckMate 274 trial were not carried out for the current DBL as insufficient OS events had occurred to trigger the analysis and the data therefore remained blinded to the company. Post-recurrence

survival was modelled using a static transition probability sourced from the literature using two sources. Bellmunt et al. describes median post-recurrence survival for patients taking cisplatin chemotherapy (12.7 months),[29] and De Santis et al. describes median post-recurrence survival for patients taking carboplatin chemotherapy (9.3 months).[30] An assumption is made of a 50:50 split between these two populations in the model, based on the literature[30-34] and expert clinical advice.[35] As such, post-recurrence survival is based on a median OS of 11.0 months. This is converted into a weekly transition probability of recurrence to death. The sensitivity of the model to these simplifying assumptions is explored in scenario analyses.

Progression post-recurrence was not modelled as it was assumed that the treatment costs and the efficacy profile applied in the post-recurrence health state were representative of any and all further lines that patients may receive.

A.10.4 *Time on treatment*

Patients enrolled in the CheckMate 274 trial were subject to a 12-month treatment stopping rule. Time on treatment was based on treatment data from the CheckMate 274 trial for both treatment arms, so has been included in the cost-effectiveness model directly from trial data. At the time of the August data cut, the Kaplan-Meier estimates for time on treatment were complete, therefore no extrapolation was considered necessary for this outcome. Time on treatment data were mature, as only 6% of patients were censored due to remaining on treatment. Trial data for the proportion of patients on treatment in any given cycle determines the application of treatment-associated costs.

A.10.5 *Health state occupancy and transition probabilities*

Health state occupancy is defined by treatment specific DFS extrapolations, alongside treatment specific estimates of death at the point of recurrence. Derivation of these estimates from available data is described in Section B.3.2.3.1.

In brief, patients remain in the initial disease-free health state based on transition probabilities derived from the DFS extrapolations. Upon the incidence of recurrence, patients are stratified into recurred and death health states based on the time- and treatment-dependent probability of death on recurrence. Subsequently, patients that have recurred and did not die immediately upon recurrence may transition to the death

health state based on transition rates derived the literature, defining mortality in patients after recurrence.

A.10.6 *Validation of clinical parameters*

In general, where no evidence was identified to validate the results of the cost-effectiveness analysis, simple assumptions were made based on independent sources, such as published literature, bladder cancer guidelines or previous NICE appraisals in the field of bladder cancer. Restricted mean estimates for DFS for treatment with placebo were validated against published data[14] to seven years and were found to be comparable. Extrapolation of DFS data from the CheckMate 274 trial was also assessed for plausibility by clinical experts, alongside assumptions about survival post-recurrence. These assumptions were assessed for clinical plausibility; uncertainty was characterised through the use of sensitivity analyses. A technical review of the cost-effectiveness model was conducted by an independent health economist. Further, the relevance of the model structure and assumptions were validated through consultation with UK clinicians. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

A.11 Key model assumptions and inputs

A summary of the main assumptions within the economic model is provided within Table 9.

Table 9. Key model assumptions and inputs

Model input and section	Source/assumption	Justification
DFS and long-term remission	After five years in disease-free, patients move to long-term remission, where they can no longer recur and experience background age-related mortality only (no disease related deaths)	Observed DFS hazards from each arm of the CheckMate 274 trial tend towards general population levels by the end of the data, suggesting low risk of recurrence in patients who have remained disease free beyond 3 years. This finding is supported by clinical advice,[8] which suggested that, after three to five years post-surgery without recurrence, patients may be considered in long-term remission. These patients would be subject to no further routine monitoring, have no risk of recurrence, and experience general population mortality.
Recurrence modelling	Local urothelial and non-urothelial/distant recurrence are not modelled separately thereby assuming the same mortality and recurrence	Due to the lack of mature post-recurrence outcome data from CheckMate 274, as well as limited data regarding the outcomes for patients after recurrence in the literature, the conservative assumption was made that all recurrences were locally advanced or metastatic. Two papers were identified that considered post-recurrence survival in similar patient populations,[29,30] however these studies did not differentiate by type of chemotherapy administered.
Survival curves (Section B.3.3.2)	Identification of most appropriate survival curves describing PFS, OS and time on treatment	Extensive analyses have been undertaken to identify appropriate and conservative survival curves describing nivolumab efficacy, with reference to the guidance from the NICE Decision Support Unit (DSU)[36] and Bagust and Beale (2014).[37] The approach and identified survival extrapolations have been validated by clinical and health economic experts.
Post recurrence costs (Section B.3.5.2.4)	Treatment post-recurrence is assumed to be an even distribution between two treatment regimens	Clinical advice suggested that the two treatment regimens identified (carboplatin + gemcitabine and cisplatin + gemcitabine) are the most likely options for patients who have experienced a recurrence, either local or metastatic. Other regimens may exist (e.g. MVAC, immunotherapies) but these are not included in the model since they are not routinely used in clinical practice (based on clinical expert feedback) or are either within or recently left the cancer drugs fund.

Post recurrence costs (Section B.3.5.2.4)	Patients are assumed not to discontinue therapy post-recurrence.	This is to capture all possible therapies that patients may subsequently receive, either sequentially or concurrently. This is a simplifying assumption applied equally to both arms and therefore not expected to preferentially benefit either treatment.
Post recurrence treatment options (B.3.3.2)	Post-recurrence treatment is assumed to be equivalent across both arms	There is currently no evidence to suggest that patients who experience a recurrence would be treated differently upon recurrence. It is acknowledged that this is largely because there are currently limited treatment options post-surgery. Immunotherapies are a potential treatment option, but are not included within the base case since they are within the cancer drugs fund and are not routine clinical practice.
Post recurrence modelling (B.3.3.2, B.3.5.2.4, B.3.5.3.2)	Those who remain in the post-recurrence state long term are assumed to have equivalent utility and cost rates to those who are in for a short term	As the post recurrence health state is considered to be a heterogenous group of any and all further lines of treatment, for simplicity it was assumed that the cyclical costs and outcomes for these patients was representative of an average of their experience.
Post recurrence modelling (B.3.3.2, B.3.5.2.4, B.3.5.3.2)	The De Santis paper[30] only included patients with distant recurrence.	The conservative assumption was made that all recurrences were distant.
Post recurrence to death modelling	A static transition probability is applied based on published literature to determine the risk of death from recurrence.	OS data from the trial is immature and therefore not a robust source of information. There have been no previous relevant publications from which OS in a relevant patient population could be sourced. As such, literature for post-recurrence survival in the two post-recurrence treatment arms was sourced using recurrence data from Bellmunt et al.[29] and De Santis et al.[30] Key baseline patient characteristics across CheckMate 274 and the two studies informing post-recurrence are similar. In the model, the midpoint of these values is taken, based on an assumption supported by clinical expert opinion that 50% of patients receive cisplatin, and the other 50% receive carboplatin. Median OS data from these studies was combined as described to estimate a static probability of death after recurrence.
DFS: disease-free survival; HRQoL: health-related quality of life; OS: overall survival.		

A.12 Deterministic ICER

Total discounted costs associated with nivolumab (with PAS), accrued over the modelled time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with BSC (routine surveillance) were notably lower. Incremental discounted costs were predicted to be [redacted] over BSC, under base case assumptions. The total discounted QALYs gained for nivolumab were predicted to be [redacted], and [redacted] for placebo, leading to an incremental QALY gain of [redacted] for nivolumab. In the nivolumab arm, [redacted] discounted life years were accrued, compared to [redacted] in the placebo arm, and therefore resulting in a [redacted] incremental life year gain. The resulting deterministic ICER estimate for nivolumab versus routine BSC was £32,838 per QALY gained. The results of the deterministic analysis are summarised in Table 10 and Table 11.

Table 10. Deterministic analysis results (with PAS)

Outcome	Nivolumab	BSC (Routine surveillance)	Incremental
Costs (discounted)	[redacted]	[redacted]	[redacted]
Life Years (undiscounted)	[redacted]	[redacted]	[redacted]
QALYs (discounted)	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£32,838
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

Table 11. Deterministic analysis: disaggregated outcomes

	Component	Nivolumab	BSC (Routine surveillance)	Incremental
Disaggregated costs (discounted)	Disease-free	[redacted]	[redacted]	[redacted]
	Disease-free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Treatment	[redacted]	[redacted]	[redacted]
	AEs	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)	Disease-free	[redacted]	[redacted]	[redacted]
	Disease-free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Clinical outcomes (years, undiscounted)	Median DFS	[redacted]	[redacted]	[redacted]
	Mean DFS	[redacted]	[redacted]	[redacted]
	Median OS	[redacted]	[redacted]	[redacted]
	Mean OS	[redacted]	[redacted]	[redacted]
Time in health state (years, undiscounted)	Disease-free	[redacted]	[redacted]	[redacted]
	Disease-free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]

AE: adverse event; DFS: disease-free survival; OS: overall survival; QALY: quality-adjusted life-year

A.13 Probabilistic sensitivity analysis

Uncertainty around the input data has been assessed using probabilistic analyses, while alternative assumptions have been examined in scenario analyses. Details of this analysis can be found in Section B.3.8. The results of 1,000 iterations of the model led to an average ICER of £32,922 (Table 12), with approximately [redacted]% being cost-effective.

Table 12. Base-case results (probabilistic) – (Section B.3.8)

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,922
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

[redacted]

Figure 8. Scatterplot of probabilistic results – (Section B.3.8.1)

A.14 Key sensitivity and scenario analyses

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses have been used to vary the data inputs by a set amount. Uncertainty around the input data has been assessed using probabilistic analyses, while alternative assumptions have been examined in scenario analyses.

Results of the deterministic sensitivity analysis are presented in Figure 9. These figures demonstrate the impact of specific parameters on ICER estimates. The factors with the greatest impact on the ICER were age, benefits discounting, and age-dependent utility decrements.

Plausible alternative inputs and assumptions were assessed as scenario analyses within Document B (Section B.3.8.3), and are summarised in Table 13.

Figure 9. Tornado diagram, deterministic sensitivity analyses (Section B.3.8.2)

Table 13. Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	ICER	Impact on base-case ICER
Base case			**£32,838**	**-**
Removal of long term remission state (Section B.3.8.1)	To reflect the long tail seen in the survival analysis, and to align with clinical expert feedback, the base case model included a long-term remission state at 5 years and beyond.	Removing this state and allowing patients who have not recurred to remain in disease-free state, keeping them at risk of recurrence.	[redacted]	[redacted]

Impact of different remission timepoints (Section B.3.8.3.2)	The base case analysis assumed that patients still in the disease-free state after 5 years would enter a long-term disease-free state to which only ACM would be applied.	A scenario analysis was undertaken to evaluate sensitivity to the point at which this happened in the model.	[redacted]	[redacted]
Alternative survival curve extrapolation (Section B.3.8.3.3)	To explore the impact of an alternative survival curve extrapolation for DFS.	Assessing the impact of using exponential curve extrapolation instead of Weibull. Additionally, explored the impact of different Kaplan	[redacted]	[redacted]

		Meier cut-off points.		
Altered recurrence to death transition (Section B.3.8.3.6)	In the base case, the recurrence to death transition was informed by the literature.	Assessment of the model sensitivity to this value, since it was not directly informed by the trial, through arbitrary doubling and halving of survival (months) after recurrence.	[redacted]	[redacted]
Stratification of recurrence type (Section B.3.8.3.6)	In the base case all recurrences were assumed to be distant/non-urothelial	Evaluating splitting of recurrence into local urothelial recurrence, and distant/non-urothelial recurrence	[redacted]	[redacted]

	recurrence.	, with corresponding impacts on mortality and health state costs.		

A.15 Innovation

Nivolumab is a checkpoint inhibitor immunotherapy agent whose innovative mechanism of action utilises the body's own immune system to destroy cancer cells. Since its launch it has been approved, as monotherapy or in combination with ipilimumab or cabozantinib, for the treatment of a range of tumour types, including as a monotherapy for locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.[18]

Adjuvant nivolumab therapy has significant benefits in high-risk MIUC. Median DFS was 20.8 with nivolumab vs 10.8 months with placebo, a risk reduction of [redacted]% (HR = 0.70 [98.22% CI: 0.55, 0.90]).[21,24] Median NUTRFS was 22.9 vs 13.7 months, a risk reduction of [redacted]% (HR = 0.72 [95% CI: 0.59, 0.89]).[21,24] There was no detriment to HRQoL compared with placebo, and adverse events were manageable.[21,23]

Nivolumab is the first and only immunotherapy to demonstrate superior efficacy to placebo in the adjuvant setting after radical surgery for MIUC. The introduction of nivolumab for adjuvant treatment of high-risk MIUC would represent a significant advance in the management of these patients, as there is currently no effective treatment available to reduce the risk of recurrence after resection. The clinical evidence indicates that nivolumab may represent a new standard of care in the adjuvant treatment setting for this population.

For further information see the section on innovation in the main submission: B.2.12.

A.16 Budget impact

Table 14. Budget impact – Budget Impact Submission document

	Company estimate	Cross reference
Number of people in England who would have treatment	885	Company budget impact analysis submission, eligible population (Section 4.5)
Average treatment cost per person	Since all treatment is contained within the first year only, only total costs are shown here. Including administration cost Nivolumab (with PAS): [redacted] Comparators (without PAS): • Cisplatin + gemcitabine: £9,397 • Carboplatin + gemcitabine: £9,653 • Routine surveillance (BSC): £0	Budget Impact Model
Estimated annual budget impact on the NHS in England	Nivolumab vs Cisplatin/Carboplatin (with PAS) • → Year 1: [redacted] • → Year 2: [redacted] • → Year 3: [redacted]	Company budget impact analysis submission, expected five year budget impact (Section 7)

A.17 Interpretation and conclusions of the evidence

- Adjuvant nivolumab therapy significantly improved disease-free survival and NUTRFS in the CheckMate 274 study. Median DFS with nivolumab was 20.8 vs 10.8 months with placebo, almost doubling disease-free survival time, with similar results for median NUTRFS (22.9 vs 13.7 months, respectively).[21] NUTRFS captures non-urothelial tract recurrences, which are known to be associated with poor prognosis.

- Treatment with nivolumab does not impair HRQoL compared with placebo (analogous to the current clinical practice of BSC in the form of surveillance), as measured by EORTC QLQ-C30 and EQ-5D-3L instruments over the course of treatment and during follow-up.[23]

- Overall survival data are not yet available, but the doubling of DFS is expected to translate to OS gains, as longer DFS has been shown to predict longer OS.[13,14,27] Furthermore, as most recurrences occur in the first 3 years[12-14,27] and recurrence after 5 years is uncommon,[12] nivolumab is expected to increase the proportion of patients who enter long-term remission.

- Adverse effects were manageable and consistent with the established safety profile of nivolumab, and AEs leading to discontinuation were reported in [redacted]% and [redacted]% of patients in the nivolumab and placebo arms, respectively.[23]

- The cost-utility model evaluates nivolumab vs BSC for adjuvant UC. The model captures key outcomes: time spent in disease-free status, proportion of patients disease-free, time to recurrence, and death. The model utilises a semi-Markov approach as it allows time-dependency (e.g. DFS curve) as well as the use of static transition probabilities (e.g. recurrence-to-death transition from the literature).

- The deterministic economic modelling estimates that use of nivolumab is associated with gains of [redacted] life years, [redacted] QALYs and £[redacted] in additional costs compared with BSC, leading to an ICER of £32,838.

- The probabilistic economic modelling (using 1,000 cycles) estimates that nivolumab is associated with gains of [redacted] life years, [redacted] QALYs, and [redacted] in additional costs compared with BSC, leading to an ICER of £32,922.

A.18 References

1. Leow JJ, Chong KT, Chang SL, et al. Upper tract urothelial carcinoma: a different disease entity in terms of management. ESMO Open. 2016;1(6):e000126.
2. Roupret M, Mabjuk M, Bohle A, et al. EAU Guidelines on Urothelial Carcinomas of the Upper Urinary Tract. European Association of Urology (EAU), 2016.
3. Cancer Research UK. Bladder cancer incidence statistics. 2020. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence#heading-Zero [Accessed 15 December 2020].
4. Office of National Statistics. Cancer survival in England - adults diagnosed: 2013 - 2017 edition. 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 4 January 2021].
5. Cancer Research UK. Bladder cancer treatment statistics: Surgery to remove the tumour for bladder cancer. 2017. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/diagnosis-and-treatment#heading-One [Accessed 19 February 2021].
6. National institute for Health and Care Excellence. Bladder cancer: diagnosis and management. NICE Guideline 2. Full Guideline. 2015.
7. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet. 2020;395(10232):1268-77.
8. Bristol Myers Squibb. Advisory board: Nivolumab for post-resection adjuvant treatment of high-risk muscle invasive urothelial cancer. 2021.
9. Stein JP, Lieskovsky G, Cote R, et al. Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients. Journal of Clinical Oncology. 2001;19(3):666-75.
10. Sargos P, Baumann BC, Eapen L, et al. Risk factors for loco-regional recurrence after radical cystectomy of muscle-invasive bladder cancer: A systematic-review and framework for adjuvant radiotherapy. Cancer Treat Rev. 2018;70:88-97.
11. Leow JJ, Orsola A, Chang SL, et al. A contemporary review of management and prognostic factors of upper tract urothelial carcinoma. Cancer Treat Rev. 2015;41(4):310-9.
12. Yoo SH, Kim H, Kwak C, et al. Late Recurrence of Bladder Cancer following Radical Cystectomy: Characteristics and Outcomes. Urol Int. 2019;103(3):291-6.
13. Hautmann RE, de Petriconi RC, Pfeiffer C, et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol. 2012;61(5):1039-47.
14. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol. 2015;16(1):76-86.

15. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management [NG2]. UK: NICE, 2015.
16. Zhegalik AG, Polyakov SL, Rolevich AI, et al. Long-term results of a single-center prospective randomized trial assessing efficacy of a shortened course of adjuvant chemotherapy after radical cystectomy in patients with locally advanced bladder cancer. Cent European J Urol. 2020;73(1):26-32.
17. Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol. 2012;23(3):695-700.
18. Bristol Myers Squibb. Summary of Product Characteristics. OPDIVO 10 mg/mL concentrate for solution for infusion. . 2021.
19. British National Formulary. Nivolumab solution for infusion. 2021. Available at: https://bnf.nice.org.uk/medicinal-forms/nivolumab.html [Accessed 31 January 2021].
20. ClinicalTrials.gov. An Investigational Immuno-therapy Study of Nivolumab, Compared to Placebo, in Patients With Bladder or Upper Urinary Tract Cancer, Following Surgery to Remove the Cancer (CheckMate 274). 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT02632409 [Accessed 5 January 2021].
21. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. New England Journal of Medicine. 2021;384(22):2102-14.
22. Bajorin DF, Witjes JA, Gschwend J, et al. First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab versus placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma. Journal of Clinical Oncology. 2021;39(6_suppl).
23. Bristol Myers Squibb. Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2020.
24. Bristol Myers Squibb. Erratum to Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2021.
25. Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. The Lancet Oncology. 2016;17(11):1590-8.
26. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017;18(3):312-22.
27. Griffiths G, Hall R, Sylvester R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011;29(16):2171-7.
28. Office of National Statistics. National life tables: UK. 2020. Available at: [Accessed

29. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-13.
30. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30(2):191-9.
31. National Institute for Health and Care Excellence. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA492]. 2017. Available at: https://www.nice.org.uk/guidance/TA492 [Accessed 11 January 2021].
32. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. J Clin Oncol. 2009;27(33):5634-9.
33. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006;107(3):506-13.
34. Reesink DJ, van de Garde EMW, Peters BJM, et al. Treatment patterns and clinical outcomes of chemotherapy treatment in patients with muscle-invasive or metastatic bladder cancer in the Netherlands. Scientific Reports. 2020;10(1):15822-.
35. Bristol Myers Squibb. Clinical expert consultation. 2021.
36. National Institute for Health and Care Excellence. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf [Accessed
37. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making. 2014;34(3):343-51.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Clarification questions

September 2021

File name	Version	Contains confidential information	Date
ID2694 Nivolumab adj UC ERG clarification letter	0.4	Yes	01/10/21

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searching

A1. Company submission (CS) Appendices D and G. Both the clinical and economic systematic literature reviews (SLRs) state that "searches for relevant literature were conducted in Embase, Medline (In-Process), and Cochrane". Did the company also search the full version of MEDLINE (including "online ahead of print")?

Yes, the full Medline database has been searched, including online ahead of print.

A2. CS Appendices D and G. The ERG's usual practice for systematic reviews is to recommend searching databases one at a time, to gain maximum benefit from advanced features such as subject indexing and limits. Please comment on your reasons for searching EMBASE and Medline together with a single strategy and any limitations this may have had on your search.

The ProQuest search engine that was used for the searches allows to search Embase and Medline simultaneously. The search strategy is developed in such a way that the subject indexing and limits match both the Embase and Medline databases, so that no relevant publications are missed out. The main advantage of using this ProQuest search engine is that duplicate references between Embase and Medline will be removed from the final search count.

A3. CS Appendix D section 2.2, page 15. The PICOS for the clinical SLR as presented in Table 2-1 states that case-control studies are eligible for inclusion if they include relevant outcomes – indeed, specific search terms related to case-control studies are included (lines 58, 65 and 72 of the Embase/MEDLINE strategy). However, line 96 of the same strategy excludes "case NEAR/1 study" (i.e. "case" occurring within one word of "study")". Did the search retrieve any case control studies and if not, might this be an explanation?

Yes, these were identified with the search and one case-control study was considered eligible for inclusion. The search string "case NEAR/1 study" was specifically designed to exclude "case study".

A4. CS Appendices D and G. The ERG notes that for both the clinical and economic SLRs, search terms relating to radical resection are present in both the population facet (e.g. line 8 of the MEDLINE/EMBASE clinical search) and the intervention facet (e.g. line 13 of the same strategy). Please explain the reasoning behind including this concept in both facets rather than one or the other.

To have consistency between the clinical and economic SLR, it was decided to have the same search strategy approach for population terms. As for the economic SLR no interventions are being incorporated, the terms for radical/complete resection needed to be part of the population search strategy. To identify only clinical studies assessing adjuvant therapy (i.e. post-surgery) it was decided to include terms for post-surgery, to reflect the eligibility criteria of the clinical SLR.

A5. CS Appendices D and G. It is conventional practice in database searches to deduplicate results at the end of the search. Please comment on your reasons for deduplicating line-by-line and any implications this may have had on your results.

When searching Embase and Medline through ProQuest, the search engine combines the results from both databases and removes duplicates from the search. ProQuest identifies duplicate documents in general databases based on the following fields: article title, publication title, publication year and author (in the case of short titles). In each search line, one reference/entry of the duplicate pair will

remain in the results. Therefore, when multiple search lines are combined, no references are missed by the search even though the individual search line results have been duplicated. To our knowledge, no references have previously been missed by this approach in previous systematic literature reviews.

A6. CS Appendix D and G. The ERG notes that in each of the search strategies presented, filters based on those developed by the Scottish Intercollegiate Guidelines Network have been used to limit the results to eligible types of study. Please describe how you ensured that these filters, originally designed for single database use, were optimised for use in a multi-file search context (providing citations to any published studies which validate the effectiveness of this approach).

The SIGN filters were translated while consulting the search syntax guides of the original search engines, the search syntax guide of ProQuest and the publication by Neyt and Chalon (2013),[1] as additional guidance. The translated search syntax has been replicated as closely as possible. When this would not be possible, the safer alternative has been chosen. For instance, if a Boolean operator for NEAR was not available, this would be replaced by an AND operator.

CheckMate 274 trial

A7. Priority: CS Figures 11 and 12, pages 59 and 60. The figures are used to suggest that nivolumab has no detrimental effect on utility. Please clarify the extent to which this could be confounded by patients not having progressed in the nivolumab arm which would be associated with utility improvement over placebo.

Although this query references Figures 11 and 12 from the CS, a review of the utility analyses presented in Appendix L confirms that nivolumab does not have a detrimental effect on utility. The two tables below present the mean Dolan Time Trade-off (TTO) utilities over recurrence states and the Dolan TTO utility per visit (on treatment) respectively.

TTO utilities over recurrence states:

Dataset	Nivolumab Mean (95% CI)	Placebo Mean (95% CI)	Pooled Mean (95% CI)
All pre-recurrence	[redacted]	[redacted]	[redacted]
On treatment pre-recurrence	[redacted]	[redacted]	[redacted]
Off treatment pre-recurrence	[redacted]	[redacted]	[redacted]
All pre-recurrence (exclude baseline)	[redacted]	[redacted]	[redacted]
All post-recurrence	[redacted]	[redacted]	[redacted]
CI: confidence interval			

Dolan TTO utility per visit (on treatment):

Visit	Nivolumab Mean (95% CI)	Placebo Mean (95% CI)
BASELINE	[redacted]	[redacted]
WEEK 5	[redacted]	[redacted]
WEEK 9	[redacted]	[redacted]
WEEK 13	[redacted]	[redacted]
WEEK 17	[redacted]	[redacted]
WEEK 21	[redacted]	[redacted]
WEEK 25	[redacted]	[redacted]
WEEK 31	[redacted]	[redacted]
WEEK 37	[redacted]	[redacted]
WEEK 43	[redacted]	[redacted]
CI: confidence interval; TTO: time trade-off. Limited to visits with ≥ 10 observations.		

As noted in Appendix L, patients receiving placebo reported better quality of life at baseline than patients receiving nivolumab, although the difference was not statistically significant. This trend towards higher utilities reported by patients receiving placebo was maintained throughout the trial, but no significant difference in mean utility was observed between nivolumab versus placebo in either the pre-recurrence versus post-recurrence analysis, or in week-by-week analysis of the on-treatment period.

Further to this, if taking the “on treatment pre recurrence” estimate, a value of [redacted] was reported for both nivolumab and placebo, indicating that while patients were disease free and on treatment, patients treated with nivolumab had a similar quality of life as placebo. Therefore, this supports the conclusion that nivolumab does not

have a detrimental impact on utility and this interpretation is not confounded by the improved efficacy for nivolumab.

The points above demonstrate that nivolumab does not have a detrimental impact on utility, however, it is clear that if a patient experiences recurrence (either on treatment with nivolumab or with placebo) they will also experience reduction in utility. This is evidenced through previous analyses on QoL data from CheckMate 274 based on EORTC QLQ-C30 and EQ-VAS, which have shown recurrence was associated with confirmed deterioration in QoL, irrespective of treatment received.[2] In addition, a decrement in utility of [redacted] was observed for recurrence independent of treatment arm, as shown in the EQ-5D-3L utility analysis (see table above and table 39 in CS).

Therefore, this is an important distinction to be made in that there is evidence to confirm that nivolumab does not have a detrimental impact on utility, for example the utility values for patients who are pre-recurrence and treated with nivolumab or placebo are similar. However, if a patient experiences recurrence with either nivolumab or placebo, utility will decrease as patients experience a recurrence of their cancer. As a result, given the positive efficacy results from the CheckMate 274 trial, which reported significantly improved DFS for nivolumab, it would be expected that patients who were treated with nivolumab accrue more QALYs given the longer time spent recurrence-free than placebo. Patients treated with placebo experience earlier recurrence than nivolumab, and more patients experience disease recurrence with placebo, therefore, it is expected that these patients who experience disease recurrence will also experience a decrement to their utility. The above has been considered by clinical KOLs a logical conclusion to draw from the study results,[2] and is consistent with the economic modelling, where utility values are pooled for nivolumab and placebo pre-recurrence, and then separately post-recurrence, with a decrement applied for recurrence.

A8. Priority: CS Table 16, page 53. The table shows time to recurrence data for all randomised patients.

a) **Please clarify why no Kaplan-Meier (KM) plot of time to recurrence was provided alongside Table 16.**

A time to recurrence KM plot has not been generated as the KM product-limit method is not designed to accommodate the competing risk. Therefore, given the presence of competitive risk, time to recurrence is presented in the cumulative incidence plot below. It is worth noting that the median time to recurrence is [redacted] months for nivolumab versus [redacted] months for placebo, giving a benefit in median time to recurrence of nearly a year.

Cumulative incidence of time to recurrence

b) **Please clarify whether the time of death events could be inferred if the company has the KM for DFS events and the KM for recurrence.**

The exact time of death events cannot not be inferred as there is no KM for recurrence as explained in a).

c) **Please provide breakdown of disease-free survival (DFS) events for both arms by whether the event was a disease recurrence or death. If these rates are substantially different then please incorporate this within the economic model.**

Across both arms in CheckMate 274, only [redacted] events (out of [redacted] total DFS events) were deaths, representing a very small proportion of DFS events. This represents only [redacted]% of events, and the number of death events was fairly similar between arms ([redacted] and [redacted] events per arm) as shown in the table below for placebo and nivolumab, respectively. Additionally, whilst the total number of death events is known, the company remains blinded to OS data, and, as a result, do not have information on when these death events took place (see question A19). Timing of these death events will only be ascertained when OS is fully unblinded. Due to the highly immature nature of the data for death pre-recurrence, the low number of death events, and the lack of information on the timing of these events, it is not considered appropriate to stratify these values in the economic model by treatment arm.

	Nivolumab (N=353)	Placebo (N=356)
Number of events (%)	[redacted]	[redacted]
Type of events (%)		
Disease at baseline	[redacted]	[redacted]
Recurrence	[redacted]	[redacted]
Death	[redacted]	[redacted]
Source: CSR [redacted][3] (Table S.5.26.1, p.88)		

A9. CS page 128. Please clarify whether the analysis of complete case data subset for utility EQ-5D-3L questionnaires may be confounded by informative censoring. Please also clarify why imputation was not used for sensitivity analyses.

For on-treatment patients, we do not observe much missingness with a high proportion of patients reporting. Missingness showed no strong pattern of increasing or decreasing compliance over time for nivolumab or placebo (see Appendix L: Section 3.5.1 for details) and was not clearly associated with proximity to death or recurrence. There was insufficient evidence to reject the assumption of MCAR (missing completely at random), with no need to use imputation for sensitivity analyses, as the complete data is already a good representation of the full data set.

For off-treatment there was a higher proportion of patients presenting missingness in comparison to on-treatment, however, the majority of patients who stopped treatment did continue to complete further questionnaires. Since this is consistent with the study design, namely the 12-month stopping rule, there is no obvious correlation that suggests the complete case data subset for the utility data is confounded by informative censoring that may be caused by a decline in health state for example.

Although there is a greater case for using imputation for the off-treatment case data than the on-treatment case data, using imputation has the potential to introduce a new bias. Therefore, to reduce introducing bias, it was decided to keep the goodness of representation currently in the complete case data.

A10. CS Figure 7, page 51. Please supply a version of the DFS KM function plots with 95% confidence intervals (CIs).

[redacted]

Number of cumulative censors at each 6 month interval in each arm:

Time (Months)	6	12	18	24	30	36	42	48	54
Nivolumab	[redacted]								
Placebo	[redacted]								

A11. Please provide the KM plot for time on treatment for patients on nivolumab.

[redacted]

A12. CS Figure 10, page 57. Please clarify why a mixed effects repeated measure model was needed rather than taking the mean and CIs at each timepoint.

The validity of taking the mean and CIs at each timepoint relies on the assumption that the missing observations are MCAR. The Mixed Models for Repeated Measures (MMRM) is a more robust method that takes into account missing data (including MCAR and data missing at random (MAR)) and potentially confounding variables.[4-6] The results of MMRM and simple analysis of observed means are usually consistent unless there is a systematic pattern in the missing data confounded with the outcome variable. We conducted both analyses to confirm the consistency and presented the MMRM as the most robust method for use in our analyses.

A13. CS Section 2.6, pages 50-61. Please provide results of the log-rank tests for comparison of survival between treatment arms for each of the different reported endpoints.

Results of the log-rank tests are provided in the table below.

	Nivolumab (N=353)			Placebo (N=356)			Nivolumab vs. Placebo	
Endpoint	Events n (%)	Censored n (%)	KME (95% CI) (months)	Events n (%)	Censored n (%)	KME (95% CI) (months) (1)	HR (95% CI) (2)	p-value (3)
DFS Primary definition	170 [redacted]	[redacted]	20.8 (16.5, 27.6)	204 [redacted]	[redacted]	10.8 (8.3, 13.9)	[redacted]	[redacted]
DFS Secondary definition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NUTRFS	162 [redacted]	[redacted]	22.9 (19.2, 33.4)	190 [redacted]	[redacted]	13.7 (8.4, 20.3)	0.72 (0.59, 0.89)	[redacted]
DMFS	132 [redacted]	[redacted]	40.5 (22.4, N.A.)	152 [redacted]	[redacted]	29.5 (16.7, N.A.)	0.75 (0.59, 0.94)	[redacted]

CI: confidence interval; DFS: disease-free survival; DMFS: distant metastasis-free survival; HR: hazard ratio; KME: Kaplan-Meier estimate; NUTRFS: non-urothelial tract recurrence free survival

(1) KME of median time to event. Two-sided 95% CI is computed by Brookmeyer and Crowley method (log log transformation)

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (>=1% versus <1%/indeterminate) as entered in IRT.

Source: BMS data on file,[7] Bajorin 2021[8]

A14. CS Section 2.6, page 50. Please clarify how the median follow-up time was calculated. How does the minimum follow up of 5.9 months in CheckMate 274 relate to the stated ranges with lower limits 0.1 and 0.0 in the nivolumab and placebo arms respectively?

Median follow-up is calculated at the patient level, where the extent of follow-up is derived as the time between patient's randomisation date and his/her last known alive date or death. The median, minimum and maximum values are then calculated as per usual calculation/statistics.

Conversely, minimum follow-up is calculated at the study level and is defined as time from clinical cut-off date to the last subject's randomisation date. The minimum study follow-up is thus the difference between time of when the last subject was randomised and time of the data cut-off for the database lock, being 5.9 months for the August 2020 DBL.

A15. CS Table 10, page 45. Please clarify whether those patients who continue in the study received any further treatment. In addition, please clarify why the numbers of patients who are categorised as continuing the study or discontinuing the study do not sum to the total number of treated patients.

Details of subsequent anti-cancer therapy received by patients in the study are reported in Table 25 on page 81 of the company evidence submission. Subsequent therapies included radiotherapy, surgery, systemic therapy and immunotherapy; full details of therapies are available in CSR Table 6.1-6.1, page 102.[9]

The values for the patients categorised as continuing the study or discontinuing the study do not sum to the total number of treated patients because these values refer to patients who completed or discontinued treatment in the treatment period only, and therefore, exclude those receiving ongoing treatment in the treatment period. For example, [redacted] ([redacted] + 187) nivolumab treated patients completed or discontinued treatment, and of these [redacted] patients, [redacted] continued the study and [redacted] discontinued the study.

A16. CS Table 10, page 45. Please clarify whether those patients who completed treatment ([redacted] on nivolumab versus [redacted] on placebo) are a subset of patients who discontinued treatment (187 on nivolumab versus 196 on placebo).

The patients who completed treatment are not a subset of patients who discontinued treatment. Patients were either currently on treatment, they had completed treatment or had discontinued treatment due to one of the reasons described in the 'Reasons for discontinuation of the treatment period' section of CS Table 10.

A17. CS Section 2.5, page 49. The ERG notes that assessment of included study quality has been undertaken using the CRD tool. The more recent Cochrane Risk of Bias 2 assessment tool includes an assessment of the effects of deviations from intended interventions on study outcomes and the potential risk of bias. Why did the company not apply the Cochrane Risk of Bias 2 tool?

The company followed the NICE user guide (Section 2.5) which refers to the CRD for the key aspects to be considered.[10]

A18. CS Table 11, page 46. Please provide the interquartile range and standard deviation for ages in both arms.

	Nivolumab	Placebo
Interquartile range	[redacted]	[redacted]
Standard deviation	[redacted]	[redacted]
Source: Clinical study report[9]		

A19. Please clarify when the CheckMate 274 final analysis for DFS and interim analysis for overall survival (OS) are expected. Please also clarify when the final analysis for OS is expected.

The DFS interim analysis (August 2020 database lock) met its pre-specified statistical significance criteria; therefore, it is considered the final DFS analysis. The OS IA1 (first interim analysis) was planned in [redacted], however, the number of deaths (~[redacted]) to trigger the interim analysis in all randomised patients was not reached, therefore, the company remained blinded to this data. The OS IA2 (second interim analysis) is planned when [redacted] OS events are observed, which is currently estimated to take place in [redacted]. The final analysis is planned when [redacted] OS events

are observed, projected for [redacted]. Both timelines are subject to change given the event-driven nature of the analyses.

A20. CS Section B.2.6.3.3, page 55. Please clarify the definition of "clinically meaningful" in relation to progression-free survival on next therapy line (PFS2). Given that the result is not statistically significant please comment on whether "potentially clinically meaningful" would be more appropriate.

The company agrees that "potentially clinically meaningful" is appropriate.

A21. Clarify whether the company have Early Access to Medicines Scheme (EAMS) data and whether these could have been used to inform the submission.

There are no EAMS data available for this submission.

Section B: Clarification on cost-effectiveness data

B1. Priority: Please provide an updated base case (deterministic and probabilistic) that incorporates all changes that are made following the clarification process. Provide supplementary analyses as you see fit.

Following the amendments to the model requested in B35 and B36 (i.e. amending "Total recurrence benefits [undiscounted]" column in the Control Trace to correctly refer to time in years instead of discount factor and adjusting the "Initial disease-free costs [undiscounted]" column to include the "Disease-free multiplier" column in the Control Trace), the updated deterministic base case results are presented in the table below.

Updated deterministic base case results ([redacted]% PAS)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,813
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

Compared to the initial submission, the amendments lead to a small increase in the incremental QALYs ([redacted]), resulting in a £25/QALY reduction in ICER (£32,818/QALY vs £32,838/QALY in the base case).

Deterministic base case results (initial submission)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,838
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

The probabilistic sensitivity analysis results, scatter plot of the 1,000 PSA iterations and the cost-effectiveness acceptability curve are showed below. The probability of nivolumab being cost-effective compared to BSC is 42% at a £30,000/QALY willingness-to-pay threshold.

Updated probabilistic sensitivity analysis results ([redacted]% PAS)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,917
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

Updated scatter plot

[redacted]

Updated cost-effectiveness acceptability curve

[redacted]

Probabilistic sensitivity analysis results (initial submission)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)

NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,922
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

B2. Priority: The model base case assumes that for people in the DFS state at 5 years there is no risk of disease progression beyond this time point and that all-cause mortality rates are applicable. As such, the projections of DFS beyond 5 years become irrelevant. As the Gompertz model fit the data well for the first five years please clarify why it was not used for DFS. Please provide results assuming a Gompertz distribution for the initial 5-year period for both arms.

The company base case uses a piecewise approach to modelling DFS, using KM data with a parametric extrapolation from a set cut-point. This approach minimises inaccuracy in predictions at early time points, and provides clinically valid survival estimates, as explained in the company submission (appendix K, survival report).

Upon review of fully parametric (i.e., from randomisation) models fitted to the DFS trial data, the Gompertz model has the lowest AIC and BIC for placebo, but not for nivolumab (see full company submission Appendix K, Figure 8 and Figure 9). As placebo and nivolumab are modelled independently, the selection of survival model must be optimal for both treatment arms, and Gompertz does not have the lowest AIC or BIC for nivolumab. Additionally, the Gompertz model may have the lowest AIC/BIC for a fully parametric model for placebo compared with the other parametric models, but this does not necessarily mean it is a good fit. For example, it does not accurately capture the pattern of the KM data from the trial, in particular the protocol-induced features, such as the ‘stepwise’ nature of the data, particularly in the first year (further described in Appendix K of the company submission, displayed in Figure 1 and Figure 2).

Figure 1. Investigator-assess DFS for placebo: Gompertz statistical model overlaid upon Kaplan-Meier, up to 60 months
95% confidence intervals obtained by data bootstrap (1,000 repetitions).

Figure 2. Investigator-assess DFS for nivolumab: Gompertz statistical model overlaid upon Kaplan-Meier, up to 60 months
95% confidence intervals obtained by data bootstrap (1,000 repetitions).

Additionally, no scientifically valid rationale has been provided to use a single parametric curve from randomisation, considering the steps in DFS that are observed and complex hazard pattern observed for both arms over the available trial period. These points guided the company's original approach of a piecewise approach. Piecewise semi-parametric models were fit under the assumption that the data represent a single population whose hazard profile would settle to a recognisably parametric form after a period of time. This semi-parametric approach is the preference of the company based on its ability to account for censoring, clinical feasibility for survival estimates, and utilising trial data itself, where appropriate. Upon comparing the KM data, company base case KM + Weibull approach, and Gompertz model, it can be seen that at almost every timepoint the company base case model fits better to the KM data and is therefore a more suitable modelling approach, and in particular at early timepoints less than two years, aligning with previously described protocol-induced features in the data (Table 1).

The clinical plausibility of the fully parametric Gompertz models for nivolumab and placebo is not established. Although the long term DFS projections beyond 5 years are less relevant for validation, due to background mortality hazards being applied from this timepoint, the DFS estimates up to 5 years still require validation. In particular, since DFS at 5 years drives the long-term disease-free survival for the remainder of the time horizon. Survival estimates for company's base case curves of KM + Weibull were validated based on clinical expert opinion, and Sternberg et al.[11] for the placebo arm (as described in Appendix K of the submission).

Clinical experts indicated that recurrence beyond 5 years is rare, and patients who reach 5 years following surgery without recurrence would be discharged.[12,13] Therefore, the company model substitutes DFS weekly hazards for age- and sex-matched mortality rates from UK life tables[14] from 5 years in both arms of the trial.

It follows that DFS would plateau from 5 years (regardless of treatment), given that patients who remain disease free for 5 years are unlikely to recur. Assessment of landmark survival estimates for the Gompertz curves (Table 1), and hazards (Figure 3, Figure 4) shows that this is not replicated if using the fully parametric curves. The nivolumab Gompertz curve overpredicts and then underpredicts the KM data and does not trend towards the plateau which was expected by clinical experts. In

addition, the nivolumab Gompertz curve trends down from the data, likely underestimating the proportion of patients who should return to general population mortality from 5 years. Therefore, the hazard for the nivolumab curve is not captured by Gompertz, but is captured by the company base case curve.

Conversely, the placebo DFS Gompertz model begins to approach general population hazards from approximately 3 years (Figure 4, Table 1), likely overestimating the proportion of patients who should return to general population mortality from 5 years; and deviating from the clinical expectations of general population mortality and limited recurrence (i.e. a plateau in DFS) from the later timepoint of 5 years. After 3 years in the placebo DFS Gompertz model, very few patients either recur or die from the disease-free state (as indicated by a plateau in hazards). Within the nivolumab DFS Gompertz model, clinical expert opinion, and company base case curves, survival continues to decrease up to 5 years. Therefore, it would not be clinically feasible that this change to limited recurrences and general population mortality would occur at different timepoints for each treatment arm using the same survival models (i.e., Gompertz). This adds to the argument that fully parametric Gompertz curves are not clinically justifiable. The company base case, using a KM + Weibull semi-parametric approach, provides a closer fit to the observed trial data in both arms and thus is appropriate for decision making.

Figure 3. Investigator-assessed DFS for nivolumab (CheckMate 274, August 2020 DBL): Smoothed hazard function estimates for trial data, and Gompertz model.

DFS: Disease-free survival; R-P: Royston-Parmar

Figure 4. Investigator-assessed DFS for placebo (CheckMate 274, August 2020 DBL): Smoothed hazard function estimates for trial data, and Gompertz model.

DFS: Disease-free survival; R-P: Royston-Parmar

Table 1. Landmark disease-free survival estimates up to 5 years

		Time						
		2 month	**6 month**	**1 year**	**2 year**	**3 year**	**4 year**	**5 year**
Placebo								
KM		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
KM 7.13 months + Weibull*	Raw	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% difference to KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Raw	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% difference to KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Nivolumab								
KM		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
KM 19.32 months + Weibull*	Raw	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% difference to KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Gompertz	Raw	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% difference to KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

* KM + Weibull curves were used within the base case analysis, and survival estimates from these curves have been validated based on clinical expert opinion for DFS estimates, i.e. the DFS estimates are clinically plausible.

KM = Kaplan Meier

Assuming a Gompertz distribution for the initial 5-year period for both arms provides the following results:

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,390
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

However, as noted above, the approach is not appropriate and flawed, and therefore not suitable to inform HTA decision making.

B3. Priority: Noting the caveats that the company has provided related to the indirect comparison of adjuvant nivolumab with adjuvant chemotherapy, it is anticipated that the NICE Appraisal Committee may still wish to see exploratory ICERs of this comparison in multiple sensitivity analyses.

a) Please provide an ICER using the HR presented in Section B.2.9.2.

As described in the CS it is not scientifically appropriate to compare nivolumab against adjuvant chemotherapy for reasons of clinical relevance, and concerns regarding the provided ITC, related to the limitations of the available data. From a clinical perspective the following points are noted:

- UK clinical experts confirm that BSC is the predominant strategy in the UK
- The majority of cisplatin-eligible patients will receive neoadjuvant cisplatin and therefore would not be eligible for cisplatin in the adjuvant setting
- Patients may also be ineligible for cisplatin in the adjuvant setting due to comorbidities, or simply refuse treatment

Further to this, the EAU guidelines state "*"There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy. An individual patient data meta-analysis of*

survival data from six RCTs of adjuvant chemotherapy included 491 patients (unpublished data from Otto et al., were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases). In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and Adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [485], and one trial used cisplatin monotherapy. The data were not convincing to give an unequivocal recommendation for the use of adjuvant chemotherapy."[15]

As a result, a comparison versus adjuvant chemotherapy, i.e. cisplatin, is not relevant to this clinical setting, and European international clinical guidelines do not report "unequivocal recommendation for the use of adjuvant chemotherapy". Therefore, the ITC is not relevant to this submission from a clinical perspective.

Despite this, the company provided an exploratory ITC for completeness, however, important, strong limitations related to the available data imply that results from this ITC are fundamentally flawed and thus is not suitable for decision making. It is also worth clarifying that the results are fundamentally flawed, not because of inappropriate methodology applied by the company, but due to strong limitations with the evidence base. As further detailed in section B.2.9 of the CS, these weaknesses include, but are not limited to:

- A large number of key differences existed between studies included in the ITC and the limitations impact the ability to reliably draw conclusions from the results to inform HTA decision making for this treatment comparison.

- Given the limitations in the evidence base, as detailed in the CS, the analysis used data from Group C of the CheckMate 274 trial. However, the CheckMate 274 study was neither stratified nor powered for subgroup analyses based on cisplatin eligibility.

- The analysis is based on very small sample sizes from the included studies

- As noted above, the EAU have highlighted important limitations in the evidence base regarding the use of cisplatin in this treatment setting

In conclusion, and as explained in the CS, BMS do not believe this ITC is scientifically appropriate to consider in this assessment considering the numerous scientific limitations, the irrelevance for the UK treatment setting as confirmed by clinicians, and the lack of an "unequivocal recommendation for the use of adjuvant chemotherapy" in European international clinical guidelines.

As a result, cost-effectiveness results for this comparison have not been provided as adjuvant chemotherapy i.e. cisplatin, is not relevant to the decision problem, and the available data do not facilitate robust indirect comparisons, which would be necessary to support any such decision making in this clinical setting.

Therefore, an ITC for nivolumab versus cisplatin-based adjuvant therapy is subject to major uncertainty, lacks robustness, is exploratory in nature and is insufficient to be used to inform HTA decision making.

b) Additionally, as MVAC has been shown to have 'similar effect' to GC, please pool the MVAC studies with the GC studies to re-estimate the HR, and to estimate an ICER.

In terms of study selection, the MVAC regimen (methotrexate, vinblastine, doxorubicin and cisplatin or methotrexate, vinblastine, pirubicin and cisplatin) is rarely used in UK clinical practice, according to expert clinicians consulted for the submission.[16] Clinical advice to the company stated that in the UK, gemcitabine plus cisplatin is preferred over MVAC based on a randomised trial that compared GC versus MVAC and showed similar effect of the two regimens but less haematological side effects for GC (sepsis, neutropenia).[17]

MVAC was therefore considered irrelevant to the UK setting and excluded from the ITC to remain relevant to UK clinical practice within this decision problem. An analysis using MVAC as comparator would not be appropriate to this decision problem.

c) Additionally, please undertake an analysis for UTUC patients alone, taking the UTUC patients from Group C of CheckMate 274 and the

studies in Table 3 of Appendix J that were excluded because the study was UTUC patients only to re-estimate the HR, and to estimate an ICER. If appropriate, please change the survival distribution of DFS survival to take into account that this group is UTUC patients only.

The UTUC population was too small to undertake any form of robust analysis. Also, CheckMate 274 was neither stratified nor powered for this subgroup. Therefore, an analysis using this subpopulation is not considered scientifically appropriate.

d) **Additionally, please undertake an analysis for all patients (where UTUC patients are not excluded) in Group C of Checkmate 274 to re-estimate the HR, and to estimate an ICER.**

The HR of nivolumab versus placebo from group C (including UTUC patients) was [redacted] compared to [redacted], when UTUC patients were excluded in both arms.

The HR of nivolumab from group C (including UTUC patients) versus adjuvant chemotherapy from the two GC studies and Sternberg pooled was [redacted] compared to [redacted], when UTUC patients were excluded in both arms.[18-20]

As observed, the confidence intervals around estimates are wide and crossing 1, with only marginal change to the point estimates themselves. Original estimates from the ITC were deemed insufficient to be used in HTA decision making based on the major uncertainty and lack of robustness as explained above. The impact of adding in UTUC patients into group C further introduces more heterogeneity, thus creating additional uncertainty in the analysis. The confidence intervals following inclusion of UTUC patients are similar to the ones when UTUC patients are excluded in both arms, and therefore are similarly inappropriate. Limitations are further explored in the answer to question B3 a).

e) **Please perform combinations of these analyses as deemed appropriate, for instance, provide a scenario analysis that combines all patients and includes MVAC studies pooled with GC studies.**

As described in the response to B3 a) and the subsequent responses B3 b-d), these analyses are deemed scientifically inappropriate for decision making and therefore no combinations have been analysed.

Supplemental information:

Following prior discussion with the ERG (during Zoom teleconference meeting, dated 8th October 2021), with regards to applying a random effect with informative prior, additional explanations are provided below on the rationale for the choice of fixed effect model and the appropriateness of random effect with informative prior.

When selecting a model to use for an NMA, one can choose a random-effects model, assuming there is heterogeneity across the included studies, or using a fixed-effect model, assuming that the true treatment effects for each study-comparison are the same (i.e. there is no between-study-variance). The first option can be considered more realistic when the evidence base is subject to heterogeneity, however, as there are a low number of studies included in this specific NMA (4 studies), using a vague prior on the between-study variation resulted in non-convergence of the random-effect model. A solution for this is to elicit expert opinion that can be used to set an informative prior on the between-study variance, which could lead to convergence of the random effect model. However, picking an informative prior without information of clinical expert input is problematic, as this could lead to implausible between-study variances when choosing a prior based on a half-normal or gamma distribution (as discussed in Dias et al.[21]) without clinical justification. Although the fixed effect model is subject to strong assumptions, using this model was preferred over choosing a prior for the between-study variation without clinical justification. Nonetheless, the company does not anticipate any major changes to the results or the appropriateness of this specific ITC, that could improve the robustness of the results due to the limitations in the evidence base underlying the analysis, by applying the random effect with an informative prior.

In addition, the company understood from the ERG that discrepancies in the ITC results were noticed while replicating the analysis. A small discrepancy in HR estimates for nivolumab vs. placebo within group C could be a result of the trial stratification. Namely, if no stratification factors were used in the ITC, the HR for CM-274 group C with UTUC patients excluded was [redacted]. However, to align with the methods previously applied by BMS, stratification for PDL1+ status and node status was used and therefore the HR estimate that served as an input for NMA was [redacted]. This may introduce a small difference in point estimates of the HRs between nivolumab and placebo within group C, as well as the HR for nivolumab compared with adjuvant chemotherapy. It is important to note that the results of these subgroup analyses must be interpreted with caution, as CM-274 was neither stratified by nor powered for this subgroup. As per the ERG request, the WinBUGS code that was used by the company to run the ITC is provided in Appendix A.

B4. Priority: Please clarify why it is assumed that having had urothelial cancer is not associated with a reduction in utility compared to the general population. Please explore the impact on the ICER of assuming that people in disease-free survival have a lower utility than an age- and sex-matched population, and of assuming that those who have progressed have a lower utility than those in the disease-free state. You may wish to refer to the discussions on this in the appraisal committee for NICE STA ID1676.

As discussed in Company submission B.3.4.1, no studies in relation to adjuvant treatment of MIUC were identified which were relevant to the indication and perspective under consideration, underlining the marked sparsity of utility data with which to populate the CEM. The primary source of HRQoL data used in the cost-effectiveness model was from the CheckMate 274 trial. Analysis of the trial utilities were the best available evidence but HRQoL within disease-free from the trial exceeded age-dependent general population values. To address this, all patients in the model (regardless of health state) were limited to that of an age-matched population to ensure validity to the population concerned.

A modelled patient in the disease-free state could be considered to have a similar utility to general population, as they are considered cured following surgery and

recovery. It is important to consider that general population measures, such as utility or mortality, are estimates of all individuals, rather than solely referring to “healthy” individuals. Therefore, the use of general population utility does not indicate that patients are without comorbidity, only that it is within the limits of that experienced by others of the same age.

It is acknowledged that patients who have experienced disease recurrence may have a utility lower than that of a general population group. This is particularly relevant for the patients in the recurred disease health state as they may be on further line of treatment. To adjust for this, for recurrence, the absolute difference in HRQoL ([redacted] disutility) between initial disease-free and disease recurrence observed in the trial was applied as a decrement to the age-dependent value. Therefore, those who have progressed will have a lower utility than those in the disease-free state at any time point.

B5. Priority: CS Section 3.3.2.1.4, page 118. Please provide the reasons why the overall proportion of DFS events that were deaths could not be used directly to estimate the probability of an event being a death. Please clarify the reasons for assuming that the same rate was generalisable to both arms and conduct sensitivity analyses using the estimated rate from each arm.

As described in question A8, the number of pre-recurrence death events in the CheckMate 274 trial was small ([redacted] DFS deaths for placebo, [redacted] for nivolumab; from Table S.5.26.1 in CSR [redacted]). This highlights the immaturity of this data. Additionally, although the total number of death events pre-recurrence is known, the timing of these events is not available since the company remains blinded to OS.

This is the rationale for using a logistic regression to determine the probability that a recurrence event was a death event. Further, due to the small number of events, immaturity of the data, and similarity in the data which does exist, the same rate was applied to both arms. Due to these reasons, which are further explained in question A8, additional analysis would not be appropriate.

B6. Priority: Please clarify why it is assumed that the impacts of urothelial cancer or possible characteristics associated with people who develop the disease do not impact on life-expectancy. Please perform sensitivity analyses

using varying levels of standardised mortality rates. You may wish to refer to the discussions on this in the appraisal committee for NICE STA ID1676.

After spending five years in the initial disease-free state, without recurrence occurring, patients would transition to the long-term disease-free/cure state. Feedback from clinicians described that if patients do not recur after five years post-surgery,[12] they are no longer subject to monitoring and are assumed to have mortality close to the general population, therefore not impacting life-expectancy.

It is of importance to note that general population mortality is an estimate of all individuals with different health states and comorbidities at a certain age and it is not indicative of a sample of healthy individuals only.

Moreover, the review of the smoothed underlying hazard plots, as presented in the Survival analysis report (Appendix K), for the nivolumab and placebo arms show a tendency towards age- and sex-matched lifetable hazards for patients in the CheckMate274 trial, potentially indicating long-term remission for a proportion of patients; however, the slope of the hazard is higher and illustrates a steep decline in the placebo arm, stabilising close to lifetable mortality earlier in the data than those in the nivolumab arm, where the slope is lower and this stabilisation close to the lifetable mortality happens more gradually. This is suggesting that nivolumab delays recurrence in some patients who would otherwise have experienced recurrence, as reaching the lifetable mortality means recurrence happens earlier, supporting the positive clinical benefit of nivolumab.

Investigator-assessed DFS for nivolumab (A) and placebo (B) (CheckMate 274, August 2020 DBL): Smoothed hazard function estimates.

DFS: Disease-free survival; R-P: Royston-Parmar. Confidence interval is shown around b-spline estimator

B7. Priority: CS Section 3.4.2.1, page 128. it says that treatment could go beyond 1 year at the clinician's discretion. It is noted that 6% of observations were censored due to remaining on treatment.

a) **Please clarify whether the 1-year stopping rule was a strict condition or whether dose delays could mean that the intended treatment may occur over a longer time frame.**

The trial design specifies that treatment is administered every two weeks until recurrence or discontinuation from study, for a maximum of 1 year,[9] therefore a strict treatment stopping rule is applied at 1 year.[22] This aligns with the expected marketing authorization.

At time of cut-off (27 August 2020), [redacted] patients in the nivolumab arm and [redacted] patients in the placebo arm were off treatment. The remaining [redacted] of observations were censored due to still being on treatment, not because their treatment period extended beyond 12 months.

The majority of treated patients in both arms received all doses without delay and, of those patients who did have doses delayed, only a minority had more than one delayed dose. In the nivolumab arm, [redacted] patients had at least one dose delayed with [redacted] experiencing more than one delayed dose. In the placebo arm, [redacted] patients had at least one dose delayed with [redacted] experiencing more than one delayed dose.[9] It is important to note that these patients did not receive more than the maximum possible 27 doses, as reported in Section B.2.10.1, Table 20 of the submission.

There were only [redacted] patients in the study who had a treatment duration of 12 months or longer,[redacted] patients in the nivolumab arm and [redacted] patients in the placebo arm. Of these, [redacted] patients received their final treatment exactly 1 year after their treatment start date, whereas the remaining [redacted] went beyond 12 months by a maximum of [redacted] months ([redacted] days). It is unlikely that these [redacted] patients with dose delays will impact the DFS results as they did not receive more than the maximum possible 27 doses, therefore running a scenario where stopping rule is removed is not appropriate.

b) Please clarify whether these ongoing treatment costs after 1 year are incorporated into the model.

Treatment costs comprising drug acquisition and administration past 1 year are not incorporated into the model.

c) Please provide a scenario analysis where KM data for time on treatment are used without applying the 1-year stopping rule.

While a small number ([redacted]) patients continued treatment past 1 year, they did not receive any additional doses compared to the other patients and this is exclusively due to dose delay. No patients received more than the maximum 27 doses, therefore there would be no additional treatment cost and removal of this 1 year stopping rule is not appropriate.

In the model, due to dose delays [redacted] patients and [redacted] patients receive nivolumab past 1 year, at 53 and 54 weeks. Removing the 1-year stopping rule to account for nivolumab-related treatment costs, leads to an increase in treatment costs of [redacted]QALY compared to the base case [redacted]/QALY vs [redacted]/QALY).

Scenario analysis removing the 1-year stopping rule

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,090
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

B8. Priority: CS Section 1.3.4, page 23. Based on the data within Hautmann et al, 6 years may have been a better timepoint of assuming a 'cure'? Please provide a scenario analysis assuming a 'cure' at 6 years.

Based on UK clinicians' opinion and smoothed underlying hazard plots for DFS, the Company applied a conservative approach and assumed a long-term disease free/cure at 5 years in their original submission. The study by Hautmann et al, was undertaken in Germany, therefore not reflective of the UK clinical practice.

Results using a cure of 6 years are as follows:

Scenario analysis assuming cure at 6 years

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,486
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

B9. Priority: Please provide a scenario analysis using a cohort with a starting age of 70 years and 78.9% male resembling the cohort reported in Pang et al.

The cohort reported in the Pang et al.[23] publication is not comprised of muscle-invasive urothelial carcinoma exclusively, which represents the population of interest in the CEM, but a combination of indications: non-muscle invasive bladder cancer (51.3%), muscle-invasive bladder cancer (47.2%) and in situ carcinoma (5.8%).

The population in the Pang et al. paper does not include UTUC patients either, which are included within the population of interest. Therefore, attributing baseline characteristics from Pang et al. to the modelled cohort is not appropriate, as it is not reflective of the population of interest. Additionally, this would incorporate inconsistencies into the model, since efficacy in the model is based on the characteristics of the trial population. Therefore, it would not be appropriate to simply modify the age and % male to align with that of Pang et al.

Survival analysis

B10. CS Figure 29, page 112. Please comment on whether the mode may simply be an artefact of the delay until 3 months before first assessment and whether a monotonically decreasing hazard may be more realistic as this has implications for survival model selection.

The mode is predominantly a protocol-induced feature due to the timing of the tumour assessments as the first assessment occurred at 3 months and so

cumulative recurrence in that initial 3-month period from high-risk or non-responding patients is captured at this first assessment.

As hazards tend towards general population mortality rates a monotonically decreasing hazard may be more realistic, but it is not appropriate for informing choice between models with different cut points if considering semi-parametric models. Semi-parametric piecewise curves were fit on the assumption that the complex hazard profiles underlying the DFS were an artefact of the timing of tumour assessments.

B11. CS Section 3.3.2.1.4, page 118. Please provide more details of the logistic regression used to estimate the probability a recurrence is a death. For example, were any covariates included?

The economic model consists of only three states, the transition rates between which are dependent only upon time. Therefore, additional covariates were not included in the model, as the distribution of these predictive covariates is not predicted per state within the economic model, i.e. the models are marginal. Various transforms of the time covariate, and linear combinations thereof, were explored as possible forms for the linear predictor of a logistic regression model.

B12. CS Section 3.3.2.1.5, pages 118-120. We note that in Figure 32 of the CS that (i) the base case distribution does not lie between the Bellmunt et al and De Santis et al curves between approximately 1.25 and 3 years, (ii) that the median survival in the base case is greater than in both KM curves and also that (iii) the long-term survival appears to be underpredicted in the base case suggesting that the derived curve is not appropriate. Please comment on whether it would be more appropriate to synthesise the parameters of survival models fitted to the two survival curves from the literature. If appropriate, please conduct an analysis with a better fitting distribution.

While synthesising the parameters of the survival models from the literature would have been more appropriate, it would have added more complexity to the model, with potentially little difference in the outcomes. We have conducted sensitivity analyses using doubled post-recurrence and halved post-recurrence survival based on Bellmunt et al. and de Santis et al. curves (Section B.3.8.3.5) and the changes were minimal (£34,821/QALY and £32,085/QALY,).

Therefore, the model is not sensitive to this parameter, and conducting this analysis with a more complex curve-fitting would not strongly influence the results.

Scenario analysis: impact of altered recurrence to death transition (doubled survival post-recurrence)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,821
CER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

Scenario analysis: impact of altered recurrence to death transition (halved survival post-recurrence)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,085
CER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

B13. CS Section 3.3.2.1.6, page 121. Please provide further details of how expert opinion was used in survival model selection including any elicited survival proportions which were used as selection criteria. Also, in Appendix K, Section 3.1.7, page 33. Please clarify how the clinician predictions of DFS were obtained. The value of 26% suggests that some averaging may have been used. If possible, please provide the full range of elicited values.

As described in appendix K section 3.1.7, clinical expert feedback was sought at two stages, once to initially describe general expectations of how risk would develop over time, and then the plausibility of specific curves and their survival estimates was established. After establishing an understanding of risk over time (namely that recurrence risk is minimal, and death can be assumed to be equivalent to general population mortality from 5 years), a shortlist of curves was determined.

The full decision process is summarised in Figure 16 of Appendix K of the original submission. Decisions were made to determine cut points and parametric tails for

semi-parametric models, including visual inspection of hazards and a continuing reduction in hazards over time. Visual inspection of cumulative hazards allowed selection of candidates as shown in Figures 14 and 15 of the survival report (appendix K). These candidate curves were also presented to clinicians. Clinical advice to the company highlighted that the estimates produced by the KM + Weibull model were most clinically plausible, particularly at year 10. The value of 26% was the 5-year DFS estimate produced by KM + Weibull for placebo, which clinicians agreed was appropriate and clinically plausible.

B14. Appendix K, Figure 4, page 20. Please supply a version of the DFS Hazard functions showing Kernel-smoothed and B-spline plots, together with the life-table derived hazard, with both arms on one plot, with 3-month divisions on the time axis and keeping the full-time range of the observed data.

B15. Appendix K, Figures 7 & 8, page 23. Please supply two separate larger, clearer versions of these figures excluding the exponential and Weibull models but including also the generalised-F distribution and the Exp/Weib and Lnorm/Weib mixture parametric model. As currently done, please provide separate figures for the observed period as well as the full extrapolation.

Investigator-assessed DFS for Nivolumab; requested standard statistical models (independent of background mortality) and mixture-parametric survival models overlaid upon Kaplan-Meier curve:

Investigator-assessed DFS for Placebo; requested standard statistical models (independent of background mortality) and mixture-parametric survival models overlaid upon Kaplan-Meier curve:

B16. Appendix K, Section 3.1.4, page 24. Please clarify in detail how the models fitted in this section relate to the first equation in Section 2.2.8, page 14. It is not clear whether the mixture model is modelling only the excess risk or whether one component is modelling the excess and the other modelling the LT risk. Also, please clarify if the parameter rho represents the variable p.

The mixture-cure model consists of a population consisting of a mixture of two subpopulations. The first subpopulation is subject to mortality hazard due to life table alone. The second subpopulation is subject to a mortality hazard due to life table and a parametrically described excess hazard.

Further, the parameter rho (ρ) represents the variable p (the cure fraction) in the first equation in Section 2.2.8, page 14 of Appendix K.

B17. Appendix K, Section 3.1.4, page 24. The ERG notes that just because two models agree, it doesn't mean that they are right and the model that disagrees is wrong. Please clarify whether any external data were used to inform the model choice.

In addition to the statistical fit and consideration of the hazard profile for selecting the optimal survival model (as described in appendix K), two external sources were used to inform model choice: clinical expert opinion and Sternberg et al., 2015.[11] Both were used to validate long term DFS estimates, beyond the trial data. Clinical experts agreed that although the population evaluated in Sternberg et al. is not identical to that of CheckMate 274 (for instance, the Sternberg trial excluded patients who were unfit for cisplatin, had a relatively small sample size that did not allow for robust statistical analysis of results, and imbalances were identified in prognostic factors between arms), it is reasonable to use the deferred chemotherapy arm from the study to inform long term extrapolation of CheckMate 274 placebo arm, given broad similarity of population and outcomes, and lack of alternative suitable data in the literature.

At 5 years and 10 years, the deferred treatment arm for Sternberg et al. had progression-free survival estimates of 31.8% and 25.7%. Clinical experts broadly agreed with these values but considered that they were an overestimate compared to their experience in clinical practice. Subsequently, this clinical advice, along with considerations such as statistical fit and hazard profile (as described by the algorithm

in appendix K in the original submission), was used to draw a shortlist of curves including both KM + Weibull and KM + Gompertz. The survival estimates of these curves were again considered by clinical experts, who determined that the estimates produced by KM + Weibull were most clinically plausible. Further detail on clinical advice is provided in the answer to B13.

B18. Please clarify whether there is any clinical rationale for assuming that the cut-point for changing from the KM to a parametric curve differs for nivolumab ([redacted] months) and for placebo ([redacted] months)

The selection of cut point was subject to a rigorous decision process as described in appendix K, survival report, of the original submission. This appendix provides a detailed explanation of the entire decision process.

Initially, a wide range of cut-points were chosen considering changes in hazard close to the timing of pre-specified tumour assessments. Subsequently, various decisions were made to refine the list of potential curves. The one which most reflects clinical rationale was the shape of the hazard profile. For example, curves were only selected for which the hazard decreased over time. Clinical advice given to the company stated that patients in disease free for beyond 5 years could be considered to be in remission, and their risk of recurrence or disease related death was very low. This meant that only survival profiles which had a continuing reduction in hazard up to at least 5 years were pursued. Candidate extrapolations were then refined based on face validity vs CheckMate 274 data and clinician estimates at 5 and 10 years in both arms, as described in previous questions (B13, B17). The fact that cut-points differ for nivolumab and placebo arms is a reflection of the face validity and clinical plausibility of both underlying hazards and survival estimates were the key drivers of curve selection for each arm independently, as opposed to arbitrarily stating cut points have to match between arms.

Modelling assumptions

B19. Please clarify why the utility from Janssen et al. were deemed preferable to those from Ara and Brazier (Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18), particularly when the age bands are coarse, as noted

in utilities remaining constant between the ages of 75 and 100 years. Please provide ICERs using the Ara and Brazier estimates.

The utility values from Janssen were preferred as the publication is more recent.

A scenario was examined using the formula reported by Ara and Brazier:

GP EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2

The results using the general population utilities from Ara and Brazier are presented below.

Scenario analysis using alternative general population utility based on Ara and Brazier

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,474
CER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

Compared to the original base case, using utility based on Ara and Brazier led to a decrease of [redacted] QALYs for Nivolumab ([redacted] vs [redacted] in the base case) and [redacted] QALYs for BSC ([redacted] vs [redacted] in the base case) and a subsequent ICER of £32,474/QALY.

B20. The model assumes that patients will receive chemotherapy treatment until death. However, this does not account for periods of palliative therapy and when a patient is intolerant of, or unresponsive to, further treatment. Please clarify why this assumption was made and amend the model to adjust for periods of no active treatment if present.

This is to capture all possible therapies that patients may subsequently receive, either sequentially or concurrently. This is a simplifying assumption applied equally to both arms and therefore not expected to preferentially benefit either treatment. End of life costs were applied as a one-time cost in the cycle prior to death, therefore the model accounts for periods of palliative therapy.

B21. Please comment on the exchangeability between diseases at the time at which patients would be considered 'cured' if there had not been a DFS event. It is noted that in the base case for NICE STA ID1676 that the company had used a 3-year time point, although the ERG preferred a 5-year time point. Please clarify why the company believes that it is clinically plausible that nivolumab would not provide long-term remission in urothelial cancer (as tested in a sensitivity analysis), but would in other body sites.

Nivolumab would provide long-term remission in urothelial cancer as stated below. Observed DFS hazards from each arm of the CheckMate 274 trial tend towards general population levels by the end of the follow-up period suggesting low risk of recurrence in patients who have remained disease free beyond 3 years. This finding is supported by clinical advice,[12] which suggested that, after five years post-surgery without recurrence, patients may be considered in long-term remission. Based on clinicians' feedback, transition to long-term remission/disease-free or cure was modelled at 5 years in the disease-free state. In this state, they would be subject to no further routine monitoring, have no risk of recurrence, and experience general population mortality.

Assuming that nivolumab would not provide long-term remission in urothelial cancer was only tested to present an extreme scenario analysis, and BMS do not believe such a scenario to be clinically plausible. The results of the analysis should be considered as highly conservative and were included only to reflect the impact of this assumption on the model results. Therefore, BMS do not believe this extreme scenario should be considered for decision making. In addition, this scenario testing a model assumption within this decision problem should not be translated to other disease settings as a general expectation from BMS in relation to the efficacy for nivolumab.

B22. Please clarify whether upper tract urothelial carcinoma and muscle-invasive urothelial carcinoma have similar prognosis. Are there any characteristics of these cancers that could mean that nivolumab works better in one population than the other? If there are different prognoses or different

efficacy, please clarify why ICERs were not presented individually for the UTUC and the MIUC subgroups.

Please clarify whether upper tract urothelial carcinoma and muscle-invasive urothelial carcinoma have similar prognosis.

For clarity, MIUC is a collective term for urothelial carcinoma in the urinary tract, including muscle invasive bladder cancer (MIBC) as well as invasive UTUC. UTUCs are pathologically the same and are classified in the same way as MIBC.[24-26] MIBC and invasive UTUC have very poor prognosis, both have 5-year survival rates <50% for stage II and III disease.[27,28] However, they differ in that upper tract urothelial carcinomas are more frequently high grade, show frequent variant differentiation, are higher stage at presentation, compared with UC of the bladder.

Are there any characteristics of these cancers that could mean that nivolumab works better in one population than the other?

Studies specific to the pathology of UTUC remain rare and much of what is known about UTUC is derived from studies on bladder cancer. Research into biological differences accounting for the differences between UTUC and MIBC have not resulted in clinical prognostic factors, or differences in drug target to date. Treatment pathways for UTUC patients differ from those with bladder cancer due to the location of the disease and speed of progression.[28,29]

If there are different prognoses or different efficacy, please clarify why ICERs were not presented individually for the UTUC and the MIUC subgroups.

In CheckMate 274, interaction tests demonstrate that there is no statistically significant proof of effect of tumour origin on the efficacy of nivolumab versus placebo; therefore, ICERs are not presented individually for the subgroups. In addition, any such analysis on a small subset of patients (UTUC) would be highly uncertain due to the limited patient numbers in each treatment arm.

Furthermore, during the design of CheckMate 274, the US FDA recommended all UTUC patients be considered in the same cohort as patients with UC of the bladder. Therefore, the study was not designed to detect statistically significant differences in

safety or efficacy of the UTUC subgroup separate from the overall MIUC group. The EMA regulatory filing does not distinguish between UTUC and bladder UC patients.

We have demonstrated efficacy in the overall efficacy population for which the study was powered to detect differences between nivolumab and placebo arms and in the co-primary endpoint of PD-L1 ≥ 1%, which forms the basis of the decision problem per the NICE scope. Therefore, we consider it inconsistent with the trial design, the regulatory label sought in Europe, and the scope of this assessment by NICE to present different ICERs for the UTUC separate from the bladder UC or overall MIUC group.

B23. The primary outcome measure reported DFS for all randomised patients and those with PD-L1 expression ≥ 1%. Please provide a similar table to Table 18 page 61, but for the PD-L1 < 1% group to allow a comparison based on PD-L1 status. Do prognoses or treatment efficacy differ between these groups? If yes, please clarify why ICERs were not presented for each PD-L1 expression group.

Efficacy results for patients with tumour cell PD-L1 expression level<1%, are presented below. It is important to note that while DFS benefit is lower in patients who are PD-L1<1% (HR: 0.80, 95% CI: 0.62, 1.04) compared with the benefit observed in patients with PD-L1≥1%, the wide CIs observed in the efficacy results of the PD-L1<1% subgroup indicate a less precise estimate, therefore, the results should be interpreted with caution.

CheckMate 274: PD-L1 < 1% efficacy results

Endpoint	Nivolumab (N = 207)	Placebo (N = 207)
DFS (Primary definition)*		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (% CI)	[redacted]	
6 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	[redacted]	[redacted]
NUTRFS (secondary endpoint)		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI)	[redacted]	
6 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	[redacted]	[redacted]
DMFS (exploratory endpoint)		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI)	[redacted]	
6 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	[redacted]	[redacted]

*primary definition of DFS accounts for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer. Abbreviations: CI: confidence interval, DFS: disease-free survival, DMFS: distant metastasis-free survival; NUTRFS: non-urothelial tract recurrence-free survival.

Source: CSR [redacted][3]

The company sought clinical expert opinion on prognosis by PD-L1 status, and the clinicians noted that PD-L1 status has not been confirmed to be prognostic.[12] Overall, PD-L1<1% subgroup is not powered to detect differences in outcomes in the CheckMate 274 trial. As such, the company considered it inappropriate to attempt to run any economic analyses based on the above-mentioned PD-L1 subgroup, as any such analyses are likely to produce biased and unreliable results, which will not be useful to inform economic model and therefore decision making.

B24. Please clarify whether any interaction tests were undertaken to test for differences in efficacy based on geographical region, tumour origin, previous neo-adjuvant cisplatin treatment status or previous neoadjuvant systemic therapy.

Interaction tests were undertaken and are presented below.

DFS Primary definition

DFS Primary definition	Nivolumab (N=353)			Placebo (N=356)			Nivolumab vs. Placebo		
Subgroups	n	Events n (%)	KME (95% CI) (months)	n	Events n (%)	KME (95% CI) (months) (1)	HR (95% CI) (2) (3)	p-value	Test for interaction p-value (4)(5)
Region									
US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Initial tumour origin									
Urinary bladder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal Pelvis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ureter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Prior neo-adjuvant cisplatin therapy									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Use of any prior neo-adjuvant systemic therapy									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

DFS: disease-free survival; HR = hazard ratio; KME = Kaplan-Meier estimate.

(1) KME of median time to event; (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo; (3) Unstratified Log-rank test; (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment *subgroup interaction is to assess the significance of the interaction between treatment and the subgroup; (5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

Source: BMS data on file[30]

DFS Secondary definition

DFS Secondary definition	Nivolumab (N=353)			Placebo (N=356)			Nivolumab vs. Placebo		
Subgroups	n	Events n (%)	KME (95% CI) (months)	n	Events n (%)	KME (95% CI) (months) (1)	HR (95% CI) (2) (3)	p-value	Test for interaction p-value (4)(5)
Region									
US	[redacted]								
Europe									
Asia									
Rest of the world									
Initial tumour origin									
Urinary bladder									
Renal Pelvis									
Ureter									
Prior neo-adjuvant cisplatin therapy									
Yes									
No									
Use of any prior neo-adjuvant systemic therapy									
Yes									
No									

DFS: disease-free survival; HR = hazard ratio; KME = Kaplan-Meier estimate.

(1) KME of median time to event; (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo; (3) Unstratified Log-rank test;

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment subgroup interaction is to assess the significance of the interaction between treatment and the subgroup; (5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

Source: BMS data on file[30]

DMFS

DMFS	Nivolumab (N=353)			Placebo (N=356)			Nivolumab vs. Placebo		
Subgroups	n	Events n (%)	KME (95% CI) (months)	n	Events n (%)	KME (95% CI) (months) (1)	HR (95% CI) (2)(3)	p-value	Test for interaction p-value (4)(5)
Region									
US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Initial tumour origin									
Urinary bladder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal Pelvis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ureter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Prior neo-adjuvant cisplatin therapy									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Use of any prior neo-adjuvant systemic therapy									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

DMFS: distant metastasis-free survival; HR = hazard ratio; KME = Kaplan-Meier estimate.

(1) KME of median time to event; (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo; (3) Unstratified Log-rank test; (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup; (5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

Source: BMS data on file[30]

NUTRFS

NUTRFS	Nivolumab (N=353)			Placebo (N=356)			Nivolumab vs. Placebo		
Subgroups	n	Events n (%)	KME (95% CI) (months)	n	Events n (%)	KME (95% CI) (months) (1)	HR (95% CI) (2) (3)	p-value	Test for interaction p-value (4)(5)
Region									
US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Initial tumour origin									
Urinary bladder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal Pelvis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ureter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Prior neo-adjuvant cisplatin therapy									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Use of any prior neo-adjuvant systemic therapy									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

NUTRFS: non-urothelial tract recurrence free survival; HR = hazard ratio; KME = Kaplan-Meier estimate.

(1) KME of median time to event; (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo; (3) Unstratified Log-rank test; (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup; (5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

Source: BMS data on file[30]

B25. CS Section 3.3.2.1.2, page 109. Please provide a scenario analysis in which receiving a subsequent treatment could be treated as a DFS event rather than being censored.

We acknowledge the request to classify patients who have switched treatment while disease free as a DFS event. Having reviewed the data, this scenario only applied to 3 patients (2 in the nivolumab arm and 1 in the placebo arm). We do not feel it is correct to re-classify patients in this way, given that they are disease-free and have not experienced an event; patients may have switched treatment for reasons other than progression such as tolerability, and therefore coding these patients as progressed is not appropriate. Moreover, any re-classification would simply inflate the number of DFS events in the nivolumab arm.

In addition, the study includes the results of a secondary definition of DFS, which accounted for disease assessments occurring on or after initiation of subsequent anticancer therapy. The results of which [redacted] primary definition ([redacted]).[3] The primary DFS results are shown in Table 14 and Figure 7 of document B.

Model execution and results

B26. CS Table 53, pages 143-147. Please provide the parameters used in the distributions reported rather than just the distributional form.

Base case analysis inputs

Variable	Value	Reference table in submission	Measurement of uncertainty and distribution	Reference in submission (section)
Baseline parameters	Mean (SE)			
Age, years (SE)	65.6 (0.36)	Table 28	SE (normal)	B.3.2.2
% Male	0.672 (0.152)	Table 28	SE (beta)	B.3.2.2
Survival				
DFS	KM + Weibull	-	95% CI	B.3.2.2
Post-recurrence survival	Median OS 11 months	-	SE (beta)	B.3.3.2.1.5

Variable	Value		Reference table in submission	Measurement of uncertainty and distribution	Reference in submission (section)
Adverse event incidence	% In Nivolumab arm	% In Placebo arm			
Rash	[redacted]	[redacted]	Table 38	SE (beta)	B.3.3.2.4
Rash maculopapular	[redacted]	[redacted]		SE (beta)	
Fatigue	[redacted]	[redacted]		SE (beta)	
Asthenia	[redacted]	[redacted]		SE (beta)	
Diarrhoea/colitis*	[redacted]	[redacted]		SE (beta)	
Lipase increased	[redacted]	[redacted]		SE (beta)	
Amylase increased	[redacted]	[redacted]		SE (beta)	
Blood creatinine increased	[redacted]	[redacted]		SE (beta)	
Decreased appetite	[redacted]	[redacted]		SE (beta)	
Pneumonitis*	[redacted]	[redacted]		SE (beta)	
Health state utilities (based on trial analysis)	Utility value mean (SE)				
Post-surgery (disease-free)	[redacted]		Table 39	SE (beta)	B.3.4.2.1
Recurrence	[redacted]		Table 39	SE (beta)	B.3.4.2.1
Utility decrement for recurrence	[redacted]		Table 39	SE (beta)	B.3.4.2.1
Initial Disease-free	[redacted]		Table 41	SE (beta)	B.3.4.4
Long term remission	[redacted]		Table 41	SE (beta)	B.3.4.4
Total Recurrence	[redacted]		Table 41	SE (beta)	B.3.4.4
Age-dependent utilities	Male	Female			
45-54 years	0.861	0.846	Table 42	SE (beta)	B.3.4.4
55-64 years	0.806	0.810	Table 42	SE (beta)	B.3.4.4
65-74 years	0.795	0.768	Table 42	SE (beta)	B.3.4.4
75-100 years	0.751	0.703	Table 42	SE (beta)	B.3.4.4
Adverse event disutilities	Disutility value mean (SE)				
Rash	[redacted]		Table 40	SE (beta)	B.3.4.3

Variable	Value	Reference table in submission	Measurement of uncertainty and distribution	Reference in submission (section)
Rash maculopapular	[redacted]		SE (beta)	
Fatigue	[redacted]		SE (beta)	
Asthenia	[redacted]		SE (beta)	
Diarrhoea/colitis	[redacted]		SE (beta)	
Lipase increased	[redacted]		SE (beta)	
Amylase increased	[redacted]		SE (beta)	
Blood creatinine	[redacted]		SE (beta)	
Decreased appetite	[redacted]		SE (beta)	
Pneumonitis	[redacted]		SE (beta)	
Nivolumab treatment costs	Cost (£)			
Acquisition cost (excluding PAS)	£2,633.00 (24mL)	Table 43	Not applicable	B.3.5.2
acquisition cost every two weeks in model	£2,633.00	Table 43	Not applicable	B.3.5.2
Administration cost	£159.00	Table 44	Not applicable	B.3.5.2
Total cost per two weeks within the model cycle (excluding PAS) accounting for treatment modifier	[redacted]	Table 43	Not applicable	B.3.5.2
Total cost per two weeks within the model, including PAS, including treatment modifier	[redacted]	Table 45	Not applicable	B.3.5.2
Post-recurrence treatment costs	Weekly cost (£)			
Cisplatin (with gemcitabine)	£39.75	Table 46	Not applicable	B.3.5.2.4
Gemcitabine (with cisplatin)	£119.25	Table 46	Not applicable	B.3.5.2.4

Variable	Value	Reference table in submission	Measurement of uncertainty and distribution	Reference in submission (section)
Carboplatin (with gemcitabine)	£53.00	Table 46	Not applicable	B.3.5.2.4
Gemcitabine (with carboplatin)	£106.00	Table 46	Not applicable	B.3.5.2.4
Healthcare resource use unit costs	Unit cost (£) (SE)			
Estimation glomerular filtration rate	£2.79 (£0.56)	Table 47	SE (gamma)	B.3.5.3
Cystoscopy	£240.00 (£48)	Table 47	SE (gamma)	B.3.5.3
Clinician consultation	£208.75 (£41.75)	Table 47	SE (gamma)	B.3.5.3
CT scan	£86.25 (£17.25)	Table 47	SE (gamma)	B.3.5.3
Full blood count	£2.79 (£0.56)	Table 47	SE (gamma)	B.3.5.3
Renal/hepatic function test	£1.10 (£0.22)	Table 47	SE (gamma)	B.3.5.3
GP home consultation	£67.63 (£13.53)	Table 47	SE (gamma)	B.3.5.3
Community nurse specialist visit	£49.25 (£9.85)	Table 47	SE (gamma)	B.3.5.3
Health home visitor	£39.23 (£7.85)	Table 47	SE (gamma)	B.3.5.3
Dietician	£43.43 (£8.69)	Table 47	SE (gamma)	B.3.5.3
Adverse event costs	Mean cost (SE)			
Rash	£1,027.69 (£205.54)	Table 51	SE (gamma)	B.3.5.3.4
Maculopapular rash	£1,027.69 (£205.54)	Table 51	SE (gamma)	B.3.5.3.4
Fatigue	£693.53 (£138.71)	Table 51	SE (gamma)	B.3.5.3.4
Asthenia	£693.53 (£138.71)	Table 51	SE (gamma)	B.3.5.3.4
Diarrhoea/colitis	£2,365.60 (£473.12)	Table 51	SE (gamma)	B.3.5.3.4
Lipase increased	£142,81 (£28.56)	Table 51	SE (gamma)	B.3.5.3.4
Amylase increased	£142,81 (£28.56)	Table 51	SE (gamma)	B.3.5.3.4
Blood creatinine increased	£142,81 (£28.56)	Table 51	SE (gamma)	B.3.5.3.4
Decreased appetite	£1,032.98 (£206.60)	Table 51	SE (gamma)	B.3.5.3.4

Variable	Value	Reference table in submission	Measurement of uncertainty and distribution	Reference in submission (section)
Pneumonitis	£1,147.23 (£229.45)	Table 51	SE (gamma)	B.3.5.3.4
Health state cost	Mean weekly health state cost (£) (SE)			B.3.5.3.4
Disease-free, up to 1 year	£15.33 (£3.07)	Table 48	SE (gamma)	B.3.5.3.4
Disease-free, 1 to 2 years (6.35% reduction)	£14.36 (£2.87)	Table 48	SE (beta) for % reduction	B.3.5.3.4
Disease-free, 2 to 3 years (50.07% reduction)	£7.68 (£1.54)	Table 48	SE (beta) for % reduction	B.3.5.3.4
Disease-free, 3 years to 5 years (50.07% reduction)	£7.68 (£1.54)	Table 48	SE (beta) for % reduction	B.3.5.3.4
Disease-free beyond 5 years and long-term disease-free	£0.00	Assumption, no further follow up	NA	B.3.5.3.4
Post-recurrence	£279.21 (£55.84)	Table 49	SE (gamma)	B.3.5.3.4
End of life (one off)	£7,970.55 (£1,594.11)	Table 50	SE (gamma)	B.3.5.3.4
Abbreviations: CT, computed tomography; SE, standard error *May occur in <5% of the population (any grade)				

B27. CS Figure 33, page 154. Please clarify the circumstances that exist when PSA iterations produce results that indicate that nivolumab may provide less QALYs than placebo.

82 out of 1,000 PSA iterations (0.082%) produced results that indicate nivolumab may provide less QALYs than placebo.

This is due to extreme/independent survival resampling values which leads to the hazard of a DFS event in the nivolumab arm not only to be higher than in the base case, but at points higher than in the placebo arm. While this reflects potential variation in the inputs, and should be examined, it is important to note and relate this to the likely clinical outcomes for patients and the observed evidence. The observed

evidence indicates that patients who are taking nivolumab would have a lower risk of recurrence than those in the placebo arm.

B28. CS Section 3.8.1, page 153. Please clarify what a non-parametric bootstrapping approach to PSA is, and confirm that this was used within the company's probabilistic analyses.

The variance of the survival predictions was informed by non-parametric bootstrapping, in other words multiple replications of sampling was done with replacement of the study data, followed by fitting the full piecewise model to these resampled data; the 95% confidence interval of survival predictions of these models is then provided in the model. The survival predictions are assumed to be distributed normally on the log cumulative hazard scale.

In the PSA, a single Gaussian random deviate is taken and used to specify the deviation in log cumulative hazard (when scaled by the estimated variance) that is applied to all survival predictions simultaneously. This means that a Gaussian sample which is at + 1 standard deviation will result in a survival prediction that is at +1 standard deviation on the log cumulative hazard scale at all times.

This was done in order to preserve the dependence of the extrapolative parameters upon the non-parametric portion of the curve - independent sampling of these two pieces of the survival model would inflate the variance, as the parameters of the extrapolative model would be expected to be highly correlated with the survival predictions of the non-parametric model.

B29. CS Section 3.8.1, page 153. Please provide further details on how a common random number is used for semi-parametric survival estimates. If, for example, this was meaning that the same random number was used to sample from the shape and scale of a Weibull distribution, please comment on the likelihood that this would produce more extreme values than sampling using a variance-covariance matrix.

A common random number is used for the probabilistic analysis of semi-parametric survival estimates, in the example provided this means that the same random

number is used to sample from the shape and scale of the Weibull distribution. As high early survivals are correlated with high late survivals, and can be demonstrated when undertaking the bootstrap, the method is sufficient to demonstrate the uncertainty in the survival estimations. The full range of survival expectations is covered, and the low probability combinations of low initial and high later survival, and the reverse scenario, are avoided.

Since this approach relies on the basic properties of the non-parametric bootstrap to give the mean and variance of the survival predictions over the whole model horizon, and the basic necessities of the bootstrap are present, the confidence intervals are should not be more extreme than when sampling using a variance-covariance matrix.

B30. The ERG presume half-cycle correction was not applied within the model due to the weekly time cycle. Please confirm whether this is correct.

This is correct; a half cycle correction was ruled unnecessary with such a short cycle length. It is not anticipated that important clinical events, and associated cost and utility implications, would not be represented and captured with a cycle length of one week and therefore there is no reason to implement a half cycle correction. Treatment costs would remain relatively unaffected as the majority of these are accrued in the first year.

B31. Excel model 'Data Library'!$E$277:$H$377 (Table 35 of the CS). Please explain how the mortality probabilities were calculated from the national life tables 2017-2019. The ERG notes that when converting mortality rates (qx) to probabilities, the values do not match with the mentioned Excel sheet reference.

The rates in the 'Data Library'!$E$277:$H$377 were obtained by weight averaging between male and female values. These rates were further converted to probabilities in column S in 'Treatment Trace' and 'Control Trace' sheets.

B32. Excel model, Trace sheets, Column Z. The equation converts a hard coded probability into a monthly rate. Please confirm whether this hard coded

probability is the annual probability that a recurrence is death. Also please clarify why a monthly rate is used within weekly cycles.

The hard coded probability is the monthly probability that a recurrence is death and it is transformed into a weekly probability.

B33. CS Section B.3.3.2.1.5, page 118. It is mentioned that median OS of 11 months was used to estimate post recurrence survival. In the model, an annual probability of 0.42 (SE 0.05) for transition from recurrence to death was used. Please provide the details of how this calculation was estimated.

Using a median OS of 11 months (i.e. 50% of patients are dead at 11 months), an annual rate may be calculated by: 0.5/(11/12), which is equivalent to 0.545. This can then be converted to an annual probability of 0.420 using the equation:

probability = 1-exp(-rate)

Uncertainty surrounding this OS transition probability is evaluated within scenario analyses.

B34. CS Table 49, page 139. Please clarify how the annual rates used to calculate the weighted average were derived. Does the weighted average take into account that people may live for significantly more than 1 year beyond post-recurrence?

The weighted average for post-recurrence healthcare resource use is determined by evaluating the proportion of patients who die within the first year post-recurrence, and the rate of surviving beyond the first year. These values do not explicitly take into account that people may live for significantly more than 1 year post-recurrence, however costs post-recurrence are applied for the remainder of the patients life. Based on the model structure, patients are not tracked post-recurrence and therefore this simplifying assumption was made to capture post-recurrence resource use and health state costs.

B35. Excel model, Control Trace, Column CX. The equation references column G (discounting factor) instead of column F (time in years). Please amend the error, if any.

Model amended. The updated results are summarised below. Compared to the initial submission, the currently updated model produces an increase in the incremental QALYs [redacted], thus leading to a slightly lower ICER.

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,813
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

B36. Excel model, Control Trace, Column BZ. In case of continuing resource use for patients on DFS state beyond 5 years, the equation is using 1 instead of the disease-free multiplier column (BX). Please amend if necessary.

The model has been amended to refer to the disease-free multiplier column (BX), in the Control Trace. The ICER remained unchanged.

Section C: Textual clarification and additional points

C1. CS Section 1.3.5, pages 26 & 28. Figure 3 and Figure 4 suggest that all patients have disease recurrence. Please clarify whether this was the intention, otherwise please amend the diagram to show that patients can die without recurrence.

Figure 3 and Figure 4 have been amended to include death without recurrence, as shown below.

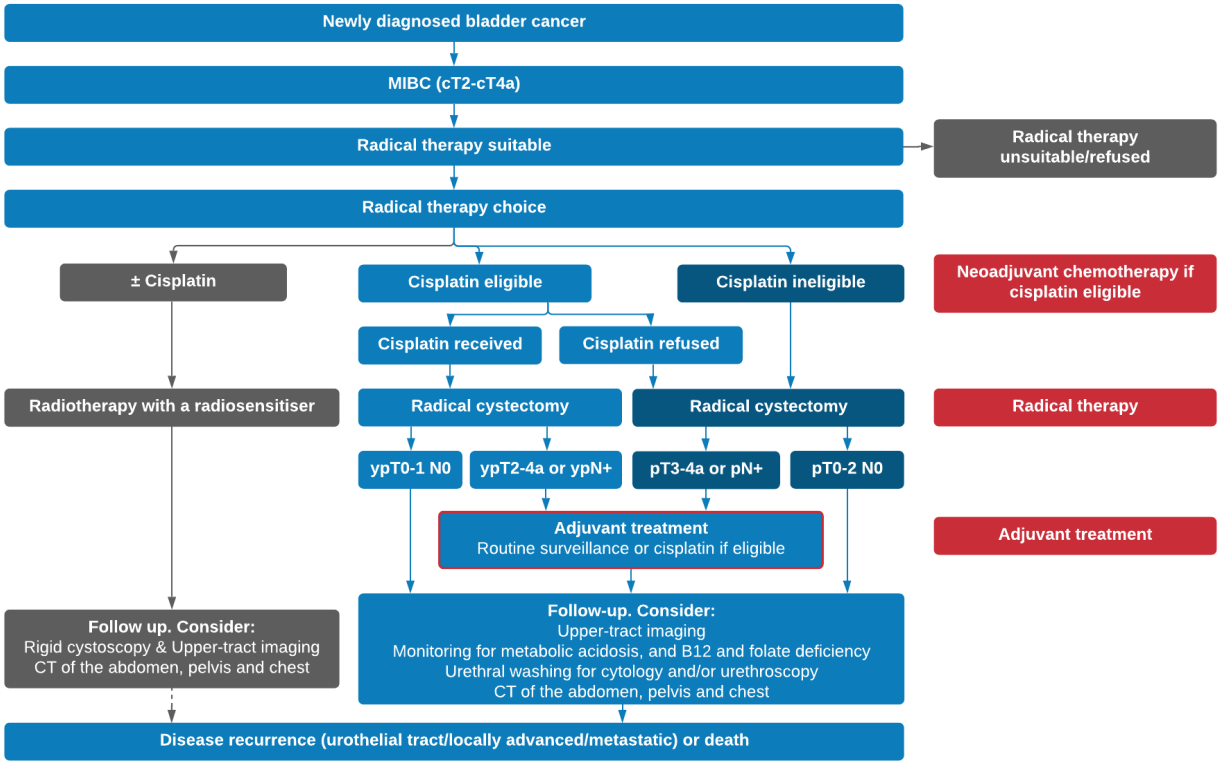


Figure 3. Detailed treatment pathway for muscle-invasive bladder cancer in the UK

Nivolumab is indicated in the adjuvant setting for high-risk patients. Adapted from NICE Guideline NG2, with additional input from UK expert clinician[12,31]

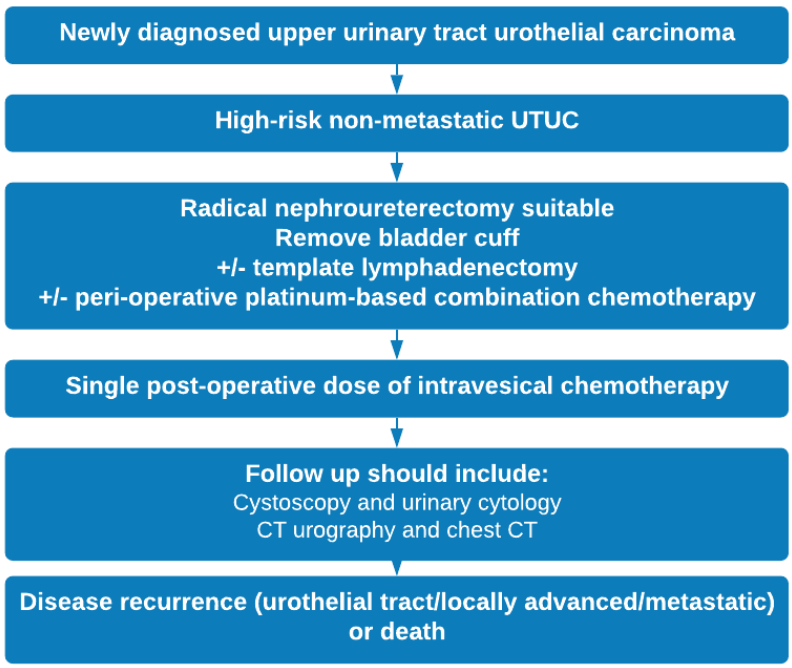


Figure 4. Summary of EAU guidelines for the surgical management of high-risk non-metastatic UTUC

Adapted from Roupret et al., 2021[28]

C2. CS Section 2.6.3.1, page 53. Please clarify whether the median CIs are reversed.

An updated Table 16, based on the updated August 2020 database lock is provided below. Please note that the 6-month rate is not available at this time.

Table 16. Time to recurrence, all randomised patients

Endpoint	Nivolumab (N = 353)	Placebo (N = 356)
Time to recurrence		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI)	[redacted]	
Abbreviations: CI: confidence interval. Source: BMS 2021[32]		

C3. CS Section 2.13.1, page 85. Please clarify whether the mentioned HRs in the first two bullet points should be marked as AIC.

The hazard ratios in the first two bullet points (HR 0.70 [98.22% CI: 0.55, 0.90] and HR 0.72, [95% CI 0.59, 0.89]) are published in the study publication Bajorin 2021.[8]

C4. CS Section 2.13.2.1, page 87. "Those patients whose DFS is extended beyond 3 years with nivolumab can be expected to have a low risk of subsequent recurrence." Should this read 5 years instead?

As described in the preceding paragraph, "the great majority of recurrences under current treatment occur in the first 3 years after surgery" and as a result, would be at low risk of recurrence, in line with the statement "Those patients whose DFS is extended beyond 3 years with nivolumab can be expected to have a low risk of subsequent recurrence." Those patients disease free after 5 years would be assumed to have very low risk of recurrence.

References

1. Neyt M, Chalon PX. Search MEDLINE for Economic Evaluations: Tips to Translate an OVID Strategy into a PubMed One. PharmacoEconomics. 2013;31(12):1087-90.
2. Galsky MD, Witjes JA, Gschwend J, et al. Impact of recurrence on health-related quality of life in patients at high risk of recurrence after radical surgery for muscle-invasive urothelial carcinoma (MIUC): Results from the phase 3 CheckMate 274 trial. Journal of Clinical Oncology. 2021;39(15_suppl):4540-.
3. Bristol Myers Squibb. Erratum to Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2021.
4. Mallinckrodt CH, Clark SW, Carroll RJ, et al. Assessing response profiles from incomplete longitudinal clinical trial data under regulatory considerations. J Biopharm Stat. 2003;13(2):179-90.
5. Mallinckrodt CH, Watkin JG, Molenberghs G, et al. Choice of the primary analysis in longitudinal clinical trials. Pharmaceutical Statistics. 2004;3(3):161-9.
6. Odom D, McLeod L, Sherif B, et al. Longitudinal Modeling Approaches to Assess the Association Between Changes in 2 Clinical Outcome Assessments. Therapeutic Innovation & Regulatory Science. 2018;52(3):306-12.
7. Bristol-Myers Squibb. Data on File. Outcome log-rank test results - Updated AUG 2020 DBL. 2021.
8. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. New England Journal of Medicine. 2021;384(22):2102-14.
9. Bristol Myers Squibb. Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2020.
10. National Institute for Health and Care Excellence. Single technology appraisal: User guide for company evidence submission template. 2015. Available at: https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333 [Accessed 7 October 2021].
11. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. The Lancet Oncology. 2015;16(1):76-86.
12. Bristol Myers Squibb. Advisory board: Nivolumab for post-resection adjuvant treatment of high-risk muscle invasive urothelial cancer. 2021.
13. Yoo SH, Kim H, Kwak C, et al. Late Recurrence of Bladder Cancer following Radical Cystectomy: Characteristics and Outcomes. Urol Int. 2019;103(3):291-6.
14. Office of National Statistics. National life tables: UK. 2020. Available at: [Accessed

15. Witjes JA, Bruins HM, Cathomas R, et al. EAU Guidelines in Muscle-invasive and Metastatic Bladder Cancer. 2021. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Muscle-Invasive-and-Metastatic-Bladder-Cancer-2021.pdf [Accessed 7 April 2021].
16. Bristol Myers Squibb. Clinical expert consultation. 2021.
17. von der Maase H, Sengelov L, Roberts JT, 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(21):4602-8.
18. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol. 2015;16(1):76-86.
19. Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol. 2012;23(3):695-700.
20. Zhegalik AG, Polyakov SL, Rolevich AI, et al. Long-term results of a single-center prospective randomized trial assessing efficacy of a shortened course of adjuvant chemotherapy after radical cystectomy in patients with locally advanced bladder cancer. Cent European J Urol. 2020;73(1):26-32.
21. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2014.
22. Bristol Myers Squibb. Summary of Product Characteristics. OPDIVO 10 mg/mL concentrate for solution for infusion. . 2021.
23. Pang KH, Thomas F, Novara G, et al. The Impact of Centralised Services on Metric Reflecting High-quality Performance: Outcomes from 1110 Consecutive Radical Cystectomies at a Single Centre. Eur Urol Focus. 2020.
24. Montironi R, Lopez-Beltran A, Scarpelli M, et al. Morphological classification and definition of benign, preneoplastic and non-invasive neoplastic lesions of the urinary bladder. Histopathology. 2008;53(6):621-33.
25. Montironi R, Mazzucchelli R, Scarpelli M, et al. Morphological diagnosis of urothelial neoplasms. J Clin Pathol. 2008;61(1):3-10.
26. Eble IN SG, Epstein JI, Sesterhenn IA, editors. . World Health Organization Classification of Tumours. Tumours of urinary system. Lyon: IARC Press; 2004. 90-2 p.
27. Office of National Statistics. Cancer survival in England - adults diagnosed: 2013 - 2017 edition. 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 4 January 2021].
28. Rouprêt M, Babjuk M, Burger M, et al. European Association of Urology (EAU) Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma. 2021. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Upper-Urinary-Tract-Urothelial-Carcinoma-2021.pdf [Accessed 7 April 2021].
29. Chitale S, Mbakada R, Irving S, et al. Nephroureterectomy for transitional cell carcinoma - the value of pre-operative histology. Ann R Coll Surg Engl. 2008;90(1):45-50.

30. Bristol-Myers Squibb. Data on File. Subgroup analysis interaction tests - Updated AUG 2020 DBL. 2021.
31. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management [NG2]. UK: NICE, 2015.
32. Bristol-Myers Squibb. Data on File. Time to Recurrence data - Updated AUG 2020 DBL. 2021.

Appendix A

```
# WINBUGS Code Cont. Models
# Fixed effects
# TSD 2 - 2-arm studies only
# ------------------------------------------------------------------------
# WINBUGS model

FEmodel_simplified <- function()
{                           # *** PROGRAM STARTS
  for(i in 1:ns2) {                 # LOOP THROUGH 2-ARM STUDIES
    y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
    var[i,2] <- pow(se[i,2],2)   # calculate variances
    prec[i,2] <- 1/var[i,2]      # set precisions
    dev[i,2] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2] #Deviance contribution
    delta[i,2] <-  d[t[i,2]] - d[t[i,1]]
  }
  totresdev <- sum(dev[,2]) #Total Residual Deviance
  d[1]<-0       # treatment effect is zero for reference treatment
  # vague priors for treatment effects
  for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }


  #TREATMENT EFFECTS (HR VERSUS COMMON COMPARATOR IN NETWORK)
  for (i in 2:nt)
  { HR_B[i] <-exp(d[i]-d[1])}


  for (c in 1:nt) {
    for (k in 1:nt) {
      HR[c,k] <- exp(d[k] - d[c])
      lnHR[c,k] <- (d[k]-d[c])

    }
  }
  # Dias Book page 42
  for (k in 1:nt) {
    rk[k] <- rank(d[], k)
    best[k] <- equals(rk[k], 1)
    ranks[k] <- rank(d[],k)
    worst[k] <- equals(ranks[k],nt)

    for (h in 1:nt) {

      prob[k,h] <- equals(h, rk[k])

      cumrank[h, k] <- sum(prob[h, 1:k]) #cum. prob

    }
    sucra[k] <- sum(cumrank[k,1:(nt - 1)])/(nt - 1)
  }
}
```

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Thank you for agreeing to give us your organisation's 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. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- 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	[redacted]

2. Name of organisation	Action Bladder Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	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 The charity is funded by private and corporate donations, legacies and fundraising events. 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.*
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of	We have received donations of £16,000 towards our core funding from Bristol-Myers Squibb during the last 12 months.

manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Our trustees are all bladder cancer patients or clinicians specialising in the treatment of bladder cancers. Our main interaction with patients is through our network of local support groups, with assistance from our own in house patient support officers. During the coronavirus pandemic we have kept many of these going by providing video link software (zoom) and training. We also provide a telephone helpline and an online query service through our website, and we maintain social media links through facebook and twitter. We also conduct patient surveys from time to time. However, we have not conducted a survey specifically related to this treatment.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	This group of patients has already gone through the mill. Initial diagnosis is invariably a shock, not just because this is cancer, but because bladder cancer is so poorly known or understood. It can be difficult to talk about, as the impact can be so personal, not just with family and friends but also with clinicians. Although treatment for non-muscle invasive bladder cancer is *relatively* straightforward and effective, that for muscle invasive bladder cancer can be drastic, less effective, and can often recur. From often quite mild symptoms they will have already experienced a battery of tests, some of which are

	intrusive such as cystoscopies and/or TURBT. A radical cystectomy is literally life changing, and, although patients may learn to live well without their bladder, some can suffer very badly from leakage causing major distress and embarrassment leading to limitations in their ability to lead a normal life. They will have experienced a roller coaster of emotions as they learn of the seriousness of their condition. Most patients in this group are older, in their sixties or seventies, and often have several unrelated underlying health issues. Their partners, carers and family members can be pretty desperate, and both patients and their families can feel hopeless. It is not just the patient, but carers, partners and the family as well can all feel physically, emotionally and mentally battered.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatment of this specific condition would normally be with adjuvant platinum based chemotherapy, or best supportive care. Chemotherapies for this group of patients is not well tolerated: *"Chemotherapy was the first time it sunk in that I was in trouble. Having that stuff injected in you is not a moment I remember with any good feelings - in fact it was the first time I wept (but not the last, as it turned out)…Nine weeks of chemo later, I had somehow spent the last four months on autopilot - floating from one scan to another, from one appointment to another - almost looking down on myself going through this experience."* Due to the relatively advanced age and other illnesses present in so many patients with advanced bladder cancer, a significant number are unable or unwilling to take cisplatin. Currently, the only other option is best supportive care, usually palliative, and so there is an urgent need for alternatives or improvements for this group of patients. Carers are forced to watch their love ones approach the end of life with increasing weakness, great discomfort and chronic pain. There is a great deal of physical, emotional and mental stress for both patients and their carers. Without treatment, there

	is no hope.
8. Is there an unmet need for patients with this condition?	Yes. Patients with metastatic bladder cancer have an average life expectancy of only a few months. About 5,000 patients die each year from this condition, and this has not improved in over 30 years. So there is a huge unmet need and bladder cancer patients in general feel overlooked. Nivolumab represents an innovative treatment and potential lifeline for patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Nivolumab represents hope for many where other treatment options have been exhausted. The main benefits include: • complete response in some cases • prolonging life • improved quality of life for patient, carers and family, as the drug is reasonably well tolerated as well as beneficial. We think a major potential benefit to both patients and those who care for them is the creation of real hope for the future where none currently exist, and has not existed for decades

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	ABC UK is not aware of any disadvantages perceived by patients or carers. However, some may find regular attendance for treatment a challenge.
Patient population	
11. 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.	Currently about 5,000 patients die each year in the UK from metastatic bladder cancer. All of these could potentially benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None known

Other issues	
13. Are there any other issues that you would like the committee to consider?	Bladder cancer is not a rare cancer. It is the 4th most prevalent cancer in men and the 7th most prevalent overall. The five year survival rate for all stages and grades of bladder cancer is only 50%. This figure has not improved at all in well over 30 years. This compares very badly with any of the other ten most prevalent cancers. For instance, the five year survival statistics for breast cancer, prostate cancer and bowel cancer show that patients are two or three times more likely to survive the disease today than 30 years ago. Bladder Cancer recurs more than any other common cancer requiring long term surveillance and repeat treatments. This makes bladder cancer one of the most expensive cancers for the NHS to treat, per patient. Bladder cancer patients are among the highest of all cancer patients who present at A&E with advanced disease. And those in this group have a mean life expectancy measured in months rather than years, typically around 15 months. Despite these bleak statistics, bladder cancer receives less than 1% of the cancer research spend. In many other cancer settings, the expected impact of immunotherapy drugs may not be particularly significant at this stage of disease, compared with available alternatives. However, in the case of cancer patients with advanced disease as here, the outlook is very poor, the patient experience often dire and there are no available treatments. There is a huge unmet need for advanced bladder cancer patients, and nivolumab offers the prospect of a step change improvement for many of the patients in this group.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • There have been few or no improvements in care for these patients in over 30 years, and they are left with ‘best supportive care’. • Patients, on average, have only a few months to live, and the last months of life are particularly harrowing for both them and their carers • This treatment has been shown to have a positive effect, and in some cases a dramatic effect, on life expectancy, and is relatively well tolerated. • Nivolumab gives hope to many for whom other treatment options have been exhausted, and for whom there is no alternative. • ABC UK strongly supports the licensing and use of the treatment within the NHS

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Thank you for agreeing to give us your organisation's 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. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- 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	[redacted]

2. Name of organisation	Fight Bladder Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight Bladder Cancer is a patient advocacy group and charity for bladder cancer, based in the UK. We run a 24/7 confidential online support group that has over 5,000 users, support groups, and a national 1 to 1 bladder buddy service. As a patient-led charity, our knowledge of the patient experience with bladder cancer is second to none in the UK. The charity is funded by individual donations, grants, and financial support from Astellas, BMS, Janssen, Merck, Pfizer, MSD, and Roche.
4b. Has the organisation received any funding from the manufacturer(s) of the	Fight Bladder Cancer received £9,000 from BMS for support, policy, awareness, and research – 9 March 2021 Fight Bladder Cancer offers support to patients with advanced cancer, including information about treatments including the technology and comparator products. Fight Bladder Cancer lists all clinical trials currently recruiting patients within the UK, including clinical trials for this technology and comparator products.

technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct	No

or indirect links with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	We reached out to people on our private online forum of 5,000 patients and carers to ask them about various aspects of bladder cancer and received 186 comments. We spoke directly to patients who have received this treatment. We also spoke to our Support Services Manager, nurses, medical oncologists to better understand the patient experience.
Living with the condition	
6. What is it like to live with the condition? What do carers	Quotes from patients:

experience when caring for someone with the condition?	“It has been 2 years since I had my radical cystectomy. My health is unpredictable at best. I've struggled with stomach-ache and cramps, diarrhoea, vomiting, breathlessness, phantom pain where things were removed. I have an itchy rash spreading over the area around my stomach. I have good days, bad days, and OK days. “Five years ago, this month was when I got my bladder cancer diagnosis. Now here it is five years later, no cancer, and millions of fabulous, unbelievably wonderful memories later. When I look back, losing my bladder was such a tiny, tiny price to pay for all of that! I've been here to see the grandchildren grow, watch them enjoy their sports, dance recitals, graduate high school, and the littlest one (now almost 6) knows who I am instead of learning who I "was". The aches and pains that I have now from older age are amazing because I'm here to complain about them!” “Four years ago, I was hooked up to the Da Vinci robot having my bladder and bits removed. I hoped I had made the right decision, and every day I've had since has made me sure that I did. 1,460 bonus days without cancer so far. I'd had hundreds of opportunities to live life, enjoy watching the grans grow up, learn new things, and try to pay it forward. What a tiny, tiny price to pay for all of that!” From carers: “My Dad was diagnosed with bladder cancer in 2006. We’d never heard of anyone having bladder cancer before. I can remember him phoning to say he was on his way home, and then walking into the kitchen and telling us he had cancer, and extremely aggressive cancer at that. We decided as a family to go straight for the RC (we just wanted it out of his body) and just weeks later we dropped him off at the hospital for his 14-hour surgery. My Dad was a very fit and healthy 70-year-old, and had no side-effects from the chemo, and it wasn’t long before he was back doing his bits of gardening for people. Apart from chronic constipation, and breaking his shoulder in two, he’s kept reasonably fit and well. That was until he developed stomach pain. During a phone call from the hospital, we were told my dad, once again, has cancer. Sadly, nothing can be done, and it’s a case of just keeping him as comfy as possible.” What do carers experience when caring for someone with the condition? For carers, the pressure is on them, from day one, to help support and care for their loved ones. Carers report that it has a substantial impact on their ability to work, ability to travel ,and ability to spend time with family and friends.

	"Caring for her means constant worry and constant vigilance. I wish we could go back to the time before 2020 when we were free of all this and could enjoy life. I have nothing to look forward to but the eventual end of her life, and then having to go on after she has left me behind."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	From patients: "Nearly 3 years on from radical cystectomy and becoming a 'bag lady' for life, and another "all clear". I don't share this to be insensitive to those who aren't dealing with such happy news, but to hopefully encourage anyone facing the daunting treatment. The new normal can, with a bit of luck, be a happy and healthy one." "6 years ago, I had my radical cystectomy, learned how to deal with a stoma, spent 16 days in hospital - had cannulas and drips in both arms for quite a few days and getting out of bed without help was impossible with drips in both arms. Eventually got out of hospital (there were days when I never thought I would), cried when I got to my brother's (stayed with him for 2 weeks). Got back to my home having not been there for a month and never looked back. Been clear of cancer and been fine ever since." "Two years ago, I was a jabbering mess sat waiting for my operation. Spent 7 days in hospital, home for Christmas and the next few weeks were very hard, but I managed to get back to work full time within 6 weeks. Not going to lie, it was tough but now I am happy with my lot, my life has not changed that much living with a bag, and I am grateful for it every day as it saved my life. Just waiting for results of my annual CT scan now (the waiting is always the worst)."
8. Is there an unmet need for patients with this condition?	From patients: "When follow up biopsies showed recurrence of high grade TCC with invasion of the lamina propria, I decided it was time for a radical cystectomy before my high-grade cancer became invasive. I did well with the surgery and didn't miss my bladder one bit, but it left me severely incontinent" From carers: "Two years ago, hubby almost died after a massive post-op infection. Since then, he's battled crippling fatigue and whole raft of other problems caused by the chemo he had prior to his radical cystectomy, some of which are now lifelong and mean he was not able to return to his old job."

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The most important advantage is increased disease-free survival. In the Checkmate 274 trial involving people with high-risk muscle-invasive bladder cancer who had undergone radical bladder surgery, disease-free survival was longer with adjuvant nivolumab than with placebo. The median disease-free survival in the intention-to-treat population was 20.8 months (95% confidence interval 16.5 to 27.6) with nivolumab and 10.8 months (95% confidence interval 8.3 to 13.9) with placebo. Health-related quality of life – as assessed by the EORTC-QLQ-C30 global score – did not deteriorate in the nivolumab versus placebo study arms. From carers: “My Dad had 13 infusions so far, every 2 weeks. He has completed 6 months on this now. My oncologist says, after recent scans and general condition of my father, the disease can be considered as stable. Thankfully, he had no major side effects from nivolumab so far. He will continue on the same with scan after next 4 infusions” “We had the first infusion. He doesn't have any side effects. The oncologist said that it might take 2 or 3 infusions to see if there is impact onto his functions. Our check point is in 4-months’ time. That when we will get some idea if this is an effective treatment.”
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	In the CheckMate 274 trial, Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 17.9% and 7.2% of patients in the nivolumab and placebo arms, respectively. From a carer: “My Dad has lower back pain and urethral region pain due to the tumours there, but pain meds help on that to some extent.”

Patient population	
11. 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 appears that the PD-L1 ≥ 1% population benefited more from treatment. It would be interesting to know why this PD-L1 ≥ 1% population has responded more positively to checkpoint inhibitors compared to other bladder clinical trials. However, Fight Bladder Cancer would be very concerned if this treatment was just restricted to just the PD-L1 ≥ 1% population, as this study also demonstrated benefit to the entire population regardless of PD-L1 status.
Equality	
12. Are there any potential equality issues that should be taken into	Women are often diagnosed much later with bladder cancer, compared to men with bladder cancer. Women are also more likely to die of bladder cancer. These issues should be considered when considering this technology.

account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	Urothelial cancer has come near 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. Over the past 20 years in England and Wales, there has only been two innovative treatments funded for bladder cancer. Pembrolizumab has been removed from the Cancer Drugs Fund [ID1536]. So far, NICE has not recommended avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]. Bladder cancer patients need access innovative treatments. They need hope.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • The most important advantage of nivolumab is increased disease-free survival from a median of 10.8 months to 20.8 months.	

- There are no other treatments currently available for this patient population. Currently after bladder removal, most patients in this population only receive best supportive care.

- Fight Bladder Cancer would be very concerned if this treatment was just restricted to just some subgroups, as this study also demonstrated benefit to the entire population.

Summary

- Adjuvant NIVO significantly improved DFS in patients with high-risk MIUC after radical surgery, both in the ITT and PD-L1 ≥ 1% populations
- NUTRFS (secondary endpoint) and DMFS (exploratory endpoint) were also improved with NIVO versus PBO in both study populations
- The safety and tolerability of NIVO monotherapy was consistent with previous reports in other tumor types, including in patients with metastatic UC[1-3]
- No deterioration in HRQoL, as measured by change in EORTC QLQ-C30 global health status score, was observed with NIVO versus PBO
- NIVO is the first systemic immunotherapy to demonstrate a statistically significant and clinically meaningful improvement in outcomes when administered as adjuvant therapy to patients with MIUC[4,5]
- These results support NIVO monotherapy as a new standard of care in the adjuvant setting for patients with high-risk MIUC after radical surgery, regardless of PD-L1 status and prior neoadjuvant chemotherapy

1. Sharma P et al. *Lancet Oncol* 2016;17:1590-1598. 2. Sharma P et al. *Lancet Oncol* 2017;18:312-322. 3. Motzer R et al. *N Engl J Med* 2015;373:1803-1813. 4. Kim HS et al. *Investig Clin Urol* 2018;59:285-296. 5. Hussain MHA et al. *J Clin Oncol* 2020;38(suppl 15):5000.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

Confidential until published

Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Geoff Holmes, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Joanna Leaviss, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Marrissa Martyn-St James, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK Jonathan Aning, Consultant Urological Surgeon, Bristol Urological Institute, Bristol, UK Yakhub Khan, Consultant Clinical Oncologist, Arden Cancer Centre, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	17/11/2021

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/39/77.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

Acknowledgements

We would like to thank Paul Tappenden, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Metry A, Holmes G, Leaviss J, Martyn-St James M, Clowes M, Aning J, Khan Y, Stevenson M. Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2021.

Contributions of authors

Mark Clowes critiqued the company's search strategy. Marrissa Martyn-St James and Joanna Leaviss summarised and critiqued the clinical effectiveness data reported within the company's submission. Geoff Holmes critiqued the statistical aspects of the submission. Jonathan Aning and Yakhub Khan provided clinical advice to the ERG, and critiqued clinical opinions stated within the company's submission. Andrew Metry and Matt Stevenson critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

Table of contents

List of tables

List of figures

List of boxes

Abbreviations

AEs	Adverse events
AIC	Akaike Information Criterion
BC	Bladder cancer
BIC	Bayesian Information Criterion
BSC	Best supportive care
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CRD	Centre for Reviews Dissemination
CS	Company's submission
CSR	Clinical Study Report
DBL	Database lock
DFS	Disease-free survival
DMFS	Distant metastasis-free survival
DSA	Deterministic sensitivity analyses
DSS	Disease-specific survival
ECOG	Eastern Co-operative Oncology Group
ECOG PS	Eastern Co-operative Oncology Group Performance Score
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels
ERG	Evidence Review Group
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMAE	Immune-mediated adverse event
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IUC	Invasive urothelial carcinoma
IV	Intravenous
KM	Kaplan-Meier
LRC	Locoregional control
LRDFS	Locoregional disease-free survival
LT DFS	Long-term disease-free survival
MCAR	Missing completely at random

MIBC	Muscle-invasive bladder cancer
MID	Minimally important difference
MIUC	Muscle-invasive urothelial cancer
MVAC	Methotrexate plus vinblastine plus doxorubicin plus cisplatin
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMIBC	Non muscle-invasive bladder cancer
NUTRFS	Non-urothelial tract recurrence-free survival
OS	Overall survival
PAS	Patient Access Scheme
PD-1	Programmed cell death 1 (receptor)
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PFS 2	Progression-free survival after the next line of the subsequent therapy
PP	Per protocol
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QLQ-C30	EORTC Quality of Life Questionnaire-Core 30
RCT	Randomised controlled trial
RDI	Relative dose intensity
RoB2	Cochrane Risk of Bias 2 tool
SAE	Serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality rate
STA	Single Technology Appraisal
TTR	Time to recurrence
UC	Urothelial carcinoma
UTUC	Upper tract urothelial cancer
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) which are specified in terms of cost per quality-adjusted life years (QALYs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the view of the ERG, and do not necessarily reflect the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Key issues identified by the ERG that impact on the incremental costs and QALYs are summarised in Table 1. A fuller description of each issue, together with potential alternative approaches, the expected impact on the ICER of such approaches and additional evidence that would resolve the issue are contained in Section 1.5

Table 1: Overview of the ERG's key issues

ID 2694	Summary of issue*
Issue 1	Exclusion of cisplatin-based adjuvant chemotherapy as a comparator
Issue 2	The use of semi-parametric models to fit to disease free survival (DFS) Kaplan Meier (KM) estimates
Issue 3	Use of utility data from Janssen *et al*.
Issue 4	The average age of patients in the UK is likely to be older than those recruited to CheckMate 274
Issue 5	Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo
Issue 6	Patients in the DFS health state have the same utility values as an age- and sex-matched population
Issue 7	Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population
Issue 8	Uncertainty surrounding the assumed cure point
Issue 9	The lack of subgroup analysis in the company's submission

*All detailed in Section 4.3.3
DFS - disease-free survival; KM - Kaplan Meier

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival (OS)) and quality of life, using QALYs. In the model, nivolumab treatment increases QALYs compared with best supportive care (BSC) by increasing both expected OS, due to elongated disease-free survival (DFS), and the average quality of life for patients, whilst alive, as disease progression (recurrence) is also delayed. In the model, the costs associated with adjuvant nivolumab treatment compared with BSC are greater, primarily due to the acquisition costs of nivolumab.

The assumptions within the company's base case modelling that the ERG believes are either incorrect, or uncertain, and that impact most on the ICER, expressed as the additional cost per QALY gained, are provided in Table 1.

1.3 The decision problem: summary of the ERG's key issues

The ERG has no key issues with the decision problem as addressed by the company but notes that the comparators used excluded cisplatin adjuvant chemotherapy, and that OS data were unavailable and therefore not explicitly modelled.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The key evidence for clinical effectiveness within the CS comprises one randomised controlled trial (RCT) of adjuvant nivolumab (n=353) versus placebo (n=356); which was relevant to the decision problem: CheckMate 274. This RCT was ongoing at the time of writing, and data were from a pre-specified interim analysis. At the data cut-off, the hazard ratio (HR) for DFS, the primary endpoint, was 0.70 (98.22% confidence interval (CI) 0.55, 0.90), favouring nivolumab over placebo. The KM estimated median DFS was 20.8 months (95% CI 16.5, 27.6) in the nivolumab arm, and 10.8 months (95% CI 8.3, 13.9) in the placebo arm. Data for OS, a secondary endpoint, were not available. All cause adverse events of grade ≥ 3 were experienced by 150 (42.7%) patients in the nivolumab group, and 128 (36.8%) patients in the placebo group. Grade ≥ 3 treatment-related adverse events (TRAEs) were experienced by 17.9% versus 7.2% in the nivolumab and placebo groups respectively.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

This section expands on the issues listed in Table 1.

Table 2: Issue 1. Exclusion of cisplatin-based adjuvant chemotherapy as a comparator

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The NICE final scope states that cisplatin-based adjuvant chemotherapy is a relevant comparator to nivolumab. However, the company only presented cost-effectiveness results for nivolumab versus BSC in their submission. Clinical advice received by the ERG suggests that for a proportion of patients, cisplatin-based adjuvant chemotherapy would be an appropriate treatment choice. The ERG believes that the ICERs presented in the company submission are applicable only to the comparison of adjuvant nivolumab and BSC.
What alternative approach has the ERG suggested?	The ERG could not conduct a formal cost-effectiveness analysis between nivolumab and cisplatin-based adjuvant chemotherapy and the company declined to do this, citing the '*considerable uncertainty*' in any indirect treatment comparison (ITC). However, a qualitative comparison was undertaken by the ERG.
What is the expected effect on the cost-effectiveness estimates?	For patients who are eligible for cisplatin-based adjuvant chemotherapy, the company's ITC results show that nivolumab is not clearly superior to cisplatin-based regimens, with the point estimate of the hazard ratio (HR) favouring adjuvant chemotherapy. In addition, cisplatin-based regimens are potentially less expensive than nivolumab and are only given for six cycles, thereby limiting the administration burden on patients. Based on the current available evidence, the ERG deems that it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY
What additional evidence or analyses might help to resolve this key issue?	A head-to-head study comparing adjuvant nivolumab treatment with cisplatin-based adjuvant chemotherapy in an appropriate population.

Table 3: Issue 2. The use of semi-parametric models to fit to DFS KM estimates

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company selected a semi-parametric distribution to model DFS using KM plots until chosen time points after which Weibull distributions are fitted to survival data for individuals who remain alive. Standard parametric fits (in particular the Gompertz distribution) were rejected for reasons with which the ERG does not agree.
What alternative approach has the ERG suggested?	The ERG prefers a Gompertz distribution to characterise DFS over the initial 5-year period.
What is the expected effect on the cost-effectiveness estimates?	Using Gompertz distributions rather than the company's approach more than doubles the ICER becoming greater than £70,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up on DFS for both the nivolumab and the BSC arms would reduce the uncertainty over the most appropriate distribution to use in the economic model.

Table 4: Issue 3. Use of utility data from Janssen *et al*.

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The data source used by the company assumes that there is no loss in utility after the age of 75 years. The ERG does not believe that this is plausible.
What alternative approach has the ERG suggested?	The use of utility data from Ara and Brazier which allows utility to decrease as patients age beyond 75 years.
What is the expected effect on the cost-effectiveness estimates?	This change has a modest impact on the ICER, increasing it by less than £500 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	-

Table 5: Issue 4. The average age of patients in the UK is likely to be older than those recruited to CheckMate 274

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	Clinical advisors to the ERG believed that patients seen in clinical practice in England would be older than those recruited to CheckMate 274. This has the implication that an intervention which had less mortality in early years would be associated with reduced QALY gains, because the life expectancy of patients would be lower.
What alternative approach has the ERG suggested?	To explore the impact of using a higher age for patients treated in England.
What is the expected effect on the cost-effectiveness estimates?	Higher ages increase the ICER. Assuming an average age of 70 rather than [redacted] years old increased the ICER by over £5,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	An audit of English practices to establish the average age of patients undergoing resection for high-risk invasive urothelial cancer.

Table 6: Issue 5. Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company has assumed that the proportion of DFS events that are deaths are independent of treatment. Data observed from the CheckMate 274 study showed a greater proportion of deaths in the nivolumab arm than the placebo arm.
What alternative approach has the ERG suggested?	The ERG explored the impact on the ICER of assuming that 8.2% of DFS events were deaths for nivolumab treated patients and 4.9% of DFS events were deaths for BSC.
What is the expected effect on the cost-effectiveness estimates?	This change has a modest impact on the ICER, increasing it by less than £500 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Further data relating to the number of DFS events in CheckMate 274, conditional on treatment arm, that were deaths or recurrence of disease.

Table 7: Issue 6. Patients in the DFS health state have the same utility values as an age- and sex-matched population

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company assumed that patients in the DFS health state have equivalent utility to an age- and sex-matched population. However, the advice from ERG's clinical experts plus published evidence indicated that history of having a resected urothelial cancer (UC) should have detrimental effect on the patient's quality of life compared with an average person of the same age and sex without resected UC.
What alternative approach has the ERG suggested?	To explore the impact of using lower utilities for patients without resected UC.
What is the expected effect on the cost-effectiveness estimates?	Decreasing the value of all health state utilities by 0.02 has a moderate impact on the ICER, increasing it by under £1000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Research assessing whether having a historical resected UC has a residual impact on a person's utility, and quantifying the decrement in utility.

Table 8: Issue 7. Patients in the long-term DFS health state have the same life expectancy as general population

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	For patients remaining in the DFS health state beyond five years, the company applied the same mortality rates as for an age- and sex-matched population. The ERG believes it is plausible that, on average, life expectancy in patients with resected UC who have not had a DFS event within five years will be shorter than that for population who do not have resected UC.
What alternative approach has the ERG suggested?	To explore the impact of using a standardised mortality rate (SMR) for patients with resected UC increasing their risk of death compared to an age- and sex-matched population.
What is the expected effect on the cost-effectiveness estimates?	Using an SMR of 1.1, the ICER increased modestly, by less than £200 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Audit data to assess whether patients with previously resected UC more than 5 years are at a higher risk of death than an age- and sex-matched population.

Table 9: Issue 8. Uncertainty surrounding the assumed cure point

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company assume that after 5 years residing in the DFS state, the patient will not have a recurrence. Clinical advice to the ERG suggests that whilst the recurrence rate diminishes as the time since resected UC increases, it is not zero after 5 years. Additionally, data from Hautmann *et al*., in patients that had not received neoadjuvant chemotherapy, suggest that a plateau of 10 years may be more appropriate.
What alternative approach has the ERG suggested?	The ERG explored using a cure point at 10 years instead of 5 years.
What is the expected effect on the cost-effectiveness estimates?	This change decreased the ICER by over £4000 per QALY gained using the company's DFS distributions but increased the ICER by over £7000 when using the Gompertz distributions.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up data regarding the times of recurrence following resected high-risk UC.

Table 10: Issue 9. The lack of subgroup analysis in the company's submission

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The NICE final scope requested that PD-L1 expression of the resected tumour be considered. The company stated that PD-L1 *"has not been confirmed to be prognostic"*, and that the CheckMate 274 trial is insufficiently powered to detect differences based on PD-L1 expression. The ERG believes illustrative ICERs should be presented for those with tumours with a PD-L1 value ≥1% and <1% noting that these were stratification factors within the study. Subgroup analyses by location of the tumour and geographical region may also be informative to the Appraisal Committee.
What alternative approach has the ERG suggested?	-
What is the expected effect on the cost-effectiveness estimates?	The ICER for nivolumab would likely be more favourable in the subgroups with a lower HR for DFS, namely patients who had a tumour PD-L1 expression ≥1%; an initial tumour origin in the urinary bladder, and those who had received prior neoadjuvant treatment cisplatin therapy or prior neoadjuvant systemic therapy
What additional evidence or analyses might help to resolve this key issue?	Further follow-up of patients and formal cost-effectiveness analyses for relevant subgroups.

1.6 Summary of ERG's preferred deterministic exploratory analyses

Table 11 provides a reference of the results from the ERG's exploratory analyses. These are detailed in Section 4.4. The ERG's most plausible ICER is £75,000 per QALY gained as explained in Section 4.4.

Table 11: Results of the ERG's deterministic exploratory analyses

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic)							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,813
ERG exploratory analysis 1: Using a Gompertz distribution to model DFS over the initial 5-year period*							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,315
ERG exploratory analysis 2: Using utility values from Ara and Brazier							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,144
ERG exploratory analysis 3: Increasing the average age of treated patients to 70 years of age							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,030
ERG exploratory analysis 4: Using the observed proportion of DFS events that were deaths							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,159
ERG exploratory analysis 5: Decreasing all health state utilities in the model by 0.02							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,685
ERG exploratory analysis 6: Assuming a standardised mortality ratio of 1.1 for patients with resected UC							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,965
ERG exploratory analysis 7a: Assuming a cure point of 10 years using the company's semi-parametric fits (ERG's optimistic scenario)							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,708
ERG exploratory analysis 7b: Assuming a cure point of 10 years using the Gompertz distribution							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,651
ERG pessimistic scenario (combining ERG exploratory analyses 1-6 and assuming a cure point of 10 years)							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£83,101

*Used as a starting point to estimate the ERG's preferred ICER of £75,000 per QALY gained.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Section B.1.3 of the CS[1] contains an accurate overview of the health problem. Urothelial carcinoma (UC) is a cancer that affects the transitional cells forming the inner lining of the bladder, urethra, ureter, and renal pelvis. It has been estimated that 90% or more of UC arise in the bladder with up to 10% being upper tract urothelial cancer (UTUC).[2, 3]

Bladder cancer was the 11th most common cancer in England in 2017 with 8,686 new cases. It affects more males than females (a 3:1 ratio) with incidence increasing as people age; over half of cases diagnosed in people aged 50 years and over.[4] Bladder cancer outcomes are influenced by how far cancer cells invade the layers of the bladder and are commonly described as either non muscle-invasive (NMIBC) or muscle-invasive bladder cancer (MIBC). MIBC is less common than NMIBC but has a higher chance of spreading to other parts of the body. The prognosis for people with MIBC mainly depends on the presence of metastases (thought to be more than 50%) and the cancer stage at diagnosis as well. One-year (age-standardised) survival rates are 74%, 69%, and 36% for patients at stage II, III and IV, which decrease to 46%, 41% and 0% at five years respectively.[5] Muscle-invasive UTUC is less common than MIBC but has similar characteristics in that more men than women are affected and incidence increases as people age.

The CS focuses on patients with muscle-invasive UC (MIUC) who have undergone radical surgery and are at high risk of recurrence; MIUC comprises of patients with MIBC and patients with UTUC.[3]

2.2 Critique of company's overview of current service provision

Section B.1.3 of the CS details current service provision in the UK. Table 3 of the CS provides the staging systems for patients with bladder carcinoma or renal pelvis and ureter carcinoma which is based on the spread of the primary tumour, an evaluation of regional lymph nodes and to what extent there has been metastasis.

A summary of relevant treatment guidelines for MIUC is provided in Table 4 of the CS. The company's interpretation of the treatment pathway for patients with MIBC who receive radical therapy is provided in Figure 1, with the company's interpretation of the treatment pathway for patients with high-risk non-metastatic UTUC who receive radical therapy is provided in Figure 2. The ERG agrees that these pathways are reasonable interpretations of current guidelines although comments that whilst the European Association of Urology guidelines[6] does not discuss the use of systemic adjuvant chemotherapy, clinical advice to the ERG suggested it could be used.

For MIBC, the company has positioned nivolumab as a direct alternative to routine surveillance for those people who receive adjuvant treatment following radical cystectomy; this is shown by the red border in Figure 1. The company did not indicate where in the treatment pathway for high-risk non-metastatic UTUC nivolumab was to be positioned although the ERG has added a text box to Figure 2 to show that this would go after radical nephroureterectomy.

Figure 1: The treatment pathway for muscle-invasive bladder cancer in the UK provided by the company (reproduced from Figure 3 of the company's clarification response)

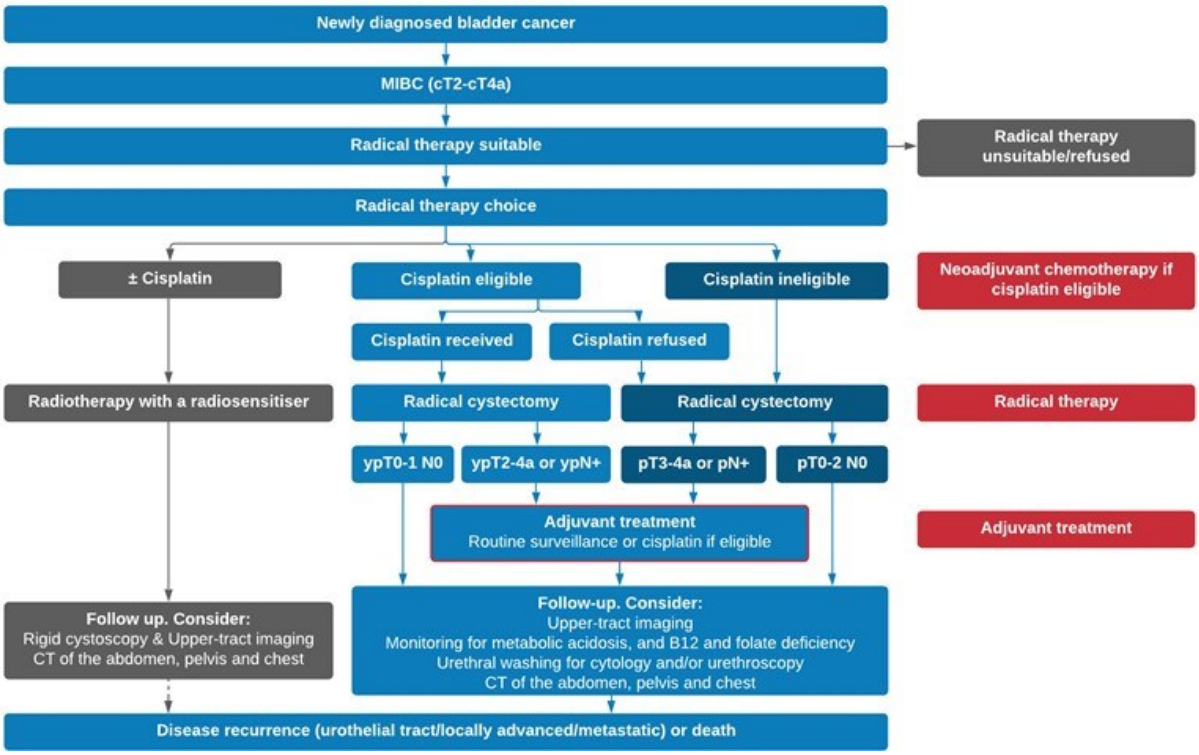
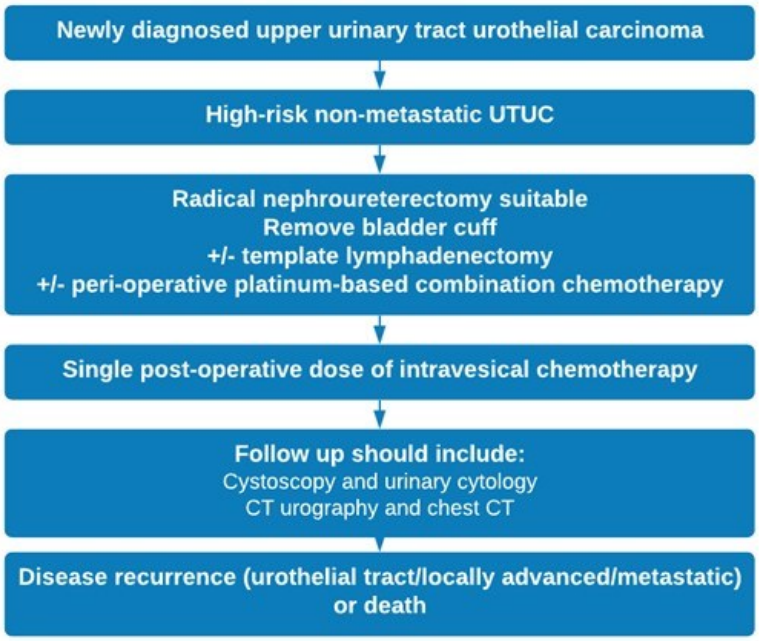


Figure 2: The treatment pathway for the surgical management of high-risk non-metastatic UTUC provided by the company (adapted from Figure 4 of the company's clarification response)



Systemic adjuvant chemotherapy is not discussed in the European Association of Urology guidelines but, if used, would be provided following radical nephroureterectomy. This is the position at which the company proposes adjuvant nivolumab should it be used.

Radical surgery is performed with the intention of curing the patient but a significant proportion has a recurrence which depends on factors such as: lymph node involvement; residual T2 disease (meaning tumour spreading to the muscle of the bladder wall); T3 disease (meaning tumour invading the perivesical tissue), if the patient did not receive neoadjuvant therapy; positive surgical margins; variant pathology; and resistance to neoadjuvant treatment.[7-9] When a carcinoma recurs it is typically in the three years following radical surgery, although a small proportion recur later. Based on data from a large multi-centre study, where patients had not received neo-adjuvant chemotherapy, an estimated 4.1% of patients recurred more than five years after radical cystectomy.[10] Data from a retrospective cohort study done by Hautmann *et al.,*[11] in patients that had not received neoajuvant chemotherapy, indicated that the risk of disease-specific survival (DSS) events declined over time, and that there were none after 120 months (10 years) [Figure 2 of Hautmann *et al.*[11]].

2.3 Critique of company's definition of the decision problem

A summary of the company's adherence to the decision problem set out in the NICE scope is provided in

Table 12. The ERG's critique of the company's deviations from the NICE scope are discussed in Section 4.3.

Table 12: Decision problem (adapted from Table 1 of the CS)

	Scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with invasive urothelial cancer who are at high-risk of recurrence following radical surgical resection	As final scope	-
Intervention	Nivolumab	Nivolumab	-
Comparators	•Adjuvant chemotherapy (e.g. cisplatin-based regimen) •BSC (monitoring and further treatment at recurrence)	BSC (monitoring and further treatment at recurrence)	The company states that the majority of patients in the UK would not be eligible for adjuvant cisplatin as they had received neoadjuvant cisplatin. Of those eligible, a proportion would refuse adjuvant chemotherapy. Additionally, the indirect treatment comparison undertaken by the company was stated to have *'important limitations'* and *'subject to considerable uncertainty'*
Outcomes	The outcome measures to be considered include: • disease-free survival • overall survival • adverse effects of treatment • health-related quality of life.	• disease-free survival • adverse effects of treatment • health-related quality of life.	The company was blinded to the overall survival data at the time of database lock (August 2020).
Subgroups to be considered	PD-L1 expression of the resected tumour	None	The company believes that the PD-L1 *"has not been confirmed to be prognostic"*, and that the CheckMate 274 trial is insufficiently powered to detect differences based on PD-L1 expression.
Special considerations	None	As final scope	-

BSC - best supportive care; PD-L1 - programmed death-ligand 1

2.3.1 Population

The CS states that nivolumab monotherapy is "*indicated for the treatment of patients with muscle-invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of IUC*." The population in the company's model is in accordance with the proposed license.

2.3.2 Intervention

Nivolumab (Opdivo®) is a fully human immunoglobin G4 monoclonal antibody that acts as a programmed cell death 1 (PD-1) immune checkpoint inhibitor, preventing tumour cells from evading

destruction. The recommended dosage of nivolumab in the adjuvant setting of MIUC is 240mg administered as one intravenous (IV) infusion every two weeks for a maximum duration of one year. This is provided as a 24mL vial with a 10 mg/mL concentration with a list price of £2,633.00. The company has proposed a patient access scheme (PAS) which takes the form of a simple price discount of [redacted].

Very common adverse events listed in the draft summary of product characteristics (SmPC)[12] are: [redacted]. Very common laboratory investigations are: [redacted].

Common AEs listed in the draft SmPC[12] are: [redacted]. Common laboratory investigations are: [redacted].

2.3.3 Comparator

The comparator chosen by the company is BSC. The company believes that the majority of cisplatin-eligible patients in the UK will receive neoadjuvant cisplatin and would therefore not be eligible for cisplatin in the adjuvant setting. Of those patients that did not receive neoadjuvant chemotherapy, but were eligible, a proportion will be ineligible for cisplatin in the adjuvant setting due to comorbidities, or may refuse adjuvant chemotherapy. Additionally, the indirect treatment comparison undertaken by the company was stated to have '*important limitations*' and '*subject to considerable uncertainty.*' As discussed in Section 4.3.3 Issue 1, the ERG believes that adjuvant chemotherapy is a comparator for a proportion of patients and should have been included in the CS. As the CS stands, the ERG believes that the cost-effectiveness results presented in this report are only relevant to those patients who are ineligible for, or who refuse adjuvant chemotherapy.

2.3.4 Outcomes

No OS KM estimates were available at the time of the submission, so the company modelled the estimated deaths occurring before, and after, recurrence separately. The methodology used by the company is detailed in Sections 4.2.3.2.2 to 4.2.3.2.4. All of the remaining outcomes shown in

Table 12 were reported in the CS and were considered in the company's model.

2.3.5 Subgroups

Although the NICE scope stated that if evidence allows, subgroup analyses should be conducted according to PD-L1 expression of the resected tumour, this was not included in the CS. The reason provided was that the company believes that PD-L1 expression "*has not been confirmed to be prognostic*", and that the CheckMate 274 trial does not have sufficient power to detect differences based on PD-L1 expression. As discussed in Section 4.3.3 Issue 9, the ERG believes that qualitative conclusions on the change in the cost-effectiveness of nivolumab based on the PD-L1 expression of the resected tumour could be provided, as could also be the case for other possible subgroups.

2.3.6 Special considerations

The NICE scope did not list any special considerations including issues related to equity or equality that should be explored. The company did not claim that special considerations were relevant to this Single Technology Appraisal (STA).

3 CLINICAL EFFECTIVENESS

This section presents a review of the clinical evidence reported in the CS[1] for nivolumab for treating IUC in people who are at high-risk of recurrence following radical resection.

3.1 Critique of the methods of review(s)

The clinical evidence provided in the CS was informed by a systematic review of studies assessing the clinical efficacy and safety of adjuvant treatment for UC (22 RCTs and 43 non-randomised studies, CS Appendix D). The clinical evidence provided in the CS was informed by CheckMate 274, an on-going phase 3, randomised, double-blind, multi-centre study of adjuvant nivolumab versus placebo. Although the CS notes that *'no studies of nivolumab in the adjuvant treatment of MIUC were identified by the SLR'*, the ERG noted that the conference proceeding reporting preliminary results of CheckMate 274 (Bajorin *et al.* 2021) was identified in the SLR. This was likely identified in the updated searches of conference proceedings conducted in February 2021. An exploratory indirect treatment comparison (ITC) comparing adjuvant nivolumab and adjuvant cisplatin chemotherapy was conducted. Four RCTs were identified in the SLR and provided the evidence base used in the exploratory ITC. However, due to limitations arising from heterogeneity and small sample sizes, this ITC was presented in the CS for completeness only and it was not used to inform the economic model. Safety evidence provided in the CS comprises a narrative synthesis of the data from CheckMate 274.

3.1.1 Searches

Appendix D of the CS reports an SLR of clinical efficacy (the literature searches are reported in Section 2 of the same Appendix).

The search strategies are long and complex, combining multiple facets of the decision problem. Unusually, search terms relating to radical resection are present in both the population facet (e.g. line 8 of the MEDLINE/EMBASE clinical search) and the intervention facet (e.g. line 13 of the same strategy). When the ERG queried this, the company responded that they had wished to use a consistent set of terms for the clinical and economic SLRs; and since the latter did not include interventions it was necessary to include this element in the population terms (clarification response, question A4).[13] It is the ERG's view that each SLR should use an independent search strategy which has been optimised for the retrieval of studies which meet the eligibility criteria for that review; this does not necessarily mean that the population terms should always match across reviews.

Searches included filters to identify study types eligible for inclusion. The filters used are based on those developed by the Scottish Intercollegiate Guidelines Network (SIGN). While the SIGN filters have not, to the ERG's knowledge, been formally validated, the ERG accepts that they are widely used

– with the caveat that, having been designed for MEDLINE, they are not necessarily optimised for use in a multi-file context. In order to mitigate the risk of missing studies, the company made minor adjustments to the filters in translation, and these erred on the side of increasing sensitivity (for e.g. using the Boolean "AND" where proximity operators were unavailable) (clarification response, question A6).[13]

Searches included all the core databases required by NICE (MEDLINE, Embase, Cochrane) as well as relevant trial registers and conference proceedings. MEDLINE and Embase were searched via a multi-file search using the ProQuest interface. This approach might reduce the transparency of the searches, since the ERG does not have access via ProQuest and cannot therefore reproduce the company's results; however, using a single search across multiple databases is likely to have associated risks. While it may appear that terms have successfully mapped across between indexing schemes, the way in which this actually happens (and hence the results retrieved by such an approach) can vary between platforms.

The company's clarification response (question A2) stated that their approach is methodologically sound and would not have missed any results, and the company explained that the decision to cross-search was made to assist in the removal of duplicates. Whereas deduplication normally takes place after a search has been run, ProQuest appears to do this on a line-by-line basis when searching in multi-file mode. This might have unanticipated and undesirable effects. For example, deduplicating sets of results, prior to them being combined with other search facets, may reduce the sensitivity of a search if the specific instance of a result which met all the search criteria (e.g. the presence of additional indexing terms unique to one of the databases being searched) had already been removed prior to the combination taking place.

For the reasons outlined above, the ERG's recommendation when searching for the purposes of SLRs is always to search databases one at a time, demonstrating that appropriate subject headings had been included. Also, this approach allows for clearer reporting of the number of results retrieved from each database prior to deduplication. However, the ERG is not aware of any studies potentailly missed by the company.

3.1.2 Inclusion criteria

The inclusion and exclusion criteria for the systematic review are reported in CS Appendix D and are broader than the NICE scope in order to retrieve studies to be included in an ITC. As CheckMate 274 was anticipated to be the only trial meeting the inclusion criteria in the NICE scope comparing nivolumab to BSC, this was considered to be an appropriate strategy. The company undertook a review of randomised and non-randomised studies in adults with IUC of the bladder, renal pelvis and ureter (upper urinary tract), who had undergone radical resection (e.g. cystectomy or nephrectomy). The

review was designed to include adjuvant treatment (platinum-based or monoclonal antibodies), with therapies compared with each other, placebo, standard of care, or investigator's choice (e.g. radiotherapy, chemotherapy, watchful waiting) (CS Appendix D). The SLR inclusion criteria included the key effectiveness outcomes (OS and DFS) and safety outcomes from the final NICE scope. Health-related quality of life (HRQoL) data were sought in a separate SLR (CS Appendix G).[13]

The inclusion and exclusion criteria for the SLR are presented in Table 13.

Table 13: Inclusion and exclusion criteria in systematic review search strategy (reproduced from Table 2-1 appendix D of the CS)

Characteristics	Inclusion criteria	Exclusion criteria
Population	• Invasive urothelial carcinoma (according to WHO 2016 criteria) of bladder, renal pelvis and ureter (upper urinary tract) • Treated with radical resection (e.g. radical resection (e.g. radical cystectomy, nephrectomy) • Subjects aged ≥18 years	• Non-invasive urothelial cancer • Metastatic cancer • Bladder preservation sparing procedure • Healthy subjects • Children (≤18 years of age)
Interventions	Adjuvant (post-surgery) treatment • Platinum-based: o Cisplatin combination therapy o Carboplatin combination therapy • Monoclonal antibodies: o Nivolumab o Pembrolizumab o Durvalumab o Atezolizumab o Avelumab	Non-adjuvant interventions and interventions not included in the inclusion criteria
Comparators	• Any of the listed interventions • Placebo/SoC/Investigator's choice, this can include but is not limited to: • Neoadjuvant chemotherapy (containing cisplatin or carboplatin) • Radiotherapy • Chemotherapy • Chemoradiation • Watchful waiting • No comparator arm	Interventions not included in the inclusion criteria

Characteristics	Inclusion criteria	Exclusion criteria
Outcomes	• OS • PFS • DFS • NUTRFS • ORR (according to RECIST criteria) • CR • PR • Duration of response • Time to treatment discontinuation • Time to symptom deterioration • Time to progression (according to RECIST criteria) • AE	Outcomes not included in the inclusion criteria
Study type	• Interventional trial o RCTs phase II and III o Non-randomised trials • Non-interventional studies o Cohort studies o Single-arm studies/uncontrolled studies o Case-control studies o Cross-sectional studies o Hospital records	• Systematic reviews and meta-analyses • Other types of studies not included in the inclusion criteria (e.g. phase I RCTs, case studies, non-human studies, biomarker investigation, genome research) • Studies which don't have an objective to investigate treatment efficacy/safety
Language	All languages	NA

OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; NUTRFS: non-urothelial tract recurrence-free survival; ORR: overall response rate; CR: complete response; PR: partial response; AE: adverse event; RCT: randomised controlled trial

Appendix D of the CS reports that for all citations, both the title/abstract and full-text screening stages of study selection were undertaken independently by two reviewers. The ERG considers this to be best practice in systematic reviewing.

3.1.3 Critique of data extraction

Details regarding the company's data extraction methods are reported in Section 2.4 of Appendix D of the CS.[1]

Data extracted from CheckMate 274 and reported in the CS are reported in Section 3.2. Although the CS reports that two reviewers were involved in the study selection process, it is unclear how many were involved in the data extraction process.

3.1.4 Quality assessment

The CS reports that a quality assessment of the CheckMate 274 RCT was undertaken which is presented in Section B.2.5 Table 13 and Appendix D. The CS reports that this was undertaken using the Centre for Reviews Dissemination (CRD) Guidance for Undertaking Reviews in Healthcare.[14] Whilst this report includes a chapter on undertaking quality assessment in systematic reviews and provides seven criteria for quality assessment, this is not a validated assessment tool for assessing the methodological quality of RCTs. The ERG considers that the use of validated tools such as the Cochrane Risk of Bias 2 (RoB2) tool[15] would have been more appropriate for assessing the quality of CheckMate 274. The quality assessment in the CS is merely a binary yes/no response to the criteria for quality assessment in the CRD handbook.[14]

The ERG sought clarification (question A17) with the company regarding why the company did not apply the Cochrane RoB2 tool. The company's clarification response[16] stated that company followed the NICE user guide[17] (Section 2.5) which refers to the CRD for the key aspects to be considered. The ERG considers that whilst the key aspects of quality to be considered outlined in the NICE user guide are appropriate for the quality assessment of RCTs, the application of a validated quality assessment instrument such as the Cochrane RoB2 tool would have allowed an assessment of the potential risk of attrition bias in the CheckMate 274 RCT, and the potential impact of this bias on study outcomes.

The ERG agrees with the company's responses to the CRD's seven quality assessment criteria. However, the ERG notes that whilst the seventh criteria asks about whether the company used appropriate methods to account for missing data in an intention-to-treat (ITT) analysis, it does not assess the potential effects of attrition bias on study outcomes, as does the Cochrane RoB2 tool. The ERG notes the high proportions of patients discontinuing treatment in the CheckMate 274 RCT, and the imbalance between arms in numbers discontinuing due to drug toxicity (which was greater with nivolumab).

Table 14 presents the company's quality assessment of the CheckMate 274 RCT and includes comments by the ERG on each quality assessment.

Table 14: Quality assessment of the CheckMate 274 RCT (adapted from Table 13 of the CS)

Quality assessment criteria	Yes / No (Company's response)	ERG comments
Was randomisation carried out appropriately?	Yes	The CSR,[18] reports that subjects assigned a subject number via an Interactive Voice Response System (IVRS). The ERG agrees with this judgement.
Was the concealment of treatment allocation adequate?	Yes	The CSR,[18] reports that subjects were enrolled into the study via an Interactive Voice Response System (IVRS). The ERG agrees with this judgement.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	The ERG agrees with this judgement.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	The protocol for Bajorin *et al*.[19] reports that the sponsor, patients, investigator and site staff were blinded to the study therapy administered. Pharmacists and site monitors were unblinded to provide oversight of drug supply and other unblinded study documentation. The ERG agrees with this judgement.
Were there any unexpected imbalances in drop-outs between groups?	No	The ERG agrees with this judgement.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The ERG agrees with this judgement.
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	The ERG agrees with this judgement. However, the ERG notes the high proportion (>50%) of patients discontinuing treatment in both arms, with a greater proportion discontinuing due to drug toxicity with nivolumab (49/351, 14%) compared to placebo (8/348, 2.3%) in the CONSORT diagram of Bajorin *et al*.[19]

3.2 Included study of nivolumab

The clinical SLR presented in the CS identified one RCT of nivolumab which was relevant to the decision problem: CheckMate 274 (NCT02632409). This formed the key evidence for clinical effectiveness and safety within the CS. The CS reports information relating to CheckMate 274 from:

- The study publication (Bajorin *et al*.[19])
- A conference presentation (Bajorin *et al*.[20])
- The clinical study report (CSR)[18] (database lock (DBL) 27th August, 2020)
- An [redacted] to the CSR[21]

The company states that OS data are not currently available as unblinding of OS is event-driven and that the number of events required to trigger it has not yet been reached (CS section B.2.2, Table 6). The company therefore remains blinded to the OS KM analyses.

The company states that there are no other ongoing studies of nivolumab in patients that have undergone radical resection of MIUC originating in the bladder or urinary tract who are at high-risk of recurrence (CS section B.2.11). The ERG believes that no relevant published RCTs of nivolumab that could have provided data on effectiveness have been omitted from the CS.

3.2.1 Study design CheckMate 274

CheckMate 274 is an ongoing Phase III, randomised (1:1 ratio), international multi-centre, double blind, placebo-controlled study initiated in March 2016 and conducted in 30 countries across 170 study locations in North America, Europe, South America, Australia, Asia and Israel. The study compared adjuvant nivolumab to placebo in adult patients who had undergone radical resection of MIUC originating in the bladder or upper urinary tract and are at high risk of recurrence. High risk of recurrence was defined as:

- pathological stage of pT3, pT4a, or pN+ and ineligible or declined adjuvant cisplatin-based combination chemotherapy for patients who had not received neoadjuvant cisplatin-based chemotherapy.
- pathological stage of ypT2 to ypT4a or ypN+ for patients who received neoadjuvant cisplatin (Bajorin *et al*.[19]).

Details of trial location, treatments and numbers randomised, prohibited concomitant medications and other relevant outcomes reported in CheckMate 274 are presented in Table 15 with details of the study characteristics provided in Table 16. Inclusion and exclusion criteria for the study are presented in Table 17.

Table 15: Check Mate 274 trial location, concomitant treatments and definition of outcomes (derived from Tables 7, 8, 9 and 10 of the CS)

Trial Location	Treatments, numbers randomised	Permitted and prohibited concomitant medication	Primary outcomes	Other outcomes used in the economic model/specified in the scope
CheckMate 274 **Multi-centre (international)**	PBO, N=356 NIVO, 240mg N=353 Both IV Q2W	Prohibited: any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment	*Disease-free survival:* - The time between the date of randomisation and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death (of any cause), whichever occurs first	*Overall survival (data unavailable at time of submission):* - Time from randomisation until death from any cause or recurrence of tumour *Adverse effects of treatment:* - Incidence of AEs, SAEs, select AEs, IMAEs *Health-related quality of life:* - EORTC QLQ-C30 and EuroQoL EQ-5D-3L

NIVO: Nivolumab; PBO: placebo; IV: Intravenous; Q2W: every two weeks; AE: adverse event; SAE: serious adverse event; IMAE: immune-mediated adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; EQ-5D-3L: EuroQoL 5-dimensional 3-level index

Table 16: CheckMate 274 study characteristics (adapted from Table 6 of the CS)

Study	Population	Intervention (N randomised)	Comparator (N randomised)	Primary outcome/other outcomes used in the economic model or specified in the scope
CheckMate 274 NCT02632409 CA209-274	Adult patients who have undergone radical resection of MIUC originating in the bladder or upper urinary tract and are at high-risk of recurrence	Nivolumab monotherapy 240mg IV over 30 minutes at 2-week intervals for a maximum of 1 year or until recurrence, unacceptable toxicity or discontinuation from the study	Placebo Administered IV over 30 minutes at 2-week intervals for a maximum of 1 year or until unacceptable toxicity or discontinuation from the study	*Primary outcome:* Disease-free survival (investigator assessed) *Other outcomes:* -Adverse effects of treatment -Health-related quality of life -Overall survival (unavailable at time of submission as unblinding is event-driven and data have not reached sufficient maturity)

Source: CSR[18]

Table 17: **Inclusion and exclusion criteria for CheckMate 274 (reproduced from Table 8 of the CS)**

Key inclusion criteria	Key exclusion criteria
• Post radical surgical resection (R0) for invasive urothelial cancer performed within 120 days prior to randomisation. • Pathologic evidence of urothelial carcinoma (originating in bladder, ureter, or renal pelvis) at high risk of recurrence based on pathologic staging of radical surgery tissue as described in one of the two below scenarios (i or ii): i) Patients who have not received neoadjuvant cisplatin chemotherapy: pT3-pT4a or pN+ and are not eligible for, or refusing, adjuvant cisplatin chemotherapy ii) Patients who received cisplatin based neoadjuvant chemotherapy: ypT2-pT4a or ypN+ • A patient must have a PD-L1 expression level classification (≥ 1%, < 1%, indeterminate) • Life expectancy ≥ 6 months • Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. ECOG PS 2 is listed as part of cisplatin ineligibility criteria. Patients who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy, may enter the study with ECOG PS 2.	• Partial cystectomy in the setting of bladder cancer primary tumour or partial nephrectomy in the setting of renal pelvis primary tumour. • Adjuvant systemic or radiation therapy for urothelial or prostatic carcinoma following radical surgical resection of urothelial carcinoma. • Any serious or uncontrolled medical disorder that may increase the risk associated with study participation or study drug administration, impair the ability of the patient to receive protocol therapy, or interfere with the interpretation of study results. • Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured. Patients with known history of recent metastatic urothelial carcinoma will be excluded. • Patients with active, known or suspected autoimmune disease. • Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration. • Patients with history of life-threatening toxicity related to prior immune therapy. • Treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

Source: CheckMate 274 protocol CA209274[22]

Seven hundred and nine patients were randomised within 120 days post-surgery to either nivolumab 240 mg or placebo (n=353 and n=356 respectively) and received treatment administered intravenously for 30 minutes every two weeks for a maximum of one year or until recurrence, unacceptable toxicity or discontinuation from the study.

Stratification factors were:

- PD-L1 status (<1% or indeterminate vs ≥1%).
- Prior neoadjuvant cisplatin-based chemotherapy (yes versus no)
- Nodal status (N+ vs N0 or NX with <10 nodes removed versus N0 with ≥10 nodes removed).

The study endpoints with definitions are presented below in

Table 18. The primary endpoint of the study was DFS, reported for the ITT population and for the subgroup of patients with PD-L1 expression level ≥1%. The company states in the CS that as the aim of the treatment is to prevent progression of disease, DFS is the most relevant endpoint in the adjuvant setting. Secondary endpoints were OS, non-urothelial tract recurrence free survival (NUTRFS), and disease-specific survival (DSS).

Exploratory endpoints were incidence of adverse events (AEs), serious adverse events (SAEs), immune-mediated adverse event (IMAEs); distant metastasis-free survival (DMFS); time to recurrence (TTR); locoregional disease-free survival (LRDFS); locoregional control (LRC); progression-free survival after next line of subsequent therapy (PFS2); efficacy by PD-L1 status; pharmacokinetics; immunogenicity and HRQoL.

Endpoints were assessed every 12 weeks from dose one until week 96, followed by assessments every 16 weeks until week 160, then every 24 weeks until either discontinuation of treatment or non-urothelial tract recurrence for a maximum of 5 years.

Table 18: Table of study endpoints in CheckMate 274 (adapted from Table 9 of the CS and Bajorin 2021 study publication)

Outcome	Definition
Primary outcome	
Disease-free survival (DFS)	The time between the date of randomisation and the date of first recurrence (local recurrence in the urothelial tract, local recurrence outside the urothelial tract, or distant recurrence), or death.
Secondary outcomes	
Non-urothelial tract recurrence free survival (NUTRFS)	The time between the date of randomisation and the date of first local recurrence outside of the urothelial tract, distant recurrence, or death.
Disease-specific survival (DSS)	The time between the date of randomisation and the date of death due to urothelial carcinoma.
Overall survival (OS)	The time between the date of randomisation and the date of death.
Exploratory outcomes	
Distant metastasis-free survival (DMFS)	The time between the date of randomisation and the date of first distant recurrence (non-local) or date of death (whatever the cause), whichever occurs first.
Time to recurrence (TTR)	The time between the date of randomisation and the date of first recurrence (local urothelial tract, local non urothelial tract or distant) or death due to disease, whichever comes first
Locoregional disease-free survival (LRDFS)	The time between the date of randomisation and the date of first locoregional recurrence (local urothelial or local non-urothelial tract) or date of death from any cause, whichever occurs first.
Progression-free survival (PFS2)	The time from randomisation to the date of investigator-defined disease progression after the subsequent next-line systemic anti-cancer therapy, or the start of second subsequent next-line systemic anti-cancer therapy, or death due to any cause, whichever comes first.

Health-related quality of life (HRQoL)	Measured by EORTC QLQ-30-C230 and EuroQoL EQ-5D-3L.

Sources: CS[1], Bajorin 2021[19]

3.2.1.1 Baseline characteristics of trial participants

Details of participant baseline characteristics in CheckMate 274 are presented in

Table 19. The CS considered baseline characteristics to be balanced across the two treatment groups. The majority of the participants in both treatment groups were male (nivolumab 75.1%, placebo 77.2%). The median age of participants was [redacted] years (range 30-92; inter-quartile range [redacted]) in the nivolumab group, and [redacted] years (range 42-88; inter-quartile range [redacted]) in the placebo group. Around three quarters of the participants were white (nivolumab 74.8%, placebo 76.4%), whilst almost a quarter were Asian (nivolumab 22.7%, placebo 21.1%).

At baseline, the majority of patients had a reported Eastern Co-operative Oncology Group performance status (ECOG PS) of either 0 or 1 (nivolumab 63.5% and 34.6% respectively, placebo 62.1% and 35.1% respectively). The tumour site in over three quarters of patients was the urinary bladder (nivolumab 79.0%, placebo 78.9%), with a minority in the renal pelvis (nivolumab 12.5%, placebo 14.6%) or ureter (nivolumab 8.5%, placebo 6.5%). Just under half of patients had received neoadjuvant cisplatin (nivolumab 43.3%, placebo 43.5%). In the nivolumab and placebo arms, [redacted] and [redacted] of patients had PD-L1 expression status of <1% versus [redacted] and [redacted] with PD-L1 status of ≥1%, respectively. At the time of resection, [redacted], [redacted], and [redacted] of all randomised patients had stage pT2, Stage pT3, and Stage pT4a respectively.

Table 19: **Baseline characteristics of participants in CheckMate 274 (reproduced from Table 11 of the CS)**

Baseline characteristic		Nivolumab	Placebo
Cohort size (N)		353†	356†
Age	Median (range), years	[redacted](30-92†)	[redacted](42-88†)
	Mean (range), years	65.3 (30-92)†	65.9 (42-88)†
Sex, n (%)	Female	88 (24.9)†	81 (22.8)†
	Male	265 (75.1)†	275 (77.2)†
Race	White	264 (74.8)†	272 (76.4)†
	Black or African American	2 (0.6)†	3 (0.8)†
	Asian	80 (22.7)†	75 (21.1)†
	Other or not reported	[redacted]	[redacted]
ECOG PS,[a] n (%)	0	224 (63.5)†	221 (62.1)†
	1	122 (34.6)†	125 (35.1)†
	2[b]	7 (2.0)†	9 (2.5)†
Tumour site, n (%)	Urinary bladder	279 (79.0)†	281 (78.9)†
	Renal pelvis	44 (12.5)†	52 (14.6)†
	Ureter	30 (8.5)†	23 (6.5)†
Minor histological variants present, n (%)	Yes	[redacted] (41.1*)	[redacted] (39.6*)
	No	[redacted]	[redacted]
Received neoadjuvant cisplatin, n (%)	Yes	153 (43.3)†	155 (43.5)†
	No	[redacted]	[redacted]
PD-L1 expression status, n (%)	< 1%	[redacted]	[redacted]
	≥ 1% and < 5%	[redacted]	[redacted]
	≥ 5% and < 10%	[redacted]	[redacted]
	≥ 10%	[redacted]	[redacted]
	≥ 5%	[redacted]	[redacted]
	≥ 1%	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Pathologic T stage at resection,[c,d] n (%)	pT0–2	[redacted] (22.7*)	[redacted] (24.2*)
	pT3	206 (58.4)†	204 (57.3)†
	pT4a	57 (16.1)†	62 (17.4)†
	Other	[redacted] (2.5*)	[redacted] (0.8*)
Nodal status at resection,[d] n (%)	N+	[redacted] (47.3*)	[redacted] (47.2*)
	N0/x with < 10 nodes removed	94 (26.6)†	99 (27.8)†
	N0 with ≥ 10 nodes removed	[redacted] (25.8*)	[redacted] (24.7*)

[a]Not reported for 1 patient in the PBO arm; [b]ECOG PS of 2 was permitted only for patients who did not receive cisplatin-based neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy. [c]The T staging included patients with N+, N0, or NX. [d]Not reported for 1 patient in each arm.

ECOG PS: Eastern Cooperative Oncology Group performance status; PD-L1: programmed death-ligand 1

Sources: CheckMate 274 CSR[18], †Bajorin *et al*.[19] and *Bajorin *et al*.[20]

3.2.2 Effectiveness study results of CheckMate 274

Median follow-up at the DBL was 20.9 months (range 0.1 to 48.3) for patients receiving nivolumab and 19.5 months (range 0 to 50) for those in the placebo group.

3.2.2.1 Disease-free survival

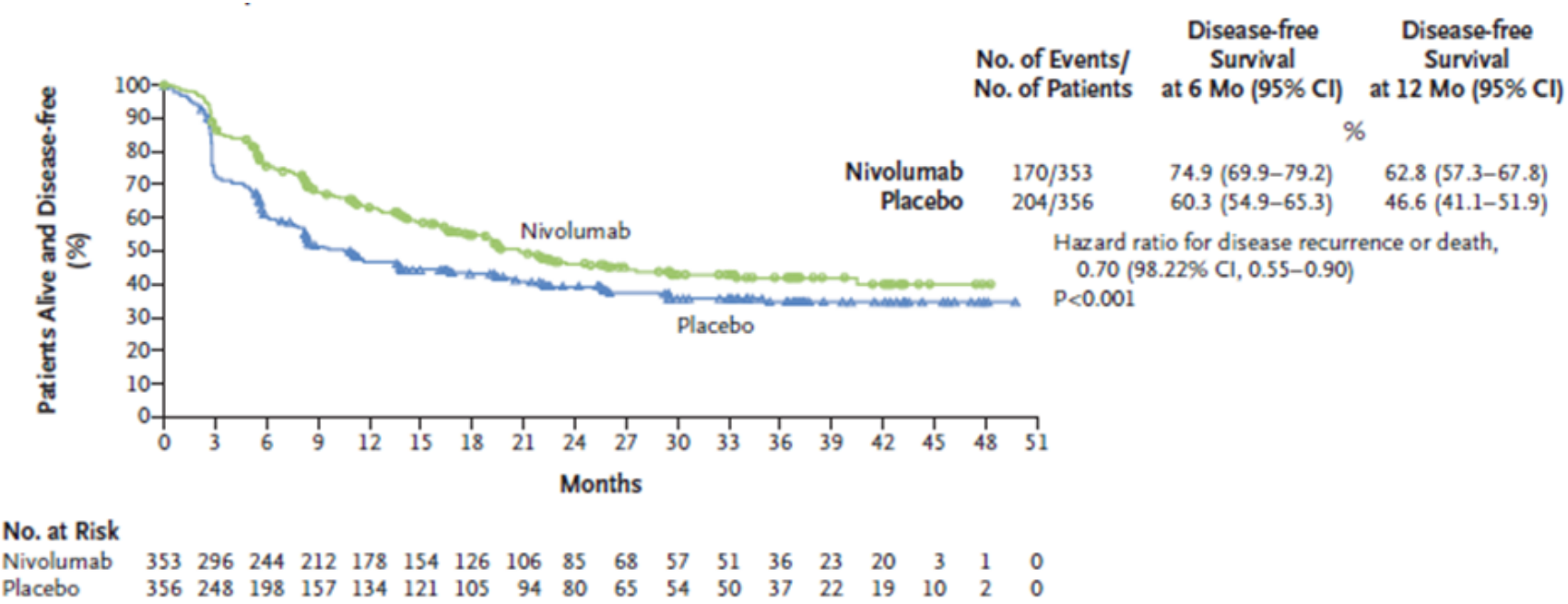
DFS was the primary endpoint for CheckMate 274. Table 20 shows DFS for all randomised patients in CheckMate 274. There were 170 DFS events in the nivolumab arm (48.2% of participants) compared to 204 events in the placebo arm (57.3% of participants). Among patients in the nivolumab group, median DFS was 20.8 months (95% CI: 16.5 to 27.6 months) compared to 10.8 months (95% CI: 8.3 to 13.9 months) in the placebo group (ITT analysis, HR 0.70 98.22% CI: 0.55 to 0.90, p<0.001). This improvement for patients treated with nivolumab is reported in the CS to be statistically significant and clinically relevant. 74.9% of patients in the nivolumab group were alive and free of disease at 6 months of follow-up, compared to 60.3% in the placebo group. At 12 months, 62.8% in the nivolumab group were alive and disease-free compared to 46.6% in the placebo group. Figure 3 shows KM curves separating after 3 months, in favour of nivolumab.

Table 20: DFS for all randomised patients in CheckMate 274 (adapted from CS Section B.2.6.1 Table 14)

DFS*	Nivolumab	Placebo
Randomised patients	353	356
DFS Events, n (%)	170 (48.2%)	204 (57.3%)
Median DFS (95% CI), months	20.8 (16.5, 27.6)	10.8 (8.3, 13.9)
Hazard Ratio (% CI)	0.70 (98.22% CI: 0.55, 0.90)	
6 months, % (95% CI)	74.9 (69.9, 79.2)	60.3 (54.9, 65.3)
12 months, % (95% CI)	62.8 (57.3, 67.8)	46.6 (41.1, 51.9)

*Primary definition of DFS – accounting for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer.
Source Bajorin *et al.*[19]

Figure 3: Kaplan-Meier plot of DFS in all randomised patients CheckMate 274 (reproduced from CS Section B.2.6.1 Figure 7)



Source: Bajorin *et al*.[19]

3.2.2.2 Other efficacy endpoints

The CS reports results of analyses for the following secondary and exploratory outcomes (Section B.2.6.2 to Section B.2.6.3.3 of the CS). As stated in Section 2.3.4, the company did not have information related to the timing of death events.

Secondary outcomes included:

- NUTRFS: A clinically meaningful improvement for patients on nivolumab compared to placebo (22.9 vs 13.7 months, HR=0.72 [95% CI: 0.59, 0.89])
- DSS: Results for DSS were not reported in the CS

Exploratory outcomes included:

- DMFS: a clinically meaningful improvement in DMFS for patients treated with nivolumab compared to those treated with placebo (40.5 vs 29.5 months, HR 0.75 [95% CI: 0.59, 0.94]). DMFS rates at 6 months were higher for nivolumab vs placebo (82.5% vs 69.8%), and also at 12 months (71.2% vs 58.6%)
- TTR: A clinically meaningful improvement in time to recurrence for patients on nivolumab compared to placebo (median [redacted] versus [redacted] months, HR [redacted]). Recurrence rates were higher in the placebo arm than the nivolumab arm at 6 months ([redacted] versus [redacted])
- LRDFS: A clinically meaningful improvement in LRDFS compared to placebo (placebo events [redacted] versus nivolumab events [redacted])
- Progression-free survival on next line systemic therapy (PFS2): [redacted] in all randomised patients (nivolumab median [redacted] months vs placebo [redacted] months, HR [redacted]. PFS2 rates at 6 months were [redacted] for nivolumab versus [redacted] for placebo

3.2.2.3 Subgroup analyses

The NICE scope specifies PD-L1 expression of the resected tumour as the only subgroup for consideration. Therefore, the primary endpoint of DFS in CheckMate 274 was analysed for all randomised patients and for patients with tumour cell PD-L1 expression ≥1% and <1%. In addition, the CS reports the following pre-planned subgroup analyses undertaken in CheckMate 274: use of prior neoadjuvant cisplatin therapy, initial tumour origin, age, gender, geographical region, race, baseline ECOG status, pathologic lymph node status, pathologic status, and time from invasive urothelial cancer surgery to randomisation.

Table 18 of the CS reports the primary endpoint of DFS; the secondary endpoint of NUTRFS; and the exploratory endpoint of DMFS for all randomised patients with tumour cell PD-L1 expression level ≥ 1% with results for the <1% subgroup reported in a CS clarification response addendum (in response to clarification question B23). Table 21 presents the HRs for each of these endpoints for the two PD-L1 subgroups compared to the overall population. Generally, it appears that nivolumab works better for patients with PD-L1 expression of ≥1% compared with patients having an expression of <1% for all endpoints. The ERG notes that the HR values for the PD-L1 <1% subgroup are not statistically significant.

Table 21: HR results of DFS, NUTRFS, and DMFS for overall population and the PD-L1 subgroups

Endpoint	Overall population	PD-L1 ≥1% subgroup	PD-L1 <1% subgroup
Sample Size			
Nivolumab	353	140 (39.7%)	207 (58.6%)
Placebo	356	142 (39.9%)	207 (58.1%)
DFS (primary definition)*			
Hazard Ratio (CI)	0.70 (98.22% CI: 0.55, 0.90)	0.55 (98.72% CI: 0.35, 0.85)	[redacted]
NUTRFS			
Hazard Ratio (95% CI)	0.72 (0.59, 0.89)	0.55 (0.39, 0.79)	[redacted]
DMFS			
Hazard Ratio (95% CI)	0.75 (0.59, 0.94)	0.61 (0.42, 0.88)	[redacted]

*Primary definition of DFS – accounting for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer.
Source Bajorin *et al*.[19] and CSR [redacted][23]

3.2.3 Health-related quality of life

Data measuring HRQoL were collected in CheckMate 274 using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) patient-reported outcome measures. A summary of results is presented in Table 22. Baseline completion rates for both instruments were above [redacted] in both nivolumab and placebo arms. At follow-up visits 1 and 2, completion rates of the EORTC QLQ-C30 dropped in both arms to [redacted] (nivolumab), and [redacted] (placebo). For EQ-5D-3L, completion rates during treatment were [redacted] (nivolumab) and [redacted] (placebo). The minimally important difference (MID) was defined as mean change in score from baseline ≥10 points. For both EORTC QLQ-C30 and

EQ-5D VAS, the CS reports that HRQoL remained stable, with no mean change in score from baseline reaching MID at any timepoint for either nivolumab or placebo, as seen in Figure 10 and Figure 12 of the CS. The mean EQ-5D-3L utility index score [redacted] both arms, as seen in Figure 11 of the CS.

Table 22: Health-related quality of life – EORTC QLQ-C30 and EQ-5D-3L for patients at baseline and follow-up in CheckMate 274

HRQoL	Nivolumab	Placebo
EORTC QLQ-C30		
Baseline completion rate % (n/N)	[redacted]	[redacted]
Follow-up visits 1 and 2 completion rate %	[redacted]	[redacted]
Summary scores	[redacted]	[redacted]
EQ-5D-3L		
Baseline completion rate % (n/N)	[redacted]	[redacted]
During treatment %	[redacted]	[redacted]
Summary scores	No mean change in score for the patient from baseline reached MID at any timepoint	No mean change in score for the patient from baseline reached MID at any timepoint

Source: CSR[18]

3.2.4 Treatment duration

Details of treatment doses received, dose intensity, and duration of therapy for the CheckMate 274 RCT are presented in Table 23. The CS reports that at the time of DBL (27 August 2020), the median number of doses received in the nivolumab arm was [redacted] (range: [redacted]) and the median in the placebo arm was [redacted] (range: [redacted]). Mean (standard deviation) values were [redacted] and [redacted] doses, respectively. In the nivolumab arm, [redacted] received 90-110% of the planned dose intensity.

The CS reports that in the nivolumab arm, the median duration of therapy was 8.8 months (range: 0-12.5 months) and in the placebo arm the median duration was 8.2 months (range: 0-12.6 months). The mean durations of therapy were [redacted] and [redacted] months respectively.

The CS reports that at the time of DBL (27 August 2020), [redacted] patients in the nivolumab arm and [redacted] patients in the placebo arm were off treatment. The proportion of all treated patients in the nivolumab arm with more than 6 months of therapy was [redacted] and the

proportion in the placebo arm was [redacted]. The proportions with more than nine months of therapy were [redacted] and [redacted] respectively, and the proportions with more than 12 months of therapy were [redacted] and [redacted] respectively.

Table 23: Details of treatment doses received and duration of therapy in the CheckMate 274 RCT (reproduced from the CS Table 20)

Number of doses received		
	Nivolumab arm (N=351†)	**Placebo arm (N=348†)**
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
Relative dose intensity (n, %)		
≥110%	[redacted]	-
90-110%	[redacted]	-
70-90%	[redacted]	-
50-70%	[redacted]	-
<50%	[redacted]	-
Duration of therapy (months)		
	Nivolumab arm (N=351†)	**Placebo arm (N=348†)**
Mean (Range)	[redacted](0.0 – 12.5†)	[redacted](0.0 – 12.6†)
Median	8.8†	8.2†
Patients (%) off treatment at clinical cut-off		
N off treatment / N treated (%)	[redacted]	[redacted]
Patients (%) with > 3, 6, 9, and 12 months of therapy		
> 3 months (%)	[redacted]	[redacted]
> 6 months (%)	[redacted]	[redacted]
> 9 months (%)	[redacted]	[redacted]
> 12 months (%)	[redacted]	[redacted]

Source: CSR,[18] †Bajorin *et al*.[19]

3.2.5 Safety study results of CheckMate 274

3.2.5.1 Adverse events

In CheckMate 274,[19] AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[24] The proportions of patients with any grade AEs (nivolumab 98.9% [347/351] and placebo 95.4% [332/348]) and Grade ≥ 3 AEs (nivolumab 42.7% [150/351] and placebo 36.8% [128/348]) were similar between arms. However, the proportions of patients reporting Grade ≥ 3 treatment-related adverse events (TRAEs) and treatment-related SAEs were higher in the

nivolumab arm than the placebo arm, 17.9% ([redacted]/351) and 7.2% ([redacted]/348), and [redacted]% ([redacted]/351) and [redacted]% ([redacted]/348), respectively.

Select AEs and IMAEs were also more frequently observed in the nivolumab arm compared with the placebo arm. The CS reports that most were Grades 1-2. A summary of AEs reported in the CheckMate 274 RCT are presented in Table 24 to Table 27.

Table 24: Summary of adverse events in the CheckMate 274 RCT (reproduced from the CS Table 21)

Summary of AEs n (%) Source: CSR,[18] †Bajorin *et al.*[19] and *Bajorin *et al.*[20]				
	Nivolumab arm (N = 351)		**Placebo (N = 348)**	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
Number of patients with AEs	347 (98.9)†	150 (42.7)†a	332 (95.4)†	128 (36.8)†a
Number of patients with AEs leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with treatment-related SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with TRAEs	[redacted] (77.5)*	[redacted] (17.9*a)	[redacted] (55.5)	[redacted] (7.2*a)
Number of patients with TRAEs leading to discontinuation of study treatment	[redacted] (12.8†)	[redacted] (7.1*a)	[redacted] (2.0†)	[redacted] (1.4*a)

AE, adverse event; CSR, clinical study report; SAE, serious adverse event; TRAE, treatment-related adverse event
[a] Grade ≥ 3

Table 25: Frequency of TRAEs in the CheckMate 274 RCT (reproduced from CS Tables 22)

Frequency of TRAEs with incidence rate > 5% n (%) (August 2020 DBL) Source: Bajorin *et al.*[19]				
	Nivolumab arm (N = 351)		Placebo arm (N = 348)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Total[b]	272 (77.5)	63 (17.9)	193 (55.5)	25 (7.2)
Pruritus	81 (23.1)	0	40 (11.5)	0
Rash	53 (15.1)	2 (0.6)	19 (5.5)	0
Rash maculo-papular	19 (5.4)	2 (0.6)	4 (1.1)	0
Fatigue	61 (17.4)	1 (0.3)	42 (12.1)	0
Asthenia	24 (6.8)	2 (0.6)	17 (4.9)	0
Diarrhoea	59 (16.8)	3 (0.9)	38 (10.9)	1 (0.3)
Nausea	24 (6.8)	0	13 (3.7)	0
Lipase increased	34 (9.7)	18 (5.1)	20 (5.7)	9 (2.6)
Amylase increase	33 (9.4)	13 (3.7)	20 (5.7)	5 (1.4)
Blood creatinine increased	20 (5.7)	1 (0.3)	11 (3.2)	0
Hypothyroidism	34 (9.7)	0	5 (1.4)	0
Hyperthyroidism	33 (9.4)	0	3 (0.9)	0
Decreased appetite	20 (5.7)	2 (0.6)	11 (3.2)	0

AE, adverse event; DBL, database lock; TRAE, treatment-related adverse event

[b] There were two treatment-related deaths due to pneumonitis in the nivolumab group

Table 26: Treatment-related select AEs in the CheckMate 274 RCT (reproduced from CS Tables 23)

Treatment-related select AEs (August 2020 DBL) Source: CSR,[18] and [†]Bajorin, 2021				
Organ class category (n, %)	Nivolumab arm (N = 351)		Placebo arm (N = 348)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Endocrine	67 (19.1)[†]	1 (0.3)[†]	13 (3.7)[†]	0[†]
Gastrointestinal	65 (18.5)[†]	6 (1.7)[†]	39 (11.2)[†]	3 (0.9)[†]
Hepatic	29 (8.3)[†]	6 (1.7)[†]	17 (4.9)[†]	1 (0.3)[†]
Pulmonary	19 (5.4)[†]	5 (1.4)[c†]	5 (1.4)[†]	0[†]
Renal	25 (7.1)[†]	4 (1.1)[†]	12 (3.4)[†]	0[†]
Skin	143 (40.7)[†]	6 (1.7)[†]	62 (17.8)[†]	0[†]
Hypersensitivity/Infusion reactions	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; immune-mediated adverse event; DBL, database lock; CSR, clinical study report

[c] One patient with grade 4 treatment-related pneumonitis and 1 patient with grade 3 treatment-related immune-mediated pneumonitis had a fatal outcome

Table 27: Summary of IMAEs in the CheckMate 274 RCT (reproduced from CS table 24)

Summary of IMAEs (n, %) (August 2020 DBL) Source: CSR[18]				
	Nivolumab arm (N = 351)		Placebo arm (N = 348)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
IMAEs in patient treated with immune modulating medication				
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea/Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis/Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/Infusion reactions	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine IMAEs in patients with or without immune modulating medication				
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]

IMAE, immune-mediated adverse event; DBL, database lock; CSR, clinical study report

3.2.5.2 Mortality

The CS[1] reports that death from any cause at the 27 August 2020 DBL occurred in [redacted] of patients in the nivolumab arm and [redacted] patients in the placebo arm. The most frequent cause of death in both treatment arms was disease progression (nivolumab [redacted] patients and placebo [redacted] patients). Death-related study drug toxicity was reported for two patients in the nivolumab arm and none in the placebo arm. Details on deaths are provided in

Table 28.

Table 28: Details of deaths in the CheckMate 274 RCT (reproduced from Table 26 of the CS)

	Nivolumab (N = 351)	Placebo (N = 348)
Number of patients who died, n (%)	[redacted]	[redacted]
Primary reason for death, n (%)		
Disease	[redacted]	[redacted]
Drug toxicity	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]

Source: CSR[18]

The CS[1] summarises that the safety profile of nivolumab in patients who have undergone radical resection of MIUC and are at high risk of recurrence can be considered acceptable and well-tolerated.

3.3 Indirect and mixed treatment comparison

The company conducted an exploratory ITC between adjuvant nivolumab and adjuvant cisplatin chemotherapy as requested by NICE. This is reported in CS Appendix J and summarised in CS Section B.2.9.

Details of the identification and methodology of the studies proposed to be included in an ITC analysis are described below.

Search Strategy

The CS states that an SLR was conducted to identify studies to facilitate an ITC of nivolumab compared to other treatments included as comparators in the NICE scope. The trials proposed to be included in the ITC were identified from the SLR, the methods of which are described in Appendix D of the CS and presented in Table 13.

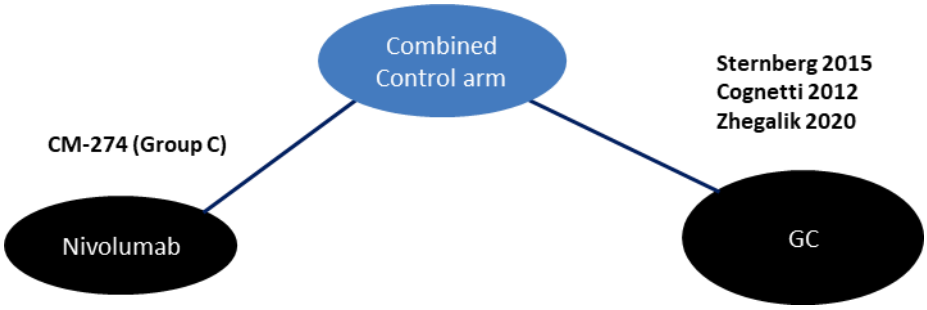
Study selection criteria

The eligibility criteria for the SLR were broader than the NICE scope in order to maximise the possibility of forming a network of trials for the ITC. The ERG does not consider that any eligible trials have been missed.

Studies identified

The inclusion criteria for the SLR were broad in order to identify trials to be included in the ITC. 15 potentially suitable RCTs, including CheckMate 274, were identified, as reported in Appendix J, Tables 2 and 3, and these were assessed for potential inclusion in the ITC. CheckMate 274 was the only study which included nivolumab and of the 14 others, 11 were excluded because the company deemed them not to be relevant. This was either because the study contained solely UTUC patients (2 studies); or because the chemotherapy treatment under investigation was methotrexate plus vinblastine plus doxorubicin plus cisplatin (MVAC) which is now rarely used in UK practice for safety reasons (8 studies); or both reasons (1 study). One of the remaining studies (Sternberg *et al.*[25]) contained a proportion of patients (16%) receiving MVAC. The retention of the study was noted by the company as a limitation. Figure 4 illustrates the evidence network used for the company's ITC.

Figure 4: The evidence network of the company's ITC (reproduced from Figure 20 of the CS)



The CS states that four RCTs met the inclusion criteria for the exploratory ITC. Of these, one study compared nivolumab to placebo (Checkmate 274), one study compared gemcitabine plus cisplatin to treatment on relapse[26], one trial compared cisplatin-based chemotherapy (MVAC, high-dose MVAC, or gemcitabine plus cisplatin) to deferred chemotherapy[25], and the remaining trial compared gemcitabine plus cisplatin to treatment on relapse. [27] Participants in each of the four studies received an adjuvant intervention, with one group in the Sternberg study receiving deferred treatment.

3.4 Critique of the company's indirect treatment comparison

The company considered that only a sub-population of the CheckMate 274 trial was relevant for the ITC; those patients were eligible for adjuvant cisplatin but actively refused this treatment (N=[redacted], of whom [redacted] were in the nivolumab group and [redacted] in the placebo group). Studies of patients with only UTUC were excluded from the ITC. The CS states (Appendix J) that neoadjuvant therapy is not common in patients with UTUC, with a generally shorter surgical recovery time. Treatment effects would therefore be expected to differ in trials of UTUC compared to those of bladder urothelial carcinoma. This left [redacted] patients with bladder cancer only ([redacted] on nivolumab and [redacted] on placebo).

The ERG notes that these study and patient exclusions reduce considerably the evidence base of the ITC. The clinicians advising the ERG stated that there was no compelling evidence that the comparative efficacy of adjuvant nivolumab versus cisplatin would differ between UTUC and MIBC patients. Additionally, the ERG notes that whilst MVAC is now rarely used for safety reasons, this does not have a bearing on its efficacy which may be considered similar to the treatment of interest (cisplatin). Therefore, it may have been possible to conduct the ITC with a much stronger evidence base.

The company assessed the four included studies for heterogeneity arising from differences in population, intervention, comparator, outcomes measured and study design. The company did not

highlight any major differences in tumour location (given that UTUC tumours were largely excluded anyway), ECOG status, sex split or age. The company presented evidence of variability in nodal status (Appendix J, Figure 2 in the CS) between the percentage in the N0 category and those in the N+ category, however, this relied on re-categorisation of nodal classification which differed between studies.

The company noted heterogeneity in the control arms of the included studies, with CheckMate 274 patients receiving placebo whilst for the other studies control was observation only or treatment on relapse. The ERG notes that since relapse / recurrence is the outcome of interest, observation and treatment on relapse are equivalent controls. The company stated that there was significant variability in the definition of outcomes between the studies. However, the ERG notes that whilst the stated outcomes are DFS and progression-free survival (PFS) in two studies each, the actual definitions do not vary significantly except that one study (Cognetti *et al*.[26]) does not explicitly mention both local and distant recurrence. Since all patients have had surgery, it is unclear how recurrence and progression would be distinct from each another.

The company also assessed possible heterogeneity arising from differences in study design. There were differences in enrolment periods and geographical locations but no judgement could be made with respect to whether these would be significant as treatment effect modifiers. The company stated that two studies (Cognetti *et al*.[26] and Zhegalik *et al*.[27]) conducted the analyses on the per protocol (PP) rather than ITT populations. However, the ERG believes that this was not the case for the survival analyses for which all analyses were undertaken using the ITT population. CheckMate 274 is the only double-blind study. The other studies are either reported as open-label (Sternberg *et al.*[25]) or can be inferred as such from the absence of a placebo. This was already noted in relation to outcomes and was therefore considered a main potential area for heterogeneity.

The company attempted to fit both fixed effect and random effects models for the ITC but noted that the random effects model failed to converge due to the limited amount of data. The company stated that the fixed effect model estimate of the HR for nivolumab versus adjuvant chemotherapy was [redacted]. The ERG notes that random effects models are preferred when pooling data from studies where there is heterogeneity and that when data are limited, a random effects model using a truncated Turner prior[28] can achieve convergence without making overly strong assumptions. Analysis by the ERG using a random effects model with a truncated Turner prior resulted in a HR of 1.26 (95% Credible interval: 0.46-3.3) which did not considerably impact on the conclusions of the ITC, with a HR greater than 1.0 and with wide credible intervals. The company's ITC still suggests, therefore, that nivolumab is not more effective than chemotherapy for the population considered.

3.5 Conclusions of the clinical effectiveness section

The ERG does not believe that there are any published studies relevant to the decision problem and that could have contributed data on clinical effectiveness, that have been omitted from the CS. The key evidence for clinical effectiveness and safety was informed by the ongoing Phase III CheckMate 274 trial of adjuvant nivolumab (n=353) versus placebo (n=356). The ERG agrees with the company's responses to the CRD quality assessment criteria, which indicate the trial is of good quality. However, the ERG notes the high proportions of patients discontinuing treatment and also notes the imbalance between arms in numbers discontinuing due to drug toxicity, which is greater with nivolumab.

CheckMate 274 is a multi-centre study with participants drawn from 30 countries. However, baseline characteristics of patients with MIUC in CheckMate 274 were considered to be demographically broadly representative of UK practice when compared with two English studies (Pang *et al.*[29], Jefferies *et al.*[30]). Participants in all three studies were predominantly male (all >75%), and older (median age in Pang 70 years, in Jefferies 69 years with the median age of CheckMate 274 participants slightly younger at 67 years).

The primary endpoint for CheckMate 274 was DFS. This endpoint was chosen over OS data as the latter require extended follow-up and can be confounded by subsequent treatments. At the time of the August 2020 DBL, there was a statistically significant advantage for nivolumab versus placebo (DFS HR = 0.70 [98.22% CI: 0.55, 0.90]). For subgroup of patients with tumour cell PD-L1 expression levels of ≥1%, those treated with nivolumab compared with placebo had a statistically significant and clinically relevant improvement in DFS (HR 0.55 [98.72% CI: 0.35, 0.85]). In contrast, there was a non-significant improvement (HR [redacted] for the patient subgroup with PD-L1 expression levels of <1%. OS data were unavailable in the CS as the number of deaths required to inform the interim analysis had not been met at the time of the DBL.

HRQoL data were collected using two patient reported outcome measures: EORTC QLQ-C30 and EQ-5D-3L, at baseline and during follow-up. Results showed no detriment to HRQoL for patients treated with nivolumab compared with placebo.

The CS reported similar proportions of patients with any grade AEs (nivolumab 98.9% and placebo 95.4%) and with Grade ≥3 AEs (nivolumab 42.7% and placebo 36.8%). Grade ≥3 TRAEs were more frequently observed in the nivolumab arm than the placebo arm (17.9% and 7.2%) respectively. A similar pattern of results was seen for treatment-related serious adverse events ([redacted] [26/351] and [redacted] [6/351]). These results suggest that the safety profile of nivolumab in patients with MIUC who have

undergone radical resection and who are at high-risk of recurrence can be considered acceptable and well-tolerated.

Based on the ITCs conducted by the company and the ERG, there was no strong evidence that nivolumab had superior efficacy to adjuvant chemotherapy although there were limitations within the ITCs.

4 COST EFFECTIVENESS

The company undertook an SLR to identify relevant cost-effectiveness studies from published literature and a pragmatic review to identify evidence from previous NICE technology appraisals.

4.1 Company's review of published cost-effectiveness studies

4.1.1 Company's search objective and methods

Appendix G of the CS reports a combined economic SLR including healthcare resource use (HCRU) and/or costs as well as HRQoL evidence. The literature searches are reported in Section 2 of Appendix G.

Searches for this SLR were conducted in two phases (February 2019 and updated in February 2021), and used the same population terms as the clinical SLR, with the addition of suitable filters to retrieve eligible study types. Filters used are based on those developed by the SIGN, Canadian Agency for Drugs and Technologies in Health (CADTH) and York Health Economic Consortium (YHEC). While the ERG maintains its concern that these filters were originally designed for single-database use, it accepts the company has made modifications which will ultimately increase the sensitivity, making it unlikely that relevant studies will have been missed.

MEDLINE, Embase and Econlit were searched via a multi-file search using the ProQuest interface. As mentioned in the critique of the clinical searches, the ERG does not have access to this platform and is therefore unable to replicate the company's searches exactly (since multi-file searches are treated differently by the platforms the ERG has access to). The company's approach offers some convenience in the deduplication of results, but at the expense of full reproducibility.

The company also searched the archives of the Health Technology Assessment database and the National Health Service (NHS) Economic Evaluation Database, via the CRD website; ISPOR proceedings (since 2016); and an appropriate selection of international HTA websites (listed in CS Appendix G section 2.1.1.2).

The ERG believes the company has made a reasonable attempt to identify all relevant evidence and it is unlikely to have missed any studies eligible for inclusion.

4.1.2 Eligibility criteria for the company's review of published economic evaluations

The inclusion and exclusion criteria used by the company are presented in CS Appendix G, Table 1. The ERG considers the inclusion criteria to be appropriate to capture recent and relevant evidence.

4.1.3 Findings of the cost effectiveness review

The results of the SLR were provided in CS Appendix G with the results from the pragmatic review of NICE appraisals presented in CS Appendix M. The SLR identified seven publications that reported economic models although one was related to this current STA where there was only a published scope[31], with three being conference abstracts only.[32-34] The remaining three papers explored the cost-effectiveness, or effectiveness in terms of QALYs, of radical cystectomy in patients with MIBC.[35-37] All three studies relate to a US setting. To supplement these papers, 10 NICE appraisals, covering the adjuvant setting for a selection of indications and different interventions were identified which were used to inform the model structure; these are discussed in detail in Appendix M of the CS.

4.1.4 Conclusions of the cost effectiveness review and the impact on the company's modelling approach

As no models were identified that fully addressed the decision problem the company built a *de novo* model. The approach taken was to use a state transition model which allowed dependency between events and health states, as detailed in Section 4.2 of this report. The ERG agrees that this approach is appropriate.

4.2 Description of company's health economic analysis

Following the clarification process, the company submitted an executable version of their economic model in Microsoft® Excel. After the clarification process, the company updated the model to include amendments of two errors the ERG identified in addition to extra scenario analysis. The updated model is discussed from Section 4.2.1 onwards.

4.2.1 Model overview

The model evaluates the use of nivolumab monotherapy for the treatment of adult patients with resected UC at high risk of recurrence, utilising evidence mainly from CheckMate 274.

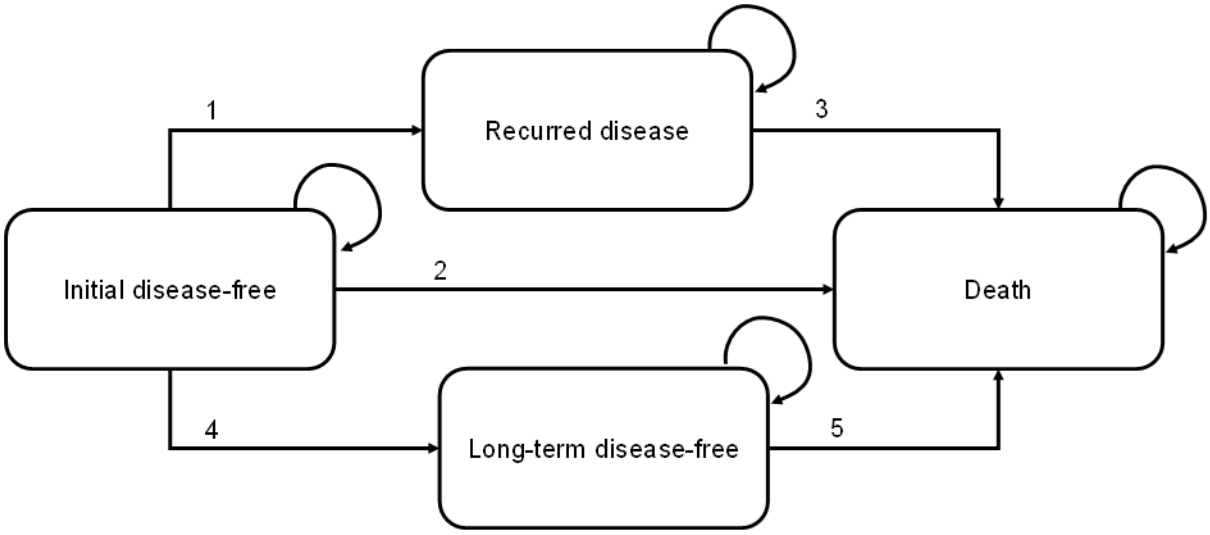
The base case model adopts an NHS and Personal Social Services (PSS) perspective. The base case model uses a 40-year time horizon with costs inflated to 2020 values using Personal Social Services Research Unit (PSSRU) inflation indices.[38] Both costs and QALYs were discounted at 3.5% per annum as recommended by NICE.[39]

The model uses weekly cycles without half cycle correction. The ERG does not consider this to be a significant limitation due to the short cycle length used.

4.2.2 Model structure and logic

The model schematic supplied by the company is reproduced in Figure 5.

Figure 5: Company's model structure (reproduced from Figure 26 of the CS)



The model includes four mutually exclusive and exhaustive health states: (i) initial DFS; (ii) long-term DFS (LT DFS); (iii) recurred disease (local or distant); and (iv) death. The company highlighted that based on clinicians' feedback, it was assumed in the company's base case that patients do not recur five years after surgery, and that they are no longer followed up or monitored with an assumed mortality rate similar to the general population. Clinical advice to the ERG concurred that there was a much lower risk of recurrence after 5 years, but that the risk was not zero.

All patients are assumed to enter the model in the initial DFS health state and remain there for five years unless they experience disease recurrence (transition 1 in Figure 5), in which case they move to the recurred disease state, or unless they die (transition 2 in Figure 5), in which case they move to the death state. After 5 years in the initial DFS health patients are assumed to be cured (that is, the cancer can no longer recur) and all patients are moved to the LT DFS health state (transition 4 in Figure 5). In the LT DFS state, the mortality risk was assumed to be the same as an age- and sex-matched general population mortality (transition 5 in Figure 5).

The probability of patients moving from the initial DFS health state is described in Section 4.2.3.2.1. DFS events were defined as recurrences or deaths with the split defined as described in Section 4.2.3.2.2. The Transition probability from the recurred disease health state to death (transition 3 in Figure 5) were informed by published literature, as described in Section 4.2.3.2.4. The model assumes

an exact surrogate relationship between DFS and OS up to the cure point where nivolumab benefit is only shown in the first five years where a DFS event is delayed or stopped if the cure point is reached.

Key structural assumptions employed within the company's model

The company's model employs the following structural assumptions:

- All patients enter the model in the initial DFS state following radical cystectomy.
- Following model entry, patients stay in the initial DFS until having a DFS event. After five years in the company's base case, remaining patients in the DFS state are assumed to be cured and would transition to the LT DFS until death.
- The health gains associated with nivolumab are assumed to result from delaying DFS events to the cure point, after which no additional benefit is assumed for nivolumab.
- The probability of a DFS event being death was assumed the same for both arms.
- Health utility is determined by the presence/absence of disease recurrence and was assumed the same regardless of the intervention used in the adjuvant setting. Due to trial-informed utilities being higher than the sex and age matched general population and in the absence of alternative values from the literature, health utility values for the DFS states were based on utility values of the age-adjusted general population. A decrement derived from the CheckMate 247 trial was applied for patients with recurrence.
- Patients on nivolumab are assumed not to require additional resource use compared to BSC.
- LT DFS mortality is assumed to reflect age- and sex-matched general population life tables.
- Following recurrence, patients are assumed to remain there until death. The mortality rate is assumed to follow an exponential distribution estimated from published literature (see Section 4.2.3.2.4).
- Following recurrence, patients are assumed to receive subsequent chemotherapy until death.
- The health gains associated with treatment are assumed to be reduced by the incidence of AEs; treatment-specific QALY losses for AEs are applied in the first model cycle only.

4.2.3 Evidence used to inform the company's model parameters

Table 29 summarises the evidence sources used to inform the parameters of the company's model. The derivation of the model parameter values using these sources is described in further detail in the following sections.

Table 29: Summary of evidence sources used to inform the model parameters

Parameter type	Parameter	Source(s)
Patient characteristics	Age	CheckMate 274[19]
	Percent male	
Transition probabilities	DFS events (recurrence/death) in the first 5 years	Models fitted to CheckMate 274 DFS data[1]
	Recurrence after 5 years	Expert opinion (assumption of a cure point)[1]
	Death for patients at the DFS health state after 5 years	Age- and sex-adjusted general population UK life tables[40]
	Death for patients at the recurred health state	Derived from Bellmunt *et al.*[41] and De Santis *et al.*[42]
AE frequency	Incidence of AEs due to adjuvant treatment	CheckMate 274[19]
Health-related quality of life	Utility – DFS health state	age- and sex-matched general population (Janssen *et al.*[43])
	Disutility due to recurrence	CheckMate 274[19]
Resource use	Dosing regimen for nivolumab	Nivolumab SmPC[12]
	Dosing intensity for nivolumab	CheckMate 274[19]
	Follow up resource use	Expert opinion[1]
Unit costs	Drug acquisition - nivolumab	British National Formulary 2021[44]
	Drug acquisition – post-recurrence	eMIT[45]
	Drug administration	NHS national tariff 2020/2021[46]
	Follow up	NHS national tariff 2020/2021[46], National cost collection for the NHS 2018/2019[47], PSSRU 2019/2020[38]
	Management of AEs	Copley Merriman *et al.*[48]
	End of life costs	Georghiou *et al.*[49]

AE – adverse event; DFS - disease-free survival; SmPC - summary of product's characteristics; eMIT - electronic market information tool; PSSRU - Personal Social Services Research Unit

4.2.3.1 Initial patient characteristics at model entry

The modelled population was assumed to be [redacted] years old at model entry and [redacted] of patients were male, in line with the baseline characteristics of patients in CheckMate 274. The ERG notes that Pang

et al. reported outcomes from 1110 consecutive radical cystectomies in the UK for time period 2008-2016;[29] this study reported a median age of 70 years and 80.2% of patients were male. In response to clarification question B9, the company claimed that the population in Pang *et al.* does not correlate with the population for this appraisal, and that efficacy is based on the trial population. The ERG received clinical advice that a more elderly population could be expected in the UK, and that it can vary by geographical location.[29, 30] Audit data from the British Association of urological surgeons show that in 2019, the median age of patients undergoing radical cystectomies was 69-70 years old.[50]

4.2.3.2 Time-to-event parameters

4.2.3.2.1 Disease-free survival events

DFS KM estimate from CheckMate 274 was used to inform transition probabilities from the initial DFS state to either recurred disease or death. Overall event hazard for DFS was estimated across time with event split between either recurrence or death being informed as explained in Section 4.2.3.2.2. The primary definition of a DFS event as per the trial endpoint assessment was the occurrence of either a recurrence of any type or a death event. Patients who began a subsequent therapy or developed a secondary primary cancer were censored. The observed KM survivor functions for CheckMate 274 are shown in Figure 3.

In assessing the underlying hazard pattern for DFS, the company noted two issues; first, there is a mode correlating with the time of first tumour assessment, second, there is a higher initial hazard for placebo that tends to plateau after a shorter time period compared to nivolumab. The company claims that this may be an indication that nivolumab delays some of the recurrences that would otherwise have happened at an earlier stage. The ERG notes that the observed hazard of DFS is not monotonic in either arm but is protocol-driven as shown later in Figure 13 and

Figure 14. This means that interval censoring (i.e. events occurring between two consecutive follow-up assessment visits not being recorded until the subsequent visit) was responsible for the shape of the underlying hazard pattern. The true pattern of the hazard remains uncertain and a monotonic hazard may be more plausible than a unimodal hazard.

The company explored the fit of different statistical survival models to the KM estimate. Initially, the assumption of proportional hazards was assessed and, as it was rejected, separate models were fitted for the intervention arm and the control arm. Six parametric models (exponential, Weibull, Gompertz, log

logistic, lognormal, and generalised gamma) were explored. Five of the models were rejected based on the visual inspection of the curve fit, with the company stating that the fits overestimate DFS in the early part of the data and underestimate it in the latter part, for both nivolumab and placebo. This is described within Appendix K of the CS. The remaining model, the Gompertz distribution, was rejected based on implausible long-term extrapolation as it failed to converge to a mean survival time, although it is noted that as the economic model assumes a cure beyond 5 years that long-term extrapolations of the parametric model are not used. In response to clarification question B2, the company reiterated that simple parametric models provide a poor fit to the KM estimate and that the Gompertz model does not plateau similarly for nivolumab as it does for placebo. The fitted parametric models are compared to the KM plots in Figure 6 (nivolumab) and
Figure 7 (placebo).

The company considered mixed parametric models *"on the assumption that there may be separate non-homogenous population distributions (representing higher- and lower-risk individuals) underlying the overall DFS hazard"*. These models estimate a separate hazard function for each of two subgroups together with a probability which describes the proportion of patients that each subgroup contains. The company stated that several of these models had a good fit to the data with the best fitting in each arm being the Weibull model for a lower risk group and the log-normal model for a higher risk group. The ERG's understanding is that this model estimated the proportions of patients in the high-risk group to be [redacted] in the nivolumab arm and [redacted] in the placebo arm (CS Appendix K Figure 9, rho: [redacted]; Figure 10, rho: [redacted]). It is not clear to the ERG whether the risk status of an individual relates to treatment received or to underlying characteristics and therefore it is not clear if these proportions are valid or meaningful.

The company also fitted Royston-Parmar restricted cubic spline models to the intervention and control DFS KM estimates altering the number and position of knots. However, this approach was rejected for the nivolumab fits based on *"uncertainty over placement of knots"* concluding that *"the nivolumab data may be too immature to allow robust extrapolation using Royston-Palmer spline models"*.

Finally, semi-parametric models were explored. The company has used this term to denote a distribution using the KM for an initial time period up to a specified cut point, after which a standard parametric model is fitted to the individuals who are still in the DF state at the cut point. The ERG has maintained this description for consistency. The company deemed this approach the most appropriate to allow for *"the complex hazard profiles underlying DFS – chiefly the steepness of the increase at 3 months – [which] were predominantly a protocol-induced feature due to the timing of tumour assessments"*. The company considered a range of cut points they deemed to be plausible based on features of the observed

hazard (18 cut points for nivolumab, 17 cut points for placebo) and five parametric models which are not specified but can be deduced to include the exponential, Weibull and lognormal as these are presented among the models deemed to fit the data well.

Overall, 90 models were fitted for nivolumab and 85 for placebo. These were reduced by rejecting models that (i) did not converge to give a finite mean DFS time; (ii) had a parametric portion fitted to fewer than 5 events; (iii) did not have decreasing hazards over time. After this process there remained 30 nivolumab and 26 placebo models which were assessed by visual inspection for correspondence to the observed cumulative hazards from the trial data. Based on these criteria, the company selected a KM and Weibull curve with a cut-off point of [redacted] months for nivolumab, and a KM and Weibull curve with a cut-off point of [redacted] months for placebo. The company's clarification response to question B18 did not provide any clinical rationale for these cut points being markedly different between the two arms.[13] The company's preferred semi-parametric models are compared to the KM plots in Figure 8.

The company (CS Appendix K) stated that *"Clinicians were initially invited to describe their general expectations of how risk would develop over time in the target population. Candidate extrapolations were then refined to meet these expectations and presented to clinicians to garner feedback on the plausibility of specific curves."*. These initial expectations included that *"patients who reach 5 years following surgery without recurrence would be discharged and no longer monitored as recurrence beyond this point is uncommon"*. Any other *a priori* expectations were not made transparent anywhere in the CS, and it is unclear how they were used to refine "candidate extrapolations" as this was not mentioned otherwise at any point in the model selection procedure as described above. The company stated also that at a later point *"clinicians suggested that plausible 5 year DFS was 35% for nivolumab and 26% for placebo and that further to this, limits of strictly less than 35% at 10 years, ideally early 30%"*. In the company's clarification response to question B13, it was made clear that the values of 35% and 26% were survival probabilities predicted by the selected semi-parametric models rather than values elicited from clinicians prior to them seeing these candidate models.[13] It is not clear how many other models were presented to the clinicians.

With this *a posteriori* clinical validation of the selected semi-parametric models (KM and Weibull with a [redacted] month cut point for nivolumab and KM and Weibull with a [redacted] month cut point for placebo), these were chosen for the company's base case. The hazards from these models were applied up to 5 years. After 5 years, the clinical expectation of functional cure was assumed by applying a general population hazard based on UK life tables after matching for age and sex to the CheckMate 274 patient characteristics.

Figure 6: **Investigator-assessed DFS for nivolumab: Standard parametric survival models overlaid upon Kaplan-Meier (short-term fit [A] and long-term projections [B]). 95% confidence intervals obtained by data bootstrap (1,000 repetitions). (reproduced from Figure 7 in the CS Appendix K)**

Figure 7: **Investigator-assessed DFS for routine surveillance: Standard parametric survival models overlaid upon Kaplan-Meier (short-term fit [A] and long-term projections [B]). 95% confidence intervals obtained by data bootstrap (1,000 repetitions). (reproduced from Figure 8 in the CS Appendix K)**

Figure 8: **Investigator-assessed DFS KM estimates for both arms and the company's preferred semi-parametric models with 5-year remission to background mortality hazard from 60 months (reproduced from Figure 17 in the CS Appendix K)**

4.2.3.2.2 Time to death from the initial DFS state

As illustrated in Figure 5 during the first five years of being at risk of recurrence, patients could experience a DFS event. DFS events comprised recurrence and 'death from any cause' events. Detailed OS data were lacking because *"the number of deaths required to inform the first OS interim analysis, approximately 230 deaths, was not reached at the time of the August 2020 Database lock."* Hence, the company could not fit parametric models and instead applied a fixed probability of [redacted] that a recurrence event is a death for both arms. This was estimated via a logistic regression on death events from DFS data in CheckMate 274. The ERG highlights that whilst patients are in the initial DFS state mortality can only occur following a DFS event.

In clarification questions A8 and B5, the ERG asked about the DFS events that were deaths in each arm. Out of [redacted] DFS events in nivolumab arm, [redacted] were deaths ([redacted]), and out of [redacted] events in the placebo arm, [redacted] deaths were observed ([redacted]). The ERG notes that in a previous appraisal of nivolumab in adjuvant treating of oesophageal or gastro-oesophageal junction cancer [ID1676], different death rates were applied between treatment arms rather than pooling one death rate for both arms.

4.2.3.2.3 Time to death after five years within the DFS health state

The model assumes that patients who remain alive and disease-free at five years have the same mortality risk as an average age- and sex-matched cohort using 2017-19 values from the UK. The ERG notes that English life tables were not used but deems that this is highly unlikely to have a substantial impact on the ICER.

In response to clarification question B6, the company declined to use standardised mortality rates to account for a sicker population, stating that the trends of the hazard plots show that the population not experiencing recurrence reaches the life table mortality risk by five years. This is discussed further in Section 4.3.3

4.2.3.2.4 Time to death from the recurred disease state

In the absence of detailed OS data from CheckMate 274 trial, the company used an alternative source to estimate the transition probabilities from the recurred health state to death. The company chose two sources; Bellmunt *et al.* and De Santis *et al.*[41, 51] The company selected these two sources based on the assumption that following recurrence, patients will receive either cisplatin+gemcitabine or carboplatin+gemcitabine.

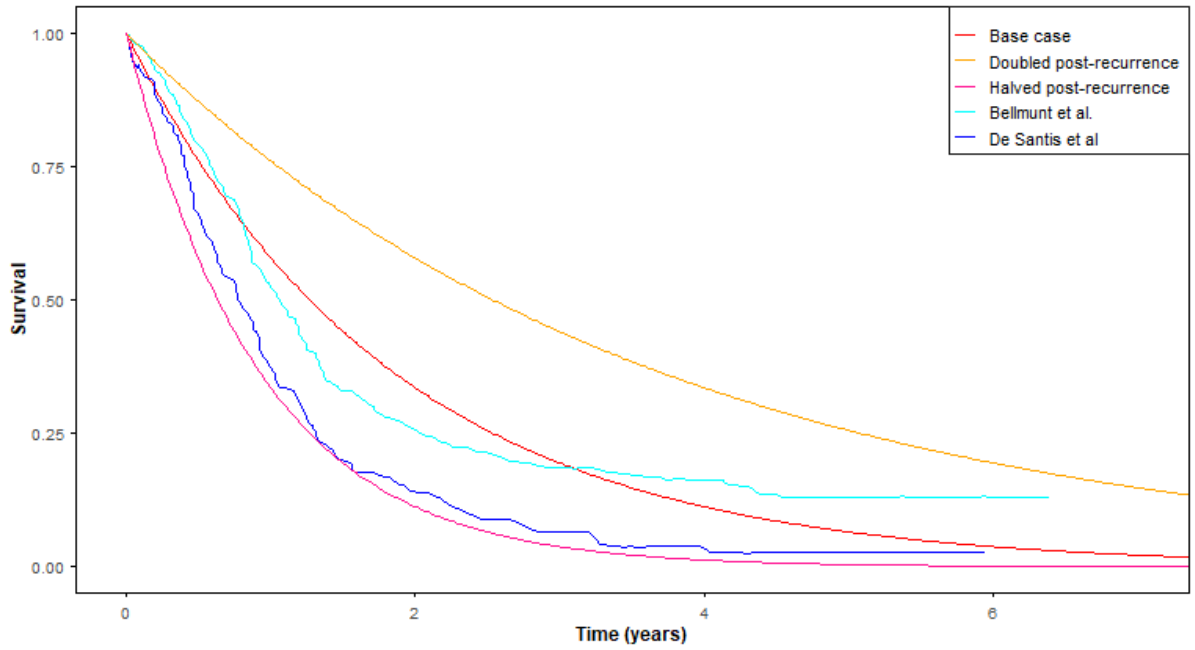
Bellmunt *et al.* is an RCT comparing paclitaxel+cisplatin+gemcitabine with cisplatin+gemcitabine in patients with locally advanced or metastatic UC and reported a median OS of 12.7 months for the

cisplatin+gemcitabine arm. De Santis *et al.* is an RCT comparing two carboplatin-based regimens and reported a median OS of 9.3 months for the carboplatin+gemcitabine arm. The company assumed a 50:50 split and took the midpoint of these two median values based on the assumption that 50% of patients are eligible to receive cisplatin and the other 50% are ineligible thus receive either carboplatin-based therapy or immunotherapy (which were in the Cancer Drugs Fund (CDF) at the time of company submission).

The midpoint median value of 11 months was then used to fit an exponential curve and estimate a fixed rate of death across time following recurrence. As

Figure 9 shows, the fitted curve overestimates survival in the three years and then underestimates thereafter, suggesting that the approach taken by the company was not optimal. In response to clarification question B12, the company acknowledge the limitation of the current fit, but argued that it will add more complexity to the model with little value in return based on that the ICER changes by £2,800/QALY gained between the two scenarios where the survival probability was either halved or doubled.

Figure 9: The estimated probability of post-recurrence survival (reproduced from Figure 32 of the CS)



4.2.3.2.5 Time on nivolumab and post-recurrence treatments

Time on nivolumab treatment is modelled directly from the time to treatment discontinuation data observed in the CheckMate 274 trial. The company applied the one-year stopping rule in the model (i.e. patients were not allowed to receive nivolumab beyond a year) in line with the trial treatment protocol and nivolumab SmPC, and introduced a relative dose intensity (RDI) of [redacted] to account for both dose delays and reduced doses. Time on nivolumab data are presented in Table 36 of the CS.

Subsequent treatments received following disease recurrence (cisplatin+gemcitabine and carboplatin+gemcitabine) were assumed to be given continuously until death. Clinical advice to the ERG indicated that patients are likely to experience tolerability problems and have breaks from chemotherapy. One expert assumed that on average for a patient with post-recurrence survival of 18 months, they may receive eight months of therapy. In their response to clarification question B20, the company acknowledge that this is a simplifying assumption.

4.2.3.3 Health-related quality of life

CheckMate 274 trial collected EQ-5D-3L data as described at Section B.2.6.4 of the CS. While on treatment, these were collected every eight weeks for the first 49 weeks and then every 12 weeks. Following discontinuation of treatment, follow-up assessments were undertaken at days 35 and 115 from discontinuation. Missing data were treated as missing completely at random (MCAR); hence, the company analysed only the completed questionnaires. The company stated that there was no difference

in results between both treatment arms and assumed that the underlying utility was dependent on health state, but not on whether nivolumab treatment was provided. In response to clarification questions A9 and A12, it was not clear whether the company was stating that the data was missing at random. In response to question A9, the company stated that *"There was insufficient evidence to reject the assumption of MCAR, with no need to use imputation for sensitivity analyses, as the complete data is already a good representation of the full data set"*. However, responding to clarification question A12, the company states that they did not base its analysis simply on means and CIs for utility scores at each timepoint because this approach *"relies on the assumption that the missing observations are MCAR"*. A mixed model for repeated measures was implemented which the company states is a more robust method to account for missing data, and that the results of this model '*seemed to be consistent with the simple analysis of observed means*'. However full details of the mixed model for repeated measures were not presented, and thus it was not clear to the ERG how the results presented in CS Figure 10 are derived from this model.

The company assumed that the utility values for patients who are disease-free would not be greater than an age- and sex-matched population and capped utilities to the values reported in Janssen *et al.*[43] As a result, the utility values from Janssen *et al.* were used for the disease-free state as shown in Table 30. The utility data estimated from CheckMate 274 were only used to calculate the difference between the disease-free and recurred disease health states, which was [redacted]; this decrement was applied to patients in the recurred disease health state as shown in Table 30.

The ERG questioned why patients at the DFS state with history of UC should be assumed to have the same utility value as the general population. In response to clarification question B5, the company stated that they consider these patients cured and therefore could have the same utility as general population. The company also stated that '*General population measures, such as utility, are estimates of all individuals, rather than solely referring to "healthy" individuals. Therefore, the use of general population utility does not indicate that patients are without comorbidity, only that it is within the limits of that experienced by others of the same age.*'

Table 30: Health state utility values from CheckMate 274 versus those used in the company's base case analysis

Health state	Utility values from CheckMate 274	Utility values used in the model
Disease-free (both arms)	[redacted]	[redacted]*
Post-recurrence (both arms)	[redacted]	[redacted]*
Recurrence related disutility	[redacted]	[redacted]

* Age- and sex-dependent value is presented for a cohort of patients aged [redacted] years with [redacted]% male.

The ERG noted that utility values from Janssen *et al.* (Table 42 of the CS) remained constant across wide age ranges, for example, it reported the same utility value for people aged between 75 and 100 years. The ERG asked clarification question B19 on why utility values from Ara and Brazier[52] were not deemed preferable. The company provided results using the utility values reported in Ara *et al.*, but did not consider this in the base case as Janssen's values are more recent. However, the ERG notes that though Janssen *et al.* was published in 2014, it sourced the English utility dataset from older references, namely the Health Survey of England 2008[53] and Kind *et al.*[54]

The company included disutility associated with AEs as per CheckMate 274 trial. The included AEs were treatment-related with incidence greater than 5%, with only Grade 3 or worse AEs considered in the model. Patients on nivolumab experienced more AEs as shown in Table 22 of the CS. Table 40 of the CS presents a summary of the disutility values used per adverse event. The company estimated the QALY loss due to AEs and, for simplicity, applied it in the first model cycle. This resulted in a QALY loss of [redacted] for nivolumab-treated patients versus [redacted] for placebo-treated patients.

4.2.3.4 Resource use and costs

The following sections detail the drug acquisition costs (including the PAS discount for nivolumab), post-recurrence treatment costs, drug administration costs, disease management costs, costs associated with managing adverse events, and end of life costs used within the model.

4.2.3.4.1 Drug acquisition costs

The recommended dosage of nivolumab in the adjuvant setting is 240mg administered as one intravenous (IV) infusion every two weeks for a maximum duration of one year. This is provided as a 24mL vial with a 10 mg/mL concentration with a list price of £2,633.00. The company has proposed a PAS which takes the form of a simple price discount of [redacted]; this results in a maximum drug acquisition cost of [redacted] for patients who receive nivolumab for the one-year period, when the RDI stated in Section 4.2.3.2.5 is accounted for. No treatment costs were applied to the comparator arm as this involves only routine surveillance.

4.2.3.4.2 Post-recurrence treatment costs

The model includes the costs of subsequent treatments following recurrence. The assumed costs, which are shown in Table 46 of the CS, were independent of whether a patient received nivolumab treatment. As mentioned in Section 4.2.3.2.4 it was assumed that post-recurrence, half the patients would get cisplatin+gemcitabine with the remainder receiving carboplatin+gemcitabine until death. This amounted to an average weekly cost of £19.62 per patient.

4.2.3.4.3 Drug administration costs

Administration costs for nivolumab were taken from NHS national tariff 2020/21 HRG code SB12Z, which reports delivering simple parenteral chemotherapy at first attendance.[46] The cost used in the model was £159.00 per nivolumab administration (every two weeks). Post-recurrence treatments were assumed to be given as IV infusions following a regimen as shown in Table 46 of the CS; the model applies the same administration cost as that for nivolumab. BSC was assumed not to be associated with administration costs.

4.2.3.4.4 Disease management costs

The resource use, unit costs and weekly cost for both the disease-free and post-recurrence health states are detailed in Table 31. The summarised weekly costs used in the model are presented in Table 32. The ERG notes that nivolumab was assumed not to require additional resource use compared to BSC. The ERG is uncertain whether this is true but deems that this is highly unlikely to have a substantial impact on the ICER.

The ERG notes that the model does not track patients post-recurrence in order to apply the appropriate health state cost (i.e. the costs post-recurrence for patients were not explicitly linked to the time since recurrence). Instead, different weights were assumed, with the company assuming that in a given cycle 54.54% of patients who had recurrence have the costs associated with the first year after recurrence and 45.45% have costs associated with more than one year after recurrence. In response to clarification question B34[16], the company states that this split is based on *"the proportion of patients who die within the first year post-recurrence, and the rate of surviving beyond the first year"* acknowledging the approach as a simplifying assumption. Unit costs for resource use were estimated from NHS national tariff[46] and PSSRU 2019/2020 costs.[38]

Table 31: Type of resources, frequencies and unit costs for disease management costs used in the model for both nivolumab and BSC

Resource	Weekly frequency of resource use	Unit cost	Weekly total
Disease-free state			
Oncologist consultation	0.0383*	£208.75	£8.00
Cystoscopy (in upper tract patients only; 21.2% of the modelled cohort)	0.0766**	£240.00	£3.89
Scans (CT/MRI)	0.0383*	£86.25	£3.31
Glomerular filtration rate	0.0383*	£2.79	£0.11
Hepatic and renal function tests	0.0192***	£1.10	£0.02
Post-recurrence state			
Community nurse specialist visit	0.9199	£49.25	£45.31
Oncologist consultation	0.0766†	£208.75	£16.00
GP home consultation	0.23	£67.63	£15.55
Dietician	0.23	£43.43	£9.99
Health home visitor	0.23	£39.23	£9.02
CT scan	0.0766†	£86.25	£6.62
Cystoscopy (in upper tract patients only; 21.2% of the modelled cohort)	0.0766†	£240.00	£3.90
Glomerular filtration rate	0.0766†	£2.79	£0.22
Hepatic and renal function tests	0.0766†	£1.10	£0.08

CT: Computerised tomography; MRI: Magnetic resonance imaging.

* For the initial 2 years only. Resource use halves at the start of the third year until the end of the fifth year, when resource use is assumed to terminate.

** For the initial year only. Resource use drops by 25% for the second year and then by a further 33% until the end of the fifth year, when resource use is assumed to terminate.

*** Until the end of the fifth year, when resource use is assumed to terminate.

† For the initial year only. Resource use halves at the start of the second year until death.

Table 32: Weekly health state costs used in the model independent of initial treatment

Health State	Mean weekly health state cost
Disease-free state	
First year	£15.33
Year 1 to 2	£14.36
Years 2 to 5	£7.68
Subsequent years	£0.00
Post-recurrence	
First year	£285.30
Subsequent years	£271.90

4.2.3.4.5 Costs associated with the management of adverse events

The definition and the incidence of the included AEs are described in Section 4.2.3.3. Table 51 of the CS presents the mean costs used for managing an AE episode. For simplicity, the estimated costs were applied in the first model cycle. These were estimated to be [redacted] for nivolumab-treated patients and [redacted] for placebo- treated patients.

4.2.3.4.6 End of life costs

End of life costs were sourced from Georghiou *et al.*, a UK study estimating hospital and non-hospital costs for people in the last 90 days of life in 2014.[49] The cost was inflated using PSSRU indices[38] and resulted in a cost of £7,970.55 that was applied to the incident number of new deaths in a given cycle.

4.2.4 Model evaluation methods

The CS presents the results of the base case analyses in terms of ICERs (cost per QALY gained) for nivolumab versus BSC. Both deterministic and 1,000 samples of probabilistic estimates are presented.

The distributions used for the probabilistic sensitivity analyses (PSA) undertaken by the company are presented in Table 53 of the CS and in more detail in response to clarification question B26, although the parameter values, for example the alpha and beta values of a beta distribution, have not been provided explicitly as they are calculated via the model macros. The results of the PSA are additionally presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs).

The company also presented a range of one-way deterministic sensitivity and scenario analyses to explore the uncertainty in parameters and structural assumptions.

4.2.5 Company's model validation and verification

The CS reports that the assumptions and parameter values used in the model were validated by clinical experts, and that a technical review of the cost-effectiveness model was conducted by an independent economist. The company stated that '*median DFS predicted from the model aligns with that of CheckMate 274*.' Comparison of model outcomes with previously published literature (previous STAs) is provided in Table 70 of the CS. This shows that healthier patients with newly diagnosed MIBC or who are not at high risk of recurrence accrue more QALYs and life years.

4.2.6 Company's cost-effectiveness results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model (named *'consolidated model'*) submitted in response to the clarification process. The results also take into consideration the corrected programming error as detailed in Section 4.3.1. This only affected the deterministic sensitivity analyses (DSA) and scenario analyses results where utility values were varied.

Central estimates of cost-effectiveness

The central estimates of cost-effectiveness generated using the company's model for the comparison of nivolumab compared with BSC are presented in

Table 33. The probabilistic version of the model suggests that nivolumab therapy is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £32,932 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £32,813 per QALY gained (an additional cost of [redacted] and an additional [redacted] QALYs). The model appears relatively linear based on the similarity of the deterministic and probabilistic estimates.

The company presents disaggregated outcomes, costs incurred, QALYs accrued and life years accrued by different elements or states in the deterministic model, these results are presented in Table 34. The additional costs are primarily associated with the acquisition cost of nivolumab whilst the most of the additional QALY gain is a consequence of the longer time spent alive in the disease-free health state.

Table 33: Company's results - base case analysis, nivolumab versus BSC

Description	Total life years accrued	QALY accrued	Total costs incurred	Incremental			ICER
				Life years	QALYs	Cost	
Probabilistic model (run by the ERG)							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,932
Deterministic model							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,813

BSC - best supportive care; QALYs - Quality-adjusted life years; ICER - Incremental cost-effectiveness ratio

Table 34: Base case disaggregated outcomes

Description	Nivolumab	BSC	Incremental
Disaggregated costs (discounted)			
Disease-free health state (initial)	[redacted]	[redacted]	[redacted]
Disease-free health state (long term)	[redacted]	[redacted]	[redacted]
Recurred health state	[redacted]	[redacted]	[redacted]
Death state	[redacted]	[redacted]	[redacted]
Treatment (nivolumab)	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)			
Disease-free health state (initial)	[redacted]	[redacted]	[redacted]
Disease-free health state (long term)	[redacted]	[redacted]	[redacted]
Recurred health state	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Clinical outcomes (undiscounted, years)			
Median disease-free survival	[redacted]	[redacted]	[redacted]
Mean disease-fee survival	[redacted]	[redacted]	[redacted]
Median overall survival	[redacted]	[redacted]	[redacted]
Mean overall survival	[redacted]	[redacted]	[redacted]
Time in health state (undiscounted, years)			
Disease-free health state (initial)	[redacted]	[redacted]	[redacted]
Disease-free health state (long term)	[redacted]	[redacted]	[redacted]
Recurred health state	[redacted]	[redacted]	[redacted]

BSC - best supportive care; QALYs - quality-adjusted life years

Health state occupancy over time is shown in

Figure 10 for both arms. For a given arm, area under the DFS curve represents patients who are disease-free whereas area under the OS curve shows surviving patients, with the area in between representing patients with a recurrence.

Figure 10: Health state occupancy for nivolumab and BSC (extracted from the company's economic model)

4.2.8 Company's PSA

As shown in

Table 33, the company's probabilistic estimate of the ICER was £32,932 per QALY gained. The company also presented scatterplots and CEACs for nivolumab compared with BSC in its clarification response. The company's base case model estimates that the probability that nivolumab generates more net benefit than BSC at a willingness-to-pay (WTP) threshold of £20,000 per QALY gained is [redacted]. Assuming a WTP threshold of £30,000 per QALY gained, the probability that nivolumab generates more net benefit than BSC is [redacted].

Figure 11 presents the company's base case CEAC for nivolumab versus BSC.

Figure 11: Company's base case CEAC. Nivolumab versus best supportive care (run by the ERG)

4.2.9 Company's DSA

DSAs are presented for nivolumab compared with BSC using tornado plots. Most of these analyses are performed by assuming that the limit was set as a 20% change in the central estimate, thus using 80% of the parameter value as a lower bound and 120% of a parameter value as an upper bound. The exceptions were: the annual discount rates for costs and benefits where the lower bound of zero and an upper bound of 6% were assumed; the percentage of the patient cohort which are assumed to be male where a lower bound of 0% and an upper bound of 100% were assumed; and the model time horizon where a lower bound of 30 years and an upper bound of 50 years were assumed.

Following the clarification process, the ERG re-ran the DSA; results are presented in Figure 12. Only analyses that markedly impact on the ICER are included in this tornado plot. Three sensitivity analyses performed by the company resulted in deterministic ICERs which are below £30,000 per QALY gained: (i) assuming that patients were 52.5 years of age at the time of starting nivolumab treatment; (ii) applying a discount rate of 0% to QALYs; (iii) increasing general population utility values by 20%. No sensitivity analysis resulted in a deterministic ICER below £20,000 per QALY gained.

Figure 12: Tornado diagram showing the company's DSA (run by the ERG)

4.2.10 Company's scenarios analyses

The company performed multiple scenario analyses, with those deemed most relevant by the ERG detailed here. Further analyses are presented in the CS[1] and in the company's response to clarification questions.[13] Where pertinent analyses were not provided by the company following the updating of the model, these were run by the ERG. The company scenarios detailed in the ERG report are: increasing the period before the patient is considered cured; assuming no cure; using utility data from Ara and Brazier[52] rather than Janssen *et al*.[43]; using alternative semi-parametric models with different shapes and cut-off points; and varying the risk of death post-recurrence. The results of these analyses are presented in Table 35. Two of these analyses resulted in ICERs which are less than £30,000 per QALY gained: when a cure point was removed, and when the cure point was assumed to be 10 years after radical surgery. Neither analysis produced an ICER below £20,000 per QALY.

The ERG notes that the ICER reduction associated with delaying the cure point is a result of the Weibull extrapolations used by the company's semi-parametric modelling approach. This approach assumes a favourable benefit for nivolumab compared to BSC at the end of the 5-year period as shown in Figure

15, and extending this benefit would increase the incremental QALYs gained for nivolumab and eventually decrease the ICER.

Table 35: The company's scenario analyses

No.	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	£32,813
1	Removal of the long-term remission state	[redacted]	[redacted]	£26,677
2	Long-term disease free starting after 3 years*	[redacted]	[redacted]	£37,246
3	Long-term disease free starting after 6 years**	[redacted]	[redacted]	£31,489
4	Long-term disease free starting after 10 years*	[redacted]	[redacted]	£28,708
5	Alternative survival model for DFS (KM+exponential with a cut-off of 25.76 and 17.71 months for nivolumab and placebo respectively)†	[redacted]	[redacted]	£34,801
6	Alternative survival model for DFS (KM+Lognormal with a cut-off of 13.8 and 4.6 months for nivolumab and placebo respectively)†	[redacted]	[redacted]	£36,817
7	Alternative survival model for DFS (KM+Weibull with a cut-off of 20.7 and 5.52 months for nivolumab and placebo respectively)†	[redacted]	[redacted]	£30,633
8	Doubling the probability of death following recurrence	[redacted]	[redacted]	£32,085
9	Halving the probability of death following recurrence	[redacted]	[redacted]	£34,383
10	Using a Gompertz distribution for DFS (for both arms)	[redacted]	[redacted]	£74,315
11	Removing the 1-year stopping rule for nivolumab treatment	[redacted]	[redacted]	£33,065
12	General population utility based on Ara and Brazier❖	[redacted]	[redacted]	£33,144

* These scenarios were re-run by the ERG as they were not updated by the company following the clarification process

** Results differ from those reported in the company's addendum to clarification response as the company unintentionally assume that resource use in the disease-free health state stops after 5 years.

† The base case model assumed KM+Weibull with a cut-off of [redacted] and [redacted] months for nivolumab and placebo respectively

❖ Results are different due to the correction of the QALY calculation programming error (as described in Section 4.3.1).

4.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS.
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.1 Model verification

The ERG believes the company's updated version of the model to be generally well programmed and free from major errors, and that the model structure and parameter values used are appropriate for the decision problem. Uncertainty was likely overestimated as some PSA iterations produced less QALYs for nivolumab treatment, but the ERG does not believe this affects the model's ability to inform decision making.

The ERG identified a programming error in calculating the QALYs for patients in the nivolumab arm where a patient's utility was always set to general population utility value. This meant that in scenario analyses where the DFS-specific utility value was intended to be lower than general population values, the latter were still being used in QALY calculations.

4.3.2 Adherence of the company's model to the NICE Reference Case

The company's economic analysis of nivolumab treatment in MIUC at high risk of recurrence is generally in line with the NICE Reference Case. The ERG's summary of the adherence of the company's model to the NICE Reference Case is provided in Table 36. For reference, the adherence of the CS to the decision problem is summarised in Table 36.

Table 36: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments (a ✔ denotes the company's analyses are in line with the reference case)
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	✔
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✔
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	✔
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	✔
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	✔
Perspective on costs	NHS and PSS	✔
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✔
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✔
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	✔

4.3.3 Main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses.

Box 1: Main issues identified within the critical appraisal undertaken by the ERG

(1) Exclusion of cisplatin-based adjuvant chemotherapy as a comparator

(2) Preference of use of semi-parametric models to fit to DFS KM estimates

(3) Use of the utility data from Janssen *et al*.

(4) The average age of patients in the UK is likely to be older than those recruited to CheckMate 274

(5) Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo

(6) Patients in the DFS health state have the same utility values as general population

(7) Patients in the long-term DFS health state have the same life expectancy as general population

(8) Uncertainty surrounding the assumed cure point

(9) The lack of subgroup analysis in the company submission

1. Exclusion of cisplatin-based adjuvant chemotherapy as a comparator

As mentioned in Section 2.3.3, the company decided to exclude cisplatin-based regimens for two primary reasons: (i) that there are only a small number of patients who are willing to take cisplatin and are eligible to receive it in the adjuvant setting, and (ii) the ITC analysis performed by the company had '*important limitations*' and the results were subject to '*considerable uncertainty*'.

While the ERG concurs that there will be uncertainty in the results of the ITC, it does not believe the first reason is sufficient to exclude cisplatin-based adjuvant chemotherapy from the decision problem; data from John *et al*.[55] indicate that only 37% of patients in the UK with MIBC receive neoadjuvant chemotherapy with the remainder potentially eligible for adjuvant chemotherapy. Clinical advice received by the ERG is that patients do receive adjuvant chemotherapy. In clarification question B3, the ERG asked for additional analyses stating that '*it is anticipated that the NICE Appraisal Committee may still wish to see exploratory ICERs*'. However, the company did not provide these and instead reiterated that '*cisplatin, is not relevant to the decision problem, and the available data do not facilitate robust indirect comparisons.*' As such, the company's economic analysis only partially addresses the decision problem and that they have only presented economic evidence for people who would not be eligible for adjuvant cisplatin. The view of the ERG on this omission is provided in Section 4.4.1.

2. Preference of use of semi-parametric models to fit to DFS KM estimates

The ERG believes that the Gompertz model could provide a better representation of the CheckMate 274 DFS data and extrapolation to five years compared to the semi-parametric models used by the company for the following reasons.

First, in its response to clarification question B2, the company states that the Gompertz model *"does not accurately capture the pattern of the KM data from the trial, in particular the protocol-induced features, such as the 'stepwise' nature of the data, particularly in the first year".* However, the ERG thinks that fitting exactly to the protocol-induced artefacts of DFS KM estimate is not desirable if this would not be replicated in real-world treatment. If so, a parametric model which smooths out the artefacts instead of "over-fitting" to them is preferable and is therefore more likely to be a reasonable description of the underlying hazard and distribution of survival times; it is efficient in its use of all the data and avoids any sensitivity to arbitrary cut points as is the case with semi-parametric models. It has the virtue of simplicity.

Second, the Gompertz model was rejected because it did not produce a finite mean survival time. However, the company's base case model structure assumption that a proportion of patients are disease-free after five years is in keeping with an infinite mean survival time for models fitted to the observed data. This is because these DFS models should not be expected to fully capture long-term other cause mortality which is captured by the application of age- and sex-matched mortality from the life tables after five years. Hence, the Gompertz model should not be rejected based on this criterion.

Third, in its response to question B2, the company also stated that *"the clinical plausibility of the fully parametric Gompertz models for nivolumab and placebo is not established"*. However, the ERG notes that the clinical validation process is not fully transparent. In particular, it is not clear whether the Gompertz model was presented to clinicians at the stage that the preferred semi-parametric models were presented. The ERG would prefer that clinicians would be asked to state *a priori* a plausible range for the survival proportion at a particular time (for example at 5 years) and the prediction of all plausible models could then be compared against that range. However, as stated in Section 4.2.3.2.1, these judgements were elicited after showing the experts the semi-parametric model predictions. Furthermore, the Gompertz function for the placebo arm is in keeping with the external evidence from Sternberg *et al*.[25] (See Figure 15) which the company presented as appropriate evidence in its response to clarification questions B2 and B17.

Fourth, the company stated in its response to question B2 that *"the hazard for the nivolumab curve is not captured by Gompertz, but is captured by the company base case curve"* (Figure 13 and

Figure 14). The ERG notes that this comment lacks clarity. The ERG is satisfied that, for each arm, the Gompertz hazard shows a reasonable comparison to the three versions of smoothed hazards (Figure 13 and

Figure 14). In particular, in the placebo arm, the Gompertz model hazard follows very closely the B-spline smoothed version of the observed hazard and converges very closely to the matched life table hazard at 5 years post-surgery. It is true that for the nivolumab arm, the Gompertz hazard is still somewhat higher than matched life-table hazard at 5 years. However, this is not inconsistent with the observed hazards which are higher than the matched hazard and the placebo arm hazard at the end of follow up. The Gompertz extrapolation of the hazard is plausible given the observed data and the uncertainty inherent at the end of the follow-up period. Moreover, the hazards predicted by the company's preferred semi-parametric models were not presented in their response to clarification question B2. It is therefore not possible to check how these hazards compare to either the Gompertz or the observed hazards after the cut point.

Figure 13: Investigator-assessed DFS for nivolumab. Smoothed hazard function estimates for trial data, and Gompertz model hazard (reproduced from Figure 4 (p23) of the clarification response)

Figure 14: Investigator-assessed DFS for placebo (CheckMate 274, August 2020 DBL): Smoothed hazard function estimates for trial data, and Gompertz model hazard (reproduced from Figure 4 (p24) of the clarification response)

Fifth, the company argued in CS Appendix K Section 3.1.8 that the CheckMate 274 data are not mature enough to consider fitting mixture-cure models. However, the company did not provide evidence that the data is mature enough to fit semi-parametric models especially with cut points (e.g. the [redacted] months in the nivolumab arm preferred model) significantly reducing the amount of data to which the parametric model was fitted.

Finally, in its response to clarification question B2, the company stated that the Gompertz model does not have the best fit according to Akaike Information Criterion (AIC) / Bayesian Information Criterion (BIC) for the nivolumab arm compared to other parametric models. The ERG notes however that differences in AIC or BIC of less than 3 are not considered to be significant.[56] On this basis, the Gompertz is not worse than the best-fitting model to the nivolumab arm.

The ERG produced a comparative plot of the company's preferred semi-parametric models, the Gompertz models and the observed KM functions as shown in Figure 15. From this plot, the ERG observes that:

- First, the company's preferred semi-parametric models may underestimate the plateauing survival probabilities in both arms and overestimate the survival advantage of nivolumab over placebo at 5 years, as whilst the hazard in the placebo arm appears to return to matched background hazard by the end of follow-up (
-

-

- Figure 14), the hazard in the nivolumab arm is still raised (Figure 13).

- Second, whilst the Gompertz model fits the nivolumab arm very similarly to the semi-parametric model and produces a comparable extrapolated probability at 5 years, there is a noticeable difference for the placebo arm between the extrapolated values at 5 years from the semi-parametric and the Gompertz distribution. The ERG notes that the prediction from the Gompertz distribution for the placebo arm is in keeping with the external evidence from Sternberg *et al*.[25]

Of the two approaches, the ERG prefers the Gompertz distribution for the reasons provided above; however, the ERG acknowledges that this distribution noticeably reduces the DFS benefit of nivolumab over placebo at 60 months compared with 36 months, which if not correct, would cause the ICER estimated using Gompertz models to be unfavourable to nivolumab treatment.

Figure 15: Investigator assessed DFS. KM functions overlaid with the Gompertz model, the company's preferred semi-parametric models and external evidence for expected 5 years survival from the deferred chemotherapy arm of Sternberg *et al*.

3. Use of the utility data from Janssen *et al.*

The company states that it chose to use data from Janssen *et al*.[43] as they were newer than those of Ara and Brazier.[52] The ERG prefers Ara and Brazier, primarily because the age categories in Janssen *et al.* are broad which results in utility being constant beyond the age of 75 years which is considered implausible by the ERG.

4. The average age of patients in the UK is likely to be older than those recruited to CheckMate 274

Clinical advice received by the ERG indicated that patients in CheckMate 274 may be slightly younger than those treated in UK practice. As mentioned in Section 3.5 and Section 4.2.3.1, the average age is reported to be around 69-70 years old.[29, 30, 50] Figure 12 shows that the ICER is sensitive to the assumed age of the population with the ICER rising from £32,813 to £53,139 when the population age was set to 78.7 years rather than [redacted] years. The 78.7 years of age value, however, represented an increase of [redacted] rather than an informed value. The increase in the ICER is due to the lower QALYs gained per person as older patients die, on average, sooner than younger patients.

The company were asked to run an analysis assuming that the average age was 70 years and that 78.9% were male to align with the cohort in Pang *et al*. (clarification question B9). However, the company declined to run this analysis, stating that this cohort was not exclusively comprised of those with MIUC and that '*this would incorporate inconsistencies into the model, since efficacy in the model is based on the characteristics of the trial population.*' The second reason concerns the ERG as it suggests that the model results would not be generalisable to the older patient population who would be treated in the NHS in England. The ERG considers that the cancer-related events observed in CheckMate 274 would largely be generalisable to a slightly older population.

5. Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo

The company assumed that the proportion of DFS events that were deaths were equal for both nivolumab and placebo. However, as discussed in Section 4.2.3.2.2, the observed proportion of deaths among DFS events were different between the trial arms: [redacted] versus [redacted] for nivolumab and placebo respectively. The ERG believes that the probability that a DFS event is death should be calculated using the data for each arm.

6. Patients in the DFS health state have the same utility values as an age- and sex-matched population

The company assumed that patients in the DFS health state have equivalent utility to an age- and sex-matched population. This was primarily because the utility values derived from CheckMate 274 were higher than the age- and sex-adjusted general population used in the model, with the latter being used

as a cap. The company mentioned in their clarification response that these patients are considered to be as healthy as the age- and sex-matched general population. However, the advice from ERG's clinical experts indicated that history of having a resected UC should have detrimental effect on the patient's quality of life compared with an average person of the same age and sex without resected UC, the ERG also notes that patients with resected UC are also likely to have other comorbidities.

Results from a cross-sectional survey, covering 10% of the English population and measuring HRQoL following treatment of bladder cancer, indicated that these patients were significantly worse than patients with colorectal and prostate cancer.[57] Moreover, a systematic review of HRQoL outcomes after radical cystectomy showed that certain health dimensions (urinary and sexual functions) remain inferior to the general population.[58]

7. Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population

For patients remaining in the DFS health state beyond five years, the company applied the same mortality rates as for an age- and sex-matched population using ONS life tables.[40] When asked to explore the impact of using standardised mortality ratios greater than 1, clarification question B6, the company declined citing clinician feedback that if '*patients do not recur after five years post-surgery, they are no longer subject to monitoring and are assumed to have mortality close to the general population.*' and provided the hazard plots which potentially indicates '*long-term remission for a proportion of patients.*' Nevertheless, the ERG believes it is plausible that, on average, life expectancy in patients with resected UC who have not had a DFS event within five years will be shorter than that for patients who do not have resected UC.

8. Uncertainty surrounding the assumed cure point

The company's economic model assumes a cure time point at five years after which patients still at the DFS health state, are assumed to have similar quality of life and life expectancy to the general population. The main reason mentioned was *"tendency towards age- and sex-matched lifetable hazards for patients in the CheckMate274 trial, potentially indicating long-term remission for a proportion of patients"* as showed in their response to clarification question B6.[16] However, the company acknowledges that this characteristic is shown earlier for placebo (~40 months) compared to nivolumab whose hazard was declining slowly but yet to approach that of age- and sex-matched general population by the end of DFS KM plots from CheckMate 274 (48 months).

Within the CS the company referenced Hautmann *et al.,*[11] which followed 1,100 patients for 20 years after a surgical cystectomy for MIBC, and did not include patients receiving neoadjuvant chemotherapy, found that DFS KM curve starts to plateau by six years and appears to have plateaued by 10 years. The

ERG's clinical experts agreed that it is not reasonable to assume that recurrence probability beyond five years is zero. Hence, the ERG is uncertain regarding the appropriateness of a five-year cure point for decision making.

9. The lack of subgroup analyses in the company submission

The NICE scope included PD-L1 expression as a subgroup to be considered but this was not undertaken by the company. In the CS, efficacy results are presented for patients with PD-L1 expression ≥1%. The ERG requested clinical results for the subgroup with expression <1%, and these were provided in response to clarification question B23.[13] The ERG notes that the difference in DFS HR (0.55 versus [redacted] for subgroups with PD-L1 expression ≥1% and <1% respectively) justifies the presentation of ICER results for each subgroup separately.

In response to clarification question B24, the company presented interaction tests for treatment effect with: region, initial tumour origin, use of prior neoadjuvant cisplatin therapy, and use of any prior neoadjuvant systemic therapy. The reported *p*-values for the interaction tests were all below [redacted] with higher HRs for Asian and European patients, those with tumour origin in the renal pelvis and ureter, those without prior neoadjuvant cisplatin therapy and those who had not had prior neoadjuvant systemic therapy.

The ERG would have liked to have seen exploratory analyses providing ICERs based on prior neoadjuvant cisplatin-based chemotherapy, and PD-L1 expression acknowledging that these would be based on lower sample sizes. Further exploratory analyses including those within a European setting and by location of tumour may have been informative, although the sample size would be decreased further and randomisation would have been broken as these were not stratification factors.

4.3.4 Minor issues identified within the critical appraisal

A number of minor issues was identified within the CS which did not noticeably affect the ICER in exploratory ERG extreme analyses, such as setting the costs of future treatments to zero. For the sake of comprehensiveness, these are listed in Box 2, with a brief description of each issue. However, these are not further explored within the ERG report as the most appropriate parameter values were unknown.

Box 2: Minor issues identified within the critical appraisal undertaken by the ERG

(1) Apparent discrepancy between the modelled risk of death after recurrence and published data

(2) Post-recurrence treatment costs do not account for periods of no therapy

(3) The weighted average used for post-recurrence healthcare resource use does not account for patients living for significantly more than one year

1. Apparent discrepancy between the modelled risk of death after recurrence and published data

As shown in

Figure 9 the post-recurrence survival probabilities used in the model did not fit the published data from Bellmunt *et al.* and De Santis *et al*. It initially overestimates survival before underestimating it.

2 Post-recurrence treatment costs do not account for periods of no therapy

The company's base case assumes that after recurrence, patients receive chemotherapy for their remaining lifetime. Hence, the model does not accurately capture periods of chemotherapy breaks and palliative treatment. While the company acknowledges this was a simplifying assumption, the model is not programmed to track patients' time post-recurrence.

3. The weighted average used for post-recurrence healthcare resource use does not account for patients living for significantly more than one year

In attempting to assign a single cost for the recurred health state, the company calculated a weighted average between resource use at the first year and subsequent years. However, it does not take into account that some patients may live for significantly more than a year, hence consume more healthcare resources than currently captured.

4.4 Exploratory analyses undertaken by the ERG

4.4.1 Overview of ERG's exploratory analyses

The exploratory analyses performed by the ERG are provided in Section 4.4.2. Where quantitative analyses could not be provided, qualitative conclusions are provided. The ERG considers that the ICERs produced by the company, and the exploratory analyses run by the ERG are suitable only for the comparison of nivolumab in a population who are cisplatin-ineligible.

For patients who are eligible for cisplatin-based adjuvant chemotherapy, the company's ITC results show that nivolumab is not clearly superior to cisplatin-based regimens, with the point estimate of the HR favouring adjuvant chemotherapy. In addition, cisplatin-based regimens are potentially less expensive than nivolumab and are only given for six cycles, thereby limiting the administration burden on patients. Based on the current available evidence, the ERG deems that it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY.

4.4.2 ERG's exploratory analyses – methods

ERG exploratory analysis 1: Using a Gompertz distribution to model DFS over the initial 5-year period

The ERG explored the impact on the ICER of using the Gompertz parametric fit to model DFS over the initial five-year period (prior to the assumed cure point).

ERG exploratory analysis 2: Using utility values from Ara and Brazier

The ERG performed an analysis where data from Ara and Brazier were used.

ERG exploratory analysis 3: Increasing the average age of treated patients

The ERG explored the impact on the ICER of increasing the average patient age from [redacted] years to 70 years.

ERG exploratory analysis 4: Using the observed proportion of DFS events that were deaths.

The ERG explored the impact on the ICER of assuming that [redacted] of DFS events were deaths for nivolumab treated patients and [redacted] of DFS events were deaths for BSC.

ERG exploratory analysis 5: Decreasing utilities in the model by 0.02.

The ERG explored the impact on the ICER of assuming that age- and sex-matched utilities were 0.02 lower than what used in the company base case. This value is arbitrary but illustrates the sensitivity of the model results to the assumption that patients with resected UC have a lower level of HRQoL than the age- and sex-matched general population.

ERG exploratory analysis 6: Assuming a standardised mortality ratio of 1.1 for patients with resected UC.

The ERG explored the impact on the ICER of assuming that patients in the long-term DFS health state would have a risk of death 10% greater than the age- and sex-matched general population.

ERG exploratory analysis 7: Assuming a cure point of 10 years

The ERG explored the impact on the ICER of assuming that the cure point applies at 10 years instead of five years as in the company's base case. The results of this analysis were deemed to vary based on the model type used to fit the DFS KM estimates from CheckMate 274. Therefore, results are presented for the company's base case semi-parametric model fitting (ERG exploratory analysis 7a) and the Gompertz parametric model fit (ERG exploratory analysis 7b).

Each individual change (ERG exploratory analysis 1 to 7) is applied to the company's base case. Combining individual changes (1 to 6 and 7b) form an ERG's pessimistic scenario with the ERG exploratory analysis 7a forming an optimistic scenario. The exploratory analysis which has the largest impact on the ICER is the use of Gompertz distributions to model DFS; the ERG believes this model is more appropriate than the semi-parametric approach favoured by the company. Whilst the ERG notes that the use of the Gompertz distributions could overestimate the ICER (see Section 4.3.3), given the

other factors that could increase the ICER, the ERG's central estimate of the ICER is that produced by individual change 1.

4.4.3 ERG's exploratory analyses - results

4.4.3.1 Quantitative changes to the company's base case

Table 37 presents the results of the ERG's deterministic exploratory analyses. As shown, using the company's deterministic model, the ICER for nivolumab treatment versus BSC is estimated to be £32,813 per QALY gained.

The largest change in the ICER is caused by switching from the semi-parametric models preferred by the company to model DFS to the use of Gompertz distributions, which increases the ICER to £74,315 per QALY gained.

Increasing the average age of patients starting treatment to 70 years, from [redacted] years, increased the ICER by over £4,000 per QALY gained. Increasing the cure point to 10 years favoured nivolumab when semi-parametric models were used, whereas it favoured placebo when the Gompertz distribution was used; this was due to the difference in DFS increasing between 5 and 10 years when semi-parametric models were used, but this difference reducing when the Gompertz distributions were used (Figure 15).

The ICER was fairly insensitive to whether utility values were based on Ara and Brazier, using the observed death probability among DFS events, decreasing all utilities in the model by 0.02, and using a SMR of 1.1 for cured patients.

The use of Gompertz distributions (exploratory analyses 1) is used as a basis to produce the ERG's preferred ICER estimate. Considering that when using the Gompertz distributions all of the remaining exploratory analyses increased the ICER, but that the Gompertz distributions may be unfavourable to nivolumab when estimating the difference in DFS between nivolumab and BSC at five years, the ERG has estimated a most-plausible ICER of £75,000.

Under the ERG's optimistic scenario, which uses the company's base case but applies a cure point at 10 years, the ICER decreases to £28,708 per QALY gained. The ERG's pessimistic scenario, which includes all six exploratory analyses whilst applying a cure point at 10 years results in an ICER of £83,101 per QALY gained.

4.4.3.2 Qualitative changes to the ERG's base case ICER

Based on the academic-in-confidence HRs provided by the company it is likely that the midpoint ICER would increase if a European population alone was used to inform the model. The midpoint ICER would

likely increase for patients where PD-L1 expression <1%; the tumour originated in the renal pelvis or ureter; and for those without prior neoadjuvant treatment cisplatin therapy or without prior neoadjuvant systemic therapy. Conversely, the ICER would decrease for those with a tumour PD-L1 expression ≥1%; an initial tumour origin in the urinary bladder, and those who had received prior neoadjuvant treatment cisplatin therapy or prior neoadjuvant systemic therapy.

Table 37: Results of the ERG's deterministic exploratory analyses

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic)							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,813
ERG exploratory analysis 1: Using a Gompertz distribution to model DFS over the initial 5-year period *							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,315
ERG exploratory analysis 2: Using utility values from Ara and Brazier							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,144
ERG exploratory analysis 3: Increasing the average age of treated patients to 70 years of age							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,030
ERG exploratory analysis 4: Using the observed proportion of DFS events that were deaths							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,159
ERG exploratory analysis 5: Decreasing all health state utilities in the model by 0.02							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,685
ERG exploratory analysis 6: Assuming a standardised mortality ratio of 1.1 for patients with resected UC							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,965
ERG exploratory analysis 7a: Assuming a cure point of 10 years using the company's semi-parametric fits (ERG's optimistic scenario)							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,708
ERG exploratory analysis 7b: Assuming a cure point of 10 years using the Gompertz distribution							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,651
ERG pessimistic scenario (combining ERG exploratory analyses 1-6 and assuming a cure point of 10 years)							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£83,101

*Used as a starting point to estimate the ERG's preferred ICER of £75,000 per QALY gained.

4.4.4 The ERG's estimate of the ICER

The exploratory analyses conducted by the ERG, which are provided in Table 37, indicate that there are plausible changes to parameter values which would increase the company's estimate of the ICER

but where the most appropriate value remains uncertain. Such parameters include: the age of treated patients; whether there is a reduced HRQoL for patients with resected UC; and whether the risk of mortality is increased.

The exploratory analysis which has the largest impact on the ICER is the use of Gompertz distributions to model DFS; the ERG believes this model is more appropriate than the semi-parametric approach favoured by the company. Whilst the ERG notes that the use of this model could overestimate the ICER (see Section 4.3.3), given that the remaining exploratory analyses increase the ICER, the ERG's most plausible estimate of the ICER for the full population is approximately £75,000 per QALY gained, although this has considerable uncertainty. The lower bound of the ICER is anticipated to be approximately £29,000 per QALY gained (the company's base case using a cure point of 10 years) with an upper bound expected to be approximately £83,000 per QALY gained.

Several factors could not be explicitly quantified as discussed in Section 4.4.3.2, but the ICER would likely be more favourable to nivolumab treatment if patients who had a tumour PD-L1 expression ≥1%; an initial tumour origin in the urinary bladder, and those who had received prior neoadjuvant treatment cisplatin therapy or prior neoadjuvant systemic therapy were targeted. Whilst the company provided relevant HRs these could not be incorporated within the current structure of the company's model.

4.5 Discussion

The model submitted by the company was implemented to a good standard. However, the ERG believes that the base case ICER is likely to be higher than that estimated by the company (deterministic ICER: £32,813 per QALY gained) and estimates an ICER of approximately £75,000 per QALY gained, with approximate bounds for the cost per QALY gained of £29,000 and £83,000. As shown in

Table 33, probabilistic ICERs were similar to the deterministic values. The largest component in increasing the ICER is the choice of distributions to model DFS. Additional data related to the hazard of DFS events, particularly 3 to 5 years after resection of high-risk UC would help to reduce the uncertainty in the most appropriate distributions to use.

5 END OF LIFE

The NICE End of Life criteria are:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company's base case analysis estimates that patients receiving BSC would live for considerably longer than 24 months and therefore the company has not made a claim that the End of Life criteria should be applied in this STA. The ERG agrees with this viewpoint.

6 OVERALL CONCLUSIONS

The key evidence for clinical effectiveness within the CS comprised one RCT (CheckMate 274) of nivolumab (n=353) versus placebo (n=356). This RCT was ongoing at the time of writing and OS data were not available to the trial investigators or staff preparing the CS. At the data cut-off, the HR for DFS was 0.70 (98.22% CI: 0.55, 0.90), statistically significantly favouring nivolumab over placebo. Grade ≥3 TRAEs were experienced by 17.9% in the nivolumab group, and 7.2% in the placebo group. Despite the inherent limitations, the company's ITC comparing nivolumab versus cisplatin adjuvant therapy did not show any superiority for nivolumab, thus the ERG considers the evidence presented in the CS and critiqued in this report only applies to cisplatin-ineligible patients.

The model submitted by the company was implemented to a good standard, although the ERG explored alternative assumptions to those used by the company. When considering all the possible amendments the ERG's preferred ICER was approximately £75,000 per QALY gained compared to the company's estimate of £32,813; this increase was driven by the ERG's preference to use Gompertz distributions instead of the semi-parametric approach used by the company. A pessimistic scenario which incorporated simultaneously all the ERG's alternative assumptions increased the deterministic ICER of nivolumab compared with BSC to over £83,000 per QALY gained. An optimistic scenario which used the company's base case but extended the time for the cure point to 10 years resulted in an ICER of less than £29,000 per QALY gained. However, there are some uncertainties that could not be resolved by the ERG. The ERG would have liked to generate illustrative ICERs for combinations of PD-L1 expression, location of tumour and those who had received prior neoadjuvant treatment cisplatin therapy or prior neoadjuvant systemic therapy subgroups; however, this was not possible due to the economic model structure which did not use HR values to model relative treatment effect but used distributions fitted to the individual arms and the ERG did not have access to individual patient level data.

7 REFERENCES

1. Bristol-Myers Squibb. Company evidence submission for nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]; 2021.
2. Leow JJ, Chong KT, Chang SL, Bellmunt J. Upper tract urothelial carcinoma: a different disease entity in terms of management. *ESMO Open* 2016;1:e000126.
3. Rouprêt M, Babjuk M, Burger M, Compérat E, Cowan NC, Gontero P*, et al.* European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma. *Journal* 2021. https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Upper-Urinary-Tract-Urothelial-Carcinoma-2021.pdf7 April 2021
4. Cancer Research UK. Bladder cancer incidence statistics. *Journal* 2020. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence#heading-Zero15 December 2020
5. Office of National S. Cancer survival in England - adults diagnosed: 2013 - 2017 edition. *Journal* 2017. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed4 January 2021
6. Roupret M, Mabjuk M, Bohle A, Burger M, Comperat E, Cowan N*, et al.* EAU Guidelines on Urothelial Carcinomas of the Upper Urinary Tract: European Association of Urology (EAU); 2016.
7. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng A-C, Boyd S*, et al.* Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients. *Journal of Clinical Oncology* 2001;19:666-75.
8. Sargos P, Baumann BC, Eapen L, Christodouleas J, Bahl A, Murthy V*, et al.* Risk factors for loco-regional recurrence after radical cystectomy of muscle-invasive bladder cancer: A systematic-review and framework for adjuvant radiotherapy. *Cancer Treat Rev* 2018;70:88-97.
9. Leow JJ, Orsola A, Chang SL, Bellmunt J. A contemporary review of management and prognostic factors of upper tract urothelial carcinoma. *Cancer Treat Rev* 2015;41:310-9.
10. Soria F, Moschini M, Wirth GJ, Gust KM, Klatte T, Briganti A*, et al.* Characterization of Late Recurrence After Radical Cystectomy in a Large Multicenter Cohort of Bladder Cancer Patients. *Urology* 2017;106:119-24.
11. Hautmann RE, de Petriconi RC, Pfeiffer C, Volkmer BG. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. *Eur Urol* 2012;61:1039-47.
12. Bristol Myers Squibb. Summary of Product Characteristics. OPDIVO 10 mg/mL concentrate for solution for infusion; 2021.
13. Bristol Myers Squibb. Advisory board: Nivolumab for post-resection adjuvant treatment of high-risk muscle invasive urothelial cancer; 2021.
14. Centre for Reviews Dissemination. CRD's guidance for undertaking reviews in healthcare: York Publ. Services; 2009.
15. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I*, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
16. Bristol Myers Squibb. Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]. Clarification response; 2021.
17. National Institute for H, Care E. Single technology appraisal: User guide for company evidence submission template. *Journal* 2015. https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-722867154193337 October 2021
18. Bristol Myers Squibb. Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma; 2020.
19. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y*, et al.* Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *New England Journal of Medicine* 2021;384:2102-14.

20. Bajorin DF, Witjes JA, Gschwend J, Schenker M, Valderrama BP, Tomita Y, *et al.* First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab versus placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma. *Journal of Clinical Oncology* 2021;39.
21. Bristol Myers Squibb. Erratum to Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma; 2021.
22. Bristol Myers Squibb. Clinical Protocol CA209274: A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma; 2019.
23. Bristol Myers S. Erratum to Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma; 2021.
24. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. June 14, 2010. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 (Accessed
25. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M, *et al.* Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol* 2015;16:76-86.
26. Cognetti F, Ruggeri EM, Felici A, Gallucci M, Muto G, Pollera CF, *et al.* Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol* 2012;23:695-700.
27. Zhegalik AG, Polyakov SL, Rolevich AI, Volkov AN, Minich AA, Vasilevich VJ, *et al.* Long-term results of a single-center prospective randomized trial assessing efficacy of a shortened course of adjuvant chemotherapy after radical cystectomy in patients with locally advanced bladder cancer. *Cent European J Urol* 2020;73:26-32.
28. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 2012;41:818-27.
29. Pang KH, Thomas F, Novara G, Din OS, Morgan SL, Hussain SA, *et al.* The Impact of Centralised Services on Metric Reflecting High-quality Performance: Outcomes from 1110 Consecutive Radical Cystectomies at a Single Centre. *Eur Urol Focus* 2020; 10.1016/j.euf.2020.05.011.
30. Jefferies ER, Cresswell J, McGrath JS, Miller C, Hounsome L, Fowler S, *et al.* Open radical cystectomy in England: the current standard of care - an analysis of the British Association of Urological Surgeons (BAUS) cystectomy audit and Hospital Episodes Statistics (HES) data. *BJU Int* 2018;121:880-5.
31. National Institute for Health and Care Excellence. Final scope for the appraisal of nivolumab for treating resected high-risk invasive urothelial cancer. 2021.
32. Suskovic N, Raldow AC, Royce TJ, Smith A. Cost-effectiveness of radical cystectomy versus trimodality therapy for muscle invasive bladder cancer. *Journal of Clinical Oncology* 2020;38:575-.
33. Magee DE, Hird AE, Cheung D, Sander B, Nam R, Sridhar SS, *et al.* Perioperative chemotherapy for upper tract urothelial carcinoma: A microsimulation Markov model. *Journal of Clinical Oncology* 2020;38:508-.
34. Magee* D, Cheung D, Hird A, Sridhar S, Catton C, Chung P, *et al.* PD50-11 TRIMODAL THERAPY VERSUS RADICAL CYSTECTOMY FOR MUSCLE INVASIVE BLADDER CANCER - A MARKOV MICROSIMULATION MODEL. *Journal of Urology* 2020;203:e1012-e.
35. Royce TJ, Feldman AS, Mossanen M, Yang JC, Shipley WU, Pandharipande PV, *et al.* Comparative Effectiveness of Bladder-preserving Tri-modality Therapy Versus Radical Cystectomy for Muscle-invasive Bladder Cancer. *Clin Genitourin Cancer* 2019;17:23-31.e3.

36. Lotan Y, Woldu SL, Sanli O, Black P, Milowsky MI. Modelling cost-effectiveness of a biomarker-based approach to neoadjuvant chemotherapy for muscle-invasive bladder cancer. *BJU international* 2018;122:434-40.
37. Stevenson SM, Danzig MR, Ghandour RA, Deibert CM, Decastro GJ, Benson MC*, et al.* Cost-effectiveness of neoadjuvant chemotherapy before radical cystectomy for muscle-invasive bladder cancer. *Urol Oncol* 2014;32:1172-7.
38. Curtis L BA. Unit Costs of Health and Social Care 2020. Personal Social Services Research Unit. *Journal* 2020. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/1 March 2021
39. National Institute for H, Care E. Guide to the methods of technology appraisal 2013. *Journal* 2013. https://www.nice.org.uk/article/pmg9January 2021
40. Office of National S. National life tables: UK. *Journal* 2020.
41. Bellmunt J, von der Maase H, Mead GM, Skoneczna I, De Santis M, Daugaard G*, et al.* Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *J Clin Oncol* 2012;30:1107-13.
42. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P*, et al.* Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009;27:5634-9.
43. Janssen B SA. Population Norms for the EQ-5D. In: Szende A JBCJ, editor. *Self-Reported Population Health: An International Perspective based on EQ-5D*Dordrecht: Springer Netherlands; 2014:19-30.
44. British National F. Nivolumab solution for infusion. *Journal* 2021. https://bnf.nice.org.uk/medicinal-forms/nivolumab.html31 January 2021
45. Department of H, Social C. Drugs and pharmaceutical electronic market information tool (eMIT). *Journal* 2020. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit5 March 2021
46. National Health S. NHS: National tariff. *Journal* 2021. england.nhs.uk/pay-syst/national-tariff/19 February 2021
47. Improvement NHS. 2018/19 National Cost Collection data. *Journal* 2020. https://improvement.nhs.uk/resources/national-cost-collection/#ncc1819
48. Copley-Merriman C, Stevinson K, Liu FX, Wang J, Mauskopf J, Zimovetz EA*, et al.* Direct costs associated with adverse events of systemic therapies for advanced melanoma: Systematic literature review. *Medicine (Baltimore)* 2018;97:e11736.
49. Georghiou T, Bardsley M. Exploring the cost of care at the end of life. *Journal* 2014. https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life
50. (BAUS) TBAoUSL. Analyses of Radical Cystectomies performed between January 1st and December 31st 2019. *Journal* 2019. https://www.baus.org.uk/_userfiles/pages/files/publications/audit/CystectomyFinalAnalyses2019.pdf
51. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P*, et al.* Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol* 2012;30:191-9.
52. Ara R, Brazier J. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010;13:509-18.
53. Health. NCfSRaUCLDoEaP. Health survey for England, 2008 [computer file]. In: [distributor] UDA, ed. 3rd edn. ed. Colchester; 2011.
54. Kind P DP, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;316:736-41.
55. John JB VM, Cooper N, Wong K, Hounsome L, Treece S, McGrath JS, Harden S. Treatment Allocation and Survival in Patients Diagnosed with Nonmetastatic Muscle-invasive Bladder

Cancer: An Analysis of a National Patient Cohort in England. *Eur Urol Focus* 2021 Mar;7:359-65.
56. Burnham KP, Anderson DR. Model selection and multi-model inference [electronic resource] : a practical information-theoretic approach. 2nd edn: New York ; London: Springer; 2002.
57. James W.F. Catto, Amy Downing, Samantha Mason, Penny Wright, Kate Absolom, Sarah Bottomley*, et al.* Quality of Life After Bladder Cancer: A Cross-sectional Survey of Patient-reported Outcomes. *European Urology* 2021;79:621-32.
58. Yang LS, Shan BL, Shan LL, Chin P, Murray S, Ahmadi N*, et al.* A systematic review and meta-analysis of quality of life outcomes after radical cystectomy for bladder cancer. *Surg Oncol* 2016;25:281-97.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 25 November** using the below 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 committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Executive summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
1.4 The clinical effectiveness evidence: summary of the ERG's key issues, p. 10 ERG states: "This RCT was ongoing at the time of writing, and data were from a pre-specified interim analysis. OS data were not available. At the data cut-off, the hazard ratio (HR) for DFS was 0.70 (98.22% confidence interval (CI) 0.55, 0.90), favouring nivolumab over placebo. The KM estimated median DFS was 20.8 months (95% CI 16.5, 27.6) in the nivolumab arm, and 10.8 months (95% CI 8.3, 13.9) in the placebo arm."	Paragraph should read: "This RCT was ongoing at the time of writing, and data were from a pre-specified interim analysis. At the data cut-off, the hazard ratio (HR) for DFS, the primary endpoint, was 0.70 (98.22% confidence interval (CI) 0.55, 0.90), favouring nivolumab over placebo. The KM estimated median DFS was 20.8 months (95% CI 16.5, 27.6) in the nivolumab arm, and 10.8 months (95% CI 8.3, 13.9) in the placebo arm. Data for OS, a secondary endpoint, were not available."	Paragraph should be amended to highlight that DFS is the primary endpoint and OS is a secondary endpoint.	Amended as suggested
1.5 The cost-effectiveness evidence: summary of the ERG's key issues, p. 11 ERG states: "In addition, cisplatin-based regimens are less expensive than nivolumab and are only given for six cycles, thereby limiting the administration burden on patients."	Sentence should be deleted as it is not clear whether cisplatin-based regimens would be less expensive, without considering the administration costs as well.	While the duration of cisplatin treatment may be shorter than nivolumab, the treatment is associated with increased resource use, specific for chemotherapy administration such as spill kits, extravasation kits, and special personnel. Therefore, it is inaccurate and potentially misleading to assume that cisplatin therapy is cheaper, without considering	We have added potentially in front of less expensive to signify that there may be some doubt in this sentence.

		the extra costs associated with administration.	
1.5 The cost-effectiveness evidence: summary of the ERG's key issues, p. 11 ERG states: "Based on the current available evidence, the ERG deems that it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY"	Sentence should be deleted as results are estimated based on assumptions, without cisplatin treatment being modelled.	It is not possible to predict cost-effectiveness estimates at this stage, in the absence of efficacy, costs and AE profiles being modelled. In addition, as noted in the CS and ERG clarification questions there are strong limitations with the available data implying the ITC is not suitable for decision making. Therefore, assuming that it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY is not appropriate.	No change as this is not a factual error, The ERG has put forward its viewpoint, with which the company can disagree. The company's rebuttal can be put forward at Technical Engagement and at the Appraisal Committee where appropriate.
1.5 The cost-effectiveness evidence: summary of the ERG's key issues, p. 14, Table 9 ERG states "Additionally, data from Hautmann *et al*. suggest that a plateau of 10 years may be more appropriate."	Sentence should be amended to "Additionally, data from Hautmann *et al*., in patients that had not received neoadjuvant chemotherapy, suggest that a plateau of 10 years may be more appropriate."	Clarification that the study only included patients that had not received neoadjuvant chemotherapy.	Amended as suggested

Issue 2 Background

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
2.2 Critique of company's overview of current service provision, p.19 The ERG state that "Based on data from a large multi-centre study, an estimated 4.1% of patients recurred more than five years after radical cystectomy.[1]", however the ERG do not mention that this population did not receive neoadjuvant chemotherapy, unlike the CheckMate 274 study.	Sentence should be amended to "Based on data from a large multi-centre study of patients that had not receive neoadjuvant chemotherapy, an estimated 4.1% of patients recurred more than five years after radical cystectomy.[1]"	Clarification that the study only included patients that had not received neoadjuvant chemotherapy.	Text amended to convey this point
2.2 Critique of company's overview of current service provision, p.19 The ERG state that "Data from a retrospective cohort study done by Hautmann *et al.*[2] indicated that… "	Sentence should be amended to "Data from a retrospective cohort study done by Hautmann *et al.*[2], in patients that had not received neoadjuvant chemotherapy, indicated that"	Clarification that the study only included patients that had not received neoadjuvant chemotherapy.	Text amended as suggested
2.3.3 Comparator, p.21-22 The ERG states that "the company believes that the majority of patients in the UK would not be eligible for adjuvant cisplatin as they would have already received neoadjuvant cisplatin. Of those eligible, a	The sentence should be amended to "The company believes that the majority of cisplatin-eligible patients in the UK will receive neoadjuvant cisplatin and would therefore not be eligible for cisplatin in the adjuvant setting. Of those patients that did not receive neoadjuvant chemotherapy, but were eligible, a proportion will be ineligible for cisplatin in the	In both the CS and ERG clarification questions the company state that the majority of cisplatin-eligible patients, not just patients, will receive neoadjuvant cisplatin. Furthermore, the company also states that there are patients that are ineligible for adjuvant cisplatin	Text amended as suggested

proportion would refuse adjuvant chemotherapy."	adjuvant setting due to comorbidities, or may refuse adjuvant chemotherapy."	because of co-morbidities, not just refusal.	

Issue 3 Clinical Effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout The ERG refer to the study publication(3) and conference presentation(4) as Banjorin *et al*. This is incorrect throughout the report.	All references to author "Banjorin" should be amended to the correct author name of "Bajorin".	Recurring typographical error of the main study publication author name.	Typo corrected as requested
2.3.2 Intervention, p.21 Missing comma [redacted]	Comma needed between [redacted] and [redacted].	Typographical error.	Typo corrected as requested
3.2.1 Study design CheckMate 274, Table 15, p.30 The ERG states this table is "adapted from Tables 8 and 9 of the CS", however, results presented in this table are derived from various sections in the CS.	In order to be accurate, the table caption should state the data reported in Table 15 are derived from Tables 7 through 10 in the CS.	Data represented in this table is derived from various tables in the CS.	Text amended to convey this point
3.2.1 Study design CheckMate 274, p.33 Exploratory endpoint PFS2 is missing from the list of exploratory endpoints.	List of exploratory endpoints should be amended to include "progression-free survival after next line of subsequent therapy (PFS2)" after "locoregional control (LRC);"	In line with Table 9 of the CS, exploratory endpoint PFS2 from CheckMate 274 should be included.	Text amended as suggested

3.2.3 Health-related quality of life, p.41 ERG states "For both EORTC QLQ-C30 and EQ-5D-3L, the CS reports that [redacted], as seen in Figure 11 and Figure 12 of the CS." The text does not refer to all the relevant figures and does not have the all confidential marking required.	In order to refer to all of the relevant figures and maintain confidentiality of the EQ-5D-3L results, the following amendments are proposed: "For both EORTC QLQ-C30 and EQ-5D VAS, the CS reports that HRQoL remained stable, with no mean change in score from baseline reaching MID at any timepoint for either nivolumab or placebo, as seen in Figure 10 and Figure 12 of the CS. The mean EQ-5D-3L utility index score [redacted] both arms, as seen in Figure 11 of the CS."	In order to encompass the EORTC QLQ-C30 results Figure 10 should also be referred to. Corrections related to confidential marking are further detailed in the corrected markings table.	Text amended as suggested

Issue 4 ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
3.4 Critique of the company's indirect treatment comparison, p.47 The ERG states "The company did not highlight any major differences in tumour location (given that UTUC tumours were largely excluded anyway), tumour characteristics (stage and nodal status), ECOG status, sex split or age.", however Appendix J reports specific data relating to variability across studies in relation to tumour stage based on the number of nodes.	The paragraph should be amended to take into consideration the variability in tumour stage based on the number of nodes, as reported in Appendix J, p.6, Figure 2.	As described in Appendix J, variability in tumour characteristics (stage and nodal status) were reported.	The text has been amended to reflect that the CS did present evidence of variability between the N0 and the N+ categories.

Issue 5 Cost effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
4.2.2 Model structure and logic, p.54. ERG states: "Health utility is determined by the presence/absence of disease recurrence and was assumed the same regardless of the intervention used in the adjuvant setting. Health utility values for the DFS states were based on utility values of the age-adjusted general population with a decrement applied for patients with recurrence"	Paragraph should read: "Health utility is determined by the presence/absence of disease recurrence and was assumed the same regardless of the intervention used in the adjuvant setting. Due to trial-informed utilities being higher than the sex and age matched general population and in the absence of alternative values from the literature, health utility values for the DFS states were based on utility values of the age-adjusted general population. A decrement derived from the CheckMate 247 trial was applied for patients with recurrence"	Data from the CheckMate 274 trial produced utility values higher than the general sex and age-adjusted population. Due to lack of available data to inform alternative utility values, the DFS utility values were based on age and sex-adjusted general population. A decrement that was informed by the difference between DFS and recurrence utility values in the trial was applied to these general population utilities to derive the recurrence values.	Text amended as suggested
4.2.3 Evidence used to inform the company's model parameters, p. 56. ERG states: "Five of the models were rejected based on a poor fit to the KM estimate, it was not specified whether this was based on Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), or another measure"	Sentence should read: "Five of the models were rejected based on a poor fit to the KM estimate, based on the visual inspection of the curve fit, as they overestimate DFS in the early part of the data and underestimate it in the latter part, for both nivolumab and placebo. This is described within Appendix K (survival report)."	The description provided by ERG is not accurate and potentially misleading. The rejection of the five models was based on poor fit to the trial data, assessed by visual inspection of the curves. This justification is provided in the Appendix K, p.22.	Text amended to convey this point

4.2.3 Evidence used to inform the company's model parameters, p.61 ERG states: "The company assumed a 50:50 split and took the midpoint of these two median values based on the assumption that 50% of patients are eligible to receive cisplatin and the other 50% are ineligible thus receive either carboplatin-based therapy or immunotherapy (which is currently in the Cancer Drugs Fund (CDF))."	Sentence should read "The company assumed a 50:50 split and took the midpoint of these two median values based on the assumption that 50% of patients are eligible to receive cisplatin and the other 50% are ineligible thus receive either carboplatin-based therapy or immunotherapy (which were in the Cancer Drugs Fund (CDF) at the time of company submission)."	The company would like to clarify that at the time of company submission, immunotherapy options were in the CDF, but the status of these drugs has now changed.	Text amended as suggested
4.2.3 Evidence used to inform the company's model parameters, p.63. ERG states: "In response to clarification question B5, the company stated that they consider these patients cured and therefore could have the same utility as general population"	Sentence should read: "In response to clarification question B5, the company stated that they consider these patients cured and therefore could have the same utility as general population. General population measures, such as utility, are estimates of all individuals, rather than solely referring to "healthy" individuals. Therefore, the use of general population utility does not indicate that patients are without comorbidity, only that it is within the limits of that experienced by others of the same age."	General population does not refer to healthy individuals only, but rather to a mix of health states and comorbidities, therefore reaching cure after bladder cancer could lead to the same utility as general population.	Text amended to convey this point. We have also made the point in 4.3.3 (6) that patients with resected UC are also likely to have comorbidities

4.2.3 Evidence used to inform the company's model parameters, p.64. ERG states: "Post-recurrence treatments were assumed to be given as IV infusions on a weekly basis, as shown in Table 46 of the CS".	Sentence should read: "Post-recurrence treatments were assumed to be given as IV infusions following a regimen as shown in Table 46 of the CS"	Treatments were not administered on a weekly basis, as showed in the column Regime in Table 46 (Cisplatin (with gemcitabine)-1 dose (70 mg/m2) per 4 weeks, Gemcitabine (with cisplatin)-3 doses (1000 mg/m2) per 4 weeks, Carboplatin (with gemcitabine)-1 dose (400 mg/m2) per 3 weeks, Gemcitabine (with carboplatin)-2 doses (1000 mg/m2) per 3 weeks) The treatments have different administration frequencies, it is the costs of the treatments that is adjusted for a week, to match the model cycle length.	Text amended as suggested
4.2.10 Company's scenario analyses, p 74, Table 35 Incorrect ICER and incremental costs values for Scenario 8 and 9	ICER and incremental costs for Scenario 8 should read £32,085 and £[redacted], respectively, and for Scenario 9 the ICER should read £34,383 and incremental costs £[redacted].	Values provided by the ERG did not account for different costs profiles for each scenario. Changing recurrence to death transition probability alters the percentage of patients surviving to one year and beyond one year post-recurrence. This is used to determine post-recurrence health resource used costs, therefore cost profiles also require updating in these scenarios.	Text amended as suggested

4.3.3 Main issues identified within the critical appraisal, p.83 ERG states “Within the CS the company referenced Hautmann *et al.,*[(2)] which followed 1,100 patients for 20 years after a surgical cystectomy for MIBC, found that DFS KM curve starts to plateau by six years and appears to have plateaued by 10 years"	Sentence should be amended to “Within the CS the company referenced Hautmann *et al.,*[(2)] which followed 1,100 patients for 20 years after a surgical cystectomy for MIBC, and did not include patients receiving neoadjuvant chemotherapy, found that DFS KM curve starts to plateau by six years and appears to have plateaued by 10 years"	Clarification that the study only included patients that had not received neoadjuvant chemotherapy.	Text amended as suggested

4.4.1 Overview of ERG's exploratory analyses, p. 85 ERG states: "In addition, cisplatin-based regimens are less expensive than nivolumab and are only given for six cycles, thereby limiting the administration burden on patients."	Sentence should be deleted as it is not clear whether cisplatin-based regimens would be less expensive, without considering the administration costs as well.	While the duration of cisplatin treatment may be shorter than nivolumab, the treatment is associated with increased resource use, specific for chemotherapy administration such as spill kits, extravasation kits, and special personnel. Therefore, it is inaccurate and potentially misleading to assume that cisplatin therapy is cheaper, without considering the extra costs associated with administration.	We have added potentially in front of less expensive to signify that there may be some doubt in this sentence.
4.4.1 Overview of ERG's exploratory analyses, p. 85 ERG states: "Based on the current available evidence, the ERG deems that it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY"	Sentence should be deleted as results are estimated based on assumptions, without cisplatin treatment being modelled.	It is not possible to predict cost-effectiveness estimates at this stage, in the absence of efficacy, costs and AEs profiles being modelled. In addition, as noted in the CS and ERG clarification questions there are strong limitations with the available data implying the ITC is not suitable for decision making. Therefore, assuming that it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY is not appropriate.	No change as this is not a factual error, The ERG has put forward its viewpoint, with which the company can disagree. The company's rebuttal can be put forward at Technical Engagement and at the Appraisal Committee where appropriate.

Issue 6 Utility

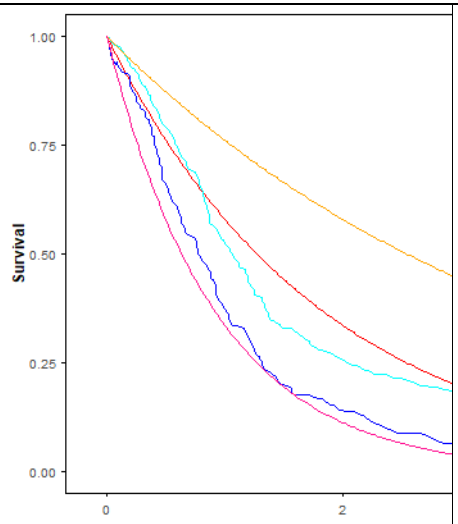
Description of problem	Description of proposed amendment	Justification for amendment	ERG response
4.2.3.3 Health-related quality of life, p.63 The ERG remains uncertain about the approach used by the company to analyse HRQoL data of CheckMate 274. **"**However, responding to question A12, the company states that they did not calculate means and CIs for utility scores at each timepoint because this approach *"relies on the assumption that the missing observations are MCAR"*. The ERG remains uncertain about the approach used by the company to analyse HRQoL data of CheckMate 274.**"**	Complete case analysis was used as there was a lack of insufficient evidence to reject an assumption of MCAR as seen in Appendix L Section 3.5. In addition, Mixed Model for Repeated Measures (MMRM) was conducted which is a more robust method that accounts for missing data.	In response to question A12 the company does not state that CIs and means for utility scores at each timepoint were not calculated. Rather, that "the validity of taking the mean and CIs at each timepoint relies on the assumption that the missing observations are MCAR". While the company does state in response to question A9 that "there was insufficient evidence to reject the assumption of MCAR, with no need to use imputation for sensitivity analyses,…" this implies that we can assume MCAR and hence the company is able to conduct the simple analysis. In addition, MMRM was conducted which seemed to be consistent with the simple analysis of observed means.	The text has been amended to remove the incorrect statement that the CIs and means were not calculated. We may have missed the point being made about data being MCAR. If the MCAR assumption was assumed to hold to use the complete data then it should also hold for the HRQoL analyses. We have added however that the MMRM model produces similar results to the simple analysis

Issue 7 Marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
3.2.1.1 Baseline characteristics of trial participants, p.35 "The median age of participants was [redacted] years (range 30-92; inter-quartile range [redacted]) in the nivolumab group, and [redacted] years (range 42-88; inter-quartile range [redacted]) in the placebo group."	Inter-quartile range values are unpublished data from CheckMate 274 and should be marked AIC	"The median age of participants was [redacted] years (range 30-92; inter-quartile range [redacted]) in the nivolumab group, and [redacted] years (range 42-88; inter-quartile range [redacted]) in the placebo group."	Marking amended as requested
3.2.1.1 Baseline characteristics of trial participants, p.35 "At the time of resection, [redacted]%, [redacted]%, and [redacted]% of all randomised patients had stage pT2, Stage pT3, and Stage pT4a respectively."	This is unpublished data from CheckMate 274 and all values should be marked AIC	"At the time of resection, [redacted]%, [redacted]%, and [redacted]% of all randomised patients had stage pT2, Stage pT3, and Stage pT4a respectively."	Marking amended as requested
3.2.2.2 Other efficacy endpoints, p.39 "[redacted] in all randomised patients (nivolumab median [redacted] months vs placebo [redacted] months, HR [redacted]). PFS2 rates at 6 months were [redacted]% for nivolumab versus [redacted]% for placebo."	PFS2 data is unpublished data from CheckMate 274 and all values should be marked AIC	"[redacted] in all randomised patients (nivolumab median [redacted] months vs placebo [redacted] months, HR [redacted]). PFS2 rates at 6 months were [redacted]% for nivolumab versus [redacted]% for placebo."	Marking amended as requested

3.2.3 Health-related quality of life, p.41 "For both EORTC QLQ-C30 and EQ-5D-3L, the CS reports that [redacted], as seen in Figure 11 and Figure 12 of the CS."	Only the results of the EORTC QLQ-C30 and EQ-5D VAS are in the public domain. Therefore the EQ-5D-3L should be AIC.	"For both EORTC QLQ-C30 and EQ-5D VAS, the CS reports that HRQoL remained stable, with no mean change in score from baseline reaching MID at any timepoint for either nivolumab or placebo, as seen in Figure 10 and Figure 12 of the CS. The mean EQ-5D-3L utility index score [redacted] both arms, as seen in Figure 11 of the CS."	Changed when identified in an earlier point.
3.2.3. Health-related quality of life, Table 22, p.41 "[redacted]"	EQ-5D-3L summary scores for nivolumab and placebo are not in the public domain	Summary scores [redacted]	
3.4 Critique of the company's indirect treatment comparison, p.47 "those patients were eligible for adjuvant cisplatin but actively refused this treatment (N=[redacted], of whom [redacted] were in the nivolumab group and [redacted] in the placebo group)."	This is unpublished data from CheckMate 274 and all values should be marked AIC, as per Appendix J.	"those patients were eligible for adjuvant cisplatin but actively refused this treatment (N=[redacted], of whom [redacted] were in the nivolumab group and [redacted] in the placebo group)."	Marking amended as requested
3.4 Critique of the company's indirect treatment comparison, p.47 "This left [redacted] patients with bladder cancer only ([redacted] on nivolumab and [redacted] on placebo)."	This is unpublished data from CheckMate 274 and all values should be marked AIC, as per Appendix J.	This left [redacted] patients with bladder cancer only ([redacted] on nivolumab and [redacted] on placebo).	Marking amended as requested

4.2.3.2.1 Disease-free survival events, p.57 "The ERG's understanding is that this model estimated the proportions of patients in the high-risk group to be [redacted]% in the nivolumab arm and [redacted]% in the placebo arm (CS Appendix K Figure 9, rho: [redacted]; Figure 10, rho: [redacted])."	This is unpublished data, the values should be marked as AIC	"The ERG's understanding is that this model estimated the proportions of patients in the high-risk group to be [redacted]% in the nivolumab arm and [redacted]% in the placebo arm (CS Appendix K Figure 9, rho: [redacted]; Figure 10, rho: [redacted])."	Marking amended as requested
4.2.3 Evidence used to inform the company's model parameters, p.60 "Out of [redacted] DFS events in nivolumab arm, [redacted] were deaths ([redacted]%), and out of [redacted] events in the placebo arm, [redacted] deaths were observed ([redacted]%)."	This is unpublished data from CheckMate 274, AIC marking is required.	"Out of [redacted] DFS events in nivolumab arm, [redacted] were deaths ([redacted]%), and out of [redacted] events in the placebo arm, [redacted] deaths were observed ([redacted]%)."	Marking amended as requested
4.2.3 Evidence used to inform the company's model, p.62 parameters "relative dose intensity (RDI) of [redacted]"	AIC marking is required instead of CIC, as used in the CS. Data derived from unpublished source (CheckMate 247)	"relative dose intensity (RDI) of [redacted]"	Marking amended as requested

4.2.3 Evidence used to inform the company's model parameters, p.62 Figure 9	AIC marking is not required as figure is based on published data. The marking was incorrect in the CS		AIC marking removed
4.2.3.3. Health-related quality of life, p.63, Table 30 Incorrect marking for the [redacted] Disease-free (both arms) utility used in the model	AIC marking is required. Information is AIC, being adjusted for the age and sex of the patients in the CheckMate 247 clinical trial	**Utility values used in the model** [redacted]*	Marking amended as requested
4.2.3 Evidence used to inform the company's model parameters, p.64 "This resulted in a QALY loss of [redacted] for nivolumab-treated patients versus [redacted] for placebo-treated patients."	AIC marking is required. Data derived from unpublished source (CheckMate 247)	"This resulted in a QALY loss of [redacted] for nivolumab-treated patients versus [redacted] for placebo-treated patients."	Marking amended as requested

4.2.3.4.5 Costs associated with the management of adverse events, p.67 "These were estimated to be [redacted] for nivolumab-treated patients and [redacted] for placebo- treated patients."	AIC marking is required, instead of CIC. Data derived from unpublished source (CheckMate 247)	"These were estimated to be £[redacted] for nivolumab-treated patients and £[redacted] for placebo- treated patients."	Marking changed to AIC
4.2.6 Company's cost-effectiveness results, p.71 Figure 10	Figure 10 based on CEM and is commercial in confidence, therefore CIC marking is required.	[redacted]	Marking amended as requested
4.2.8 Company's PSA, p. 71 "the probability that nivolumab generates more net benefit than BSC is [redacted]%"	Data is commercial in confidence, therefore CIC marking is required.	"the probability that nivolumab generates more net benefit than BSC is [redacted]%"	Marking amended as requested
4.3.3 Main issues identified within the critical appraisal, p.79 Figure 13	AIC marking (highlight and underline) is required, as presented in the ERG clarification response. Data derived from unpublished source (CheckMate 247)	[redacted]	Marking amended as requested
4.3.3 Main issues identified within the critical appraisal, p.80 Figure 14	AIC marking (highlight and underline) is required, as presented in the ERG clarification response. Data derived from unpublished source (CheckMate 247).	[redacted]	Marking amended as requested

4.3.3 Main issues identified within the critical appraisal undertaken by the ERG, p.80 "However, the company did not provide evidence that the data is mature enough to fit semi-parametric models especially with cut points (e.g. the [redacted] months in the nivolumab arm preferred model) significantly reducing the amount of data to which the parametric model was fitted."	This is unpublished data, the cut time of the curve should be marked AIC.	"However, the company did not provide evidence that the data is mature enough to fit semi-parametric models especially with cut points (e.g. the [redacted] months in the nivolumab arm preferred model) significantly reducing the amount of data to which the parametric model was fitted."	Marking amended as requested
4.3.3 Main issues identified within the critical appraisal, p.81 Figure 15	AIC marking is required. Data derived from unpublished source (CheckMate 247)	[redacted]	Marking amended as requested
4.3.3 Main issues identified within the critical appraisal, p.82 "the observed proportion of deaths among DFS events were different between the trial arms: [redacted]% versus [redacted]% for nivolumab and placebo respectively"	AIC marking is required. Data derived from unpublished source (CheckMate 247)	"the observed proportion of deaths among DFS events were different between the trial arms: [redacted]% versus [redacted]% for nivolumab and placebo respectively"	Marking amended as requested
4.3.3 Main issues identified within the critical appraisal, p.82 "the population age was set to 78.7 years rather than [redacted] years. The 78.7 years of age value, however, represented an increase of [redacted]% rather than an informed value."	AIC marking is required. Data derived from unpublished source (CheckMate 247)	"the population age was set to 78.7 years rather than [redacted] years. The 78.7 years of age value, however, represented an increase of [redacted]% rather than an informed value."	Marking amended as requested

4.4.2 ERG's exploratory analyses - methods, p.86 "that [redacted]% of DFS events were deaths for nivolumab treated patients and [redacted]% of DFS events were deaths for BSC"	AIC marking is required. Data derived from unpublished source (CheckMate 247)	"that [redacted]% of DFS events were deaths for nivolumab treated patients and [redacted]% of DFS events were deaths for BSC"	Marking amended as requested

References

1. Soria F, Moschini M, Wirth GJ, Gust KM, Klatte T, Briganti A, et al. Characterization of Late Recurrence After Radical Cystectomy in a Large Multicenter Cohort of Bladder Cancer Patients. Urology. 2017;106:119-24.
2. Hautmann RE, de Petriconi RC, Pfeiffer C, Volkmer BG. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol. 2012;61(5):1039-47.
3. Bajorin DF, Witjes JA, Gschwend J, Schenker M, Valderrama BP, Tomita Y, et al. First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab versus placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma. Journal of Clinical Oncology. 2021;39(6_suppl).
4. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. New England Journal of Medicine. 2021;384(22):2102-14.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 17 January 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Bristol-Myers Squibb Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Executive Summary

Ahead of addressing the key issues presented in the Technical Engagement response, there are two updates to the available data to be presented:

1. Updated database lock (DBL) from CheckMate 274 (11 months minimum FU)
2. Updated agreed Patient Access Scheme (PAS) for nivolumab of [redacted].

For clarity, all results and argumentation presented in this response apply to the updated database lock and PAS. Hence, the impact of these updates is briefly described below and in the appendices.

Updated clinical outcomes from CheckMate 274

As previously discussed, outcomes from an updated database lock (DBL) from CheckMate 274 (11 months minimum FU) have become available. [redacted]

These data support sustained benefits for nivolumab versus placebo (i.e. best supportive care [BSC] – routine surveillance) during CheckMate 274. Data from the updated database lock are presented in the updated survival analysis (Appendix 1) and updated indirect treatment comparison (ITC) analysis (Appendix 2).

Updated agreed PAS for nivolumab

The agreed PAS for nivolumab has been updated from [redacted]% to [redacted]% impacting on vial costs as follows:

- Nivolumab costs without PAS[2]
    - £2,633.00 per 240 mg (24 mL) vial;

  - £1,097.00 per 100 mg (10 mL) vial;
  - £439.00 per 40 mg (4 mL) vial.

- Nivolumab costs with PAS
  - [redacted] per 240 mg (24 mL) vial;
  - [redacted] per 100 mg (10 mL) vial;
  - [redacted] per 40 mg (4 mL) vial.

This updated PAS has been applied within this response. For reference, the base case from the initial submission – post-ERG clarification questions using the updated PAS is presented in Table 1 alongside the company's preferred base case post-technical engagement. Please note that the preferred base case post-technical engagement includes data from the updated DBL (11 months minimum FU), the updated PAS and updated survival modelling to include a fully parametric Gen F approach to model DFS, amongst other changes. A full set of updates to the base case are listed in the cost-effectiveness appendix (Appendix 3).

Table 1. Cost-effectiveness results

	Company submission (NICE submission post clarification questions August 2020 DBL with updated PAS)	**Post TE base case** (updated DBL [11 months minimum FU], updated PAS and updated model assumptions)
ICER for nivolumab versus BSC	£31,534/QALY	£27,030/QALY
BSC: best supportive care; DBL: database lock; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year		

As outlined in company submission, nivolumab is the first and only immunotherapy to demonstrate superior efficacy to placebo in the adjuvant setting after radical surgery for muscle-invasive urothelial carcinoma (MIUC). In addition, nivolumab does not demonstrate a negative impact on health-related quality of life. The introduction of nivolumab for adjuvant treatment of high-risk MIUC on the NHS would represent a significant advance in the management of these patients, and would also ameliorate the psychological burden and anxiety resulting from waiting for potential recurrence of disseminated disease. The clinical evidence, as presented in the initial company submission and in the associated appendices for the updated DBL (11 months minimum FU), indicates that nivolumab extends DFS and may represent a new standard of care in the adjuvant treatment setting for this population.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: **Exclusion of cisplatin-based adjuvant chemotherapy as a comparator**	No	**Cisplatin is not a relevant comparator of interest for nivolumab in this indication.** The NICE scope for the submission included adjuvant chemotherapy (e.g. cisplatin-based regimens), for the proportion of patients who are eligible for cisplatin after surgery, or best supportive care (monitoring and further treatment at recurrence) as comparators. The company excluded cisplatin-based adjuvant chemotherapy from the analysis on the basis of clinical relevance for the decision problem and the lack of any robust clinical evidence for comparison, which translated into a poor robustness of the evidence to inform the ITC, meaning the ITC was unsuitable for HTA decision making. *Pivotal trial* The pivotal CheckMate 274 trial included patients who were candidates for cisplatin-based adjuvant chemotherapy, provided that these patients had a thoroughly documented reason for patient refusal of this treatment despite being informed by the investigator about the treatment options.[3] Patients who were eligible and willing to receive adjuvant cisplatin based adjuvant chemotherapy were not eligible per study inclusion

		criteria.[3] Cisplatin-eligible patients may not have been willing to be randomized to a placebo arm.[3] As detailed in the study protocol, in order to limit heterogeneity of the population and maintain a placebo comparison, patients who were eligible for cisplatin in the adjuvant setting were excluded unless they refused adjuvant chemotherapy.[3] Therefore, there is no evidence available from CheckMate 274 for patients who would have actually received chemotherapy in a non-clinical trial setting. *Clinical relevance* The ERG stated that "data from John et al.[4] indicate that only 37% of patients in the UK with muscle invasive bladder cancer (MIBC) receive neoadjuvant chemotherapy with the remainder potentially eligible for adjuvant chemotherapy"[5(p.77)]. However, this assumption does not consider that a large proportion of the remaining patients would be clinically cisplatin-ineligible, due to comorbidities or poor performance status, or that a proportion of patients who may be clinically eligible will actively choose not to receive chemotherapy, such as those enrolled in CheckMate 274. Thus, this assumption grossly overestimates the proportion of patients who would receive adjuvant chemotherapy as only a minority of patients actually receive adjuvant cisplatin-chemotherapy. In fact, clinical experts suggest that the majority (around two thirds) of cisplatin-eligible patients in the UK would receive neoadjuvant cisplatin and therefore are not eligible for further cisplatin as adjuvant therapy.[6] In addition, the proportion of cisplatin-eligible patients in the adjuvant setting differs across centres in the UK, with proportions of less than 5% and between 30 and 40% stated by UK clinical experts,[7] both of which are lower than the figure suggested by the ERG. Thus, the true proportion is uncertain, as no definitive data is available to confirm. UK clinical experts also stated that a proportion of cisplatin-eligible patients will actively refuse adjuvant cisplatin therapy, also discussed in the CS. Reasons for refusal include concerns about treatment toxicity,

		chemotherapy side effects, and the uncertainty about the evidence of the benefit of cisplatin in the adjuvant setting.[7,8] Thus, though the ERG states that the remainder of patients in the UK with MIBC (63%) may be eligible for adjuvant cisplatin chemotherapy, a smaller proportion of patients that are eligible actually receive this therapy. Therefore, this assumption presented by the ERG is likely to overestimate the proportion of patients who receive adjuvant chemotherapy in the UK. BMS reinforce that there is no evidence from CheckMate 274 for patients who are clinically eligible for adjuvant cisplatin whom would have actually received chemotherapy as all patients who met the trial inclusion criteria and were clinically eligible for adjuvant cisplatin had actively refused therapy for inclusion in the trial, despite being informed by the investigator about treatment options. Therefore, these cisplatin-eligible patients would not have received chemotherapy in the clinical setting or on the NHS. Overall, cisplatin-based chemotherapy is therefore considered of limited relevance for this decision problem and is not a relevant comparator for the base case analysis. *Lack of consensus in European international guidelines* Additionally, there is no clear consensus on the effectiveness of cisplatin as suggested by latest guidelines from the European Association of Urology (EAU) published in 2021 on muscle invasive and metastatic bladder cancer: "adjuvant chemotherapy after radical cystectomy (RC) for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate."[8] Further to this, the EAU guidelines state "there is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy. An individual patient data meta-analysis of survival data from six RCTs of adjuvant chemotherapy included 491 patients (unpublished data from Otto et al., were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods

		and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases). In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [485], and one trial used cisplatin monotherapy. The data were not convincing to give an unequivocal recommendation for the use of adjuvant chemotherapy."[8] As indicated above, a comparison versus adjuvant chemotherapy, i.e. cisplatin, is not relevant to this clinical setting, as supported by the EAU guidelines which do not report "unequivocal recommendation for the use of adjuvant chemotherapy."[8] The population of interest in the submission also includes patients with upper tract urothelial cancer (UTUC), representing a small proportion of all UC patients (5-10%),[9,10] for which the EAU recommends post-operative systemic platinum-based chemotherapy.[10] *ITC considerations* Despite the issues around clinical relevance and substantial limitations in the evidence base, as presented in the CS, an ITC comparing nivolumab and cisplatin-based adjuvant therapy was undertaken using the updated DBL (11 months minimum FU) for completeness. As further detailed in Section B.2.9 of the CS and the updated ITC report (Appendix 2), these limitations include, but are not limited to: • There was considerable heterogeneity between studies included in the ITC, including a number of key variables such as patient population (tumour stage), control regimen and study design. This heterogeneity impacts the ability to reliably draw conclusions from the results to inform HTA decision making for this treatment comparison.

		• Limitations in the evidence base: The CheckMate 274 study assessed patients who were ineligible for (due to prior neoadjuvant cisplatin-based therapy or clinically defined ineligibility criteria) or actively refusing cisplatin-based adjuvant chemotherapy. Of the patients enrolled in CheckMate 274 (N=709), 68% (N=479) would not have been clinically eligible to receive chemotherapy, thus only those who were clinically eligible, but refused, could be used in this comparison (Group C, N=[redacted]; n=[redacted] who received nivolumab and n=[redacted] who received placebo) since they may be clinically equivalent to those who may actually receive cisplatin-based adjuvant therapy in a clinical setting. Of note, these patients would not have received cisplatin-based chemotherapy in the clinical setting due to their active refusal. It should be noted that CheckMate 274 was neither stratified nor powered for this subgroup and further, UTUC patients were removed leading to even further segmenting of the trial data, and therefore these results should be interpreted with caution. • The analysis is based on very small sample sizes from the included studies (the number of patients in each treatment arm ranged from 47-143). • As noted above, the EAU have highlighted important limitations in the evidence base regarding the use of cisplatin in this treatment setting, stating "All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases)."[8] Based on these arguments, BMS do not believe the ITC is scientifically robust or appropriate for this assessment considering the limited evidence availability, as confirmed by clinicians,[6] and the irrelevance for the UK treatment setting. As a result, the cost-effectiveness results for this comparison versus adjuvant chemotherapy have not been provided as they are not considered relevant to the indication under review, and the available data do not facilitate robust indirect comparisons, which would be necessary to support any such decision making in this clinical setting. *ITC results*

		As shown in Appendix 2, using the latest data from the updated DBL (11 months minimum FU), the updated hazard ratio (HR) of nivolumab versus placebo from group C (excluding UTUC patients from both arms) was [redacted]) and the updated HR of nivolumab from group C (UTUC patients removed) versus adjuvant chemotherapy from the two gemcitabine studies and Sternberg pooled was [redacted]. However, the important limitations in the evidence base meant that the results were subject to a high degree of uncertainty and thus are not considered suitable to inform decision-making. **Therefore, the ITC for nivolumab compared to cisplatin-based adjuvant therapy is subject to major uncertainty, lacks robustness, is exploratory in nature and is insufficient to be used to inform HTA decision making**.
Issue 2: **The use of semi-parametric models to fit to disease-free survival (DFS) Kaplan-Meier estimates**	Yes – the survival analysis has been updated using the CheckMate 274 updated DBL (11 months minimum FU), described in Appendix 1. The cost effectiveness analysis for	**Based on updated DBL analysis, the company has adopted a fully parametric generalised F distribution in both treatment arms (as further described in Appendix 1)** *Updated database lock data* Since the original company submission, an updated confidential discount (see executive summary), and updated DBL have been released, see Appendix 1. Survival analysis has been undertaken for the updated DBL (11 months minimum FU). In addition, other inputs within the model have been updated to reflect the updated DBL including: • Time on treatment data • Rate of death upon recurrence The survival analysis appendix (Appendix 1) using the updated DBL (11 months minimum FU) includes technical description of the methods used, and rationale for the selected approach. The issue response herein focuses on the outcomes of that report in the context of the ERG issue/question.

	the updated base case includes both the updated survival analysis and further inputs updated from the updated DBL.	*Use of fully parametric modelling vs semi-parametric modelling* The ERG provided three reasons regarding their preference for fully parametric over semi-parametric modelling. These included a preference to use smoothed curves as opposed to 'over-fitting' to protocol-induced steps in the data, the limited relevance of implausible long term DFS estimates with certain curves due to application of all-cause mortality from five years, and the perceived lack of maturity to suggest specific 'cut-points' in semi-parametric modelling. Based on analysis of the updated DBL, the assessment of fully parametric curves fit to the more mature data, and ERG preference, the company proceeds with a fully parametric approach using a best fitting generalised F model. *Statistical fit: AIC & BIC* A fully parametric Gompertz approach was the ERG's choice for survival modelling for the original DBL. One of the key factors in the ERG choosing the Gompertz approach was that it was the closest statistical fit to the Kaplan-Meier (KM) data, as indicated by having the lowest AIC and BIC values of the explored fully parametric options (which notably did not include generalised F). BMS reiterate that the Gompertz model was inappropriate to capture the complex hazard pattern observed in the trial data. Statistical fit of curves is determined by selecting curves with the lowest Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, but also through examination of the differences of AIC and BIC with the best-fitting curve. (AIC differences described by Burnham and Anderson, 2004;[11] BIC differences reported by Raftery, 1995)[12]. In both cases, a difference of < 2 in AIC/BIC denotes weak evidence of a difference between two curves, and a difference of > 10 denotes strong evidence of a difference between two curves (Figure 1).

AIC difference	Evidence for a specific model	BIC difference	Evidence of difference to alternative model
≤ 2	Substantial support	0-2	Weak
2 < Δ < 4		2-6	Positive
4 ≤ Δ ≤ 7	Considerably less support	6-10	Strong
7 < Δ ≤ 10		>10	Very strong
Δ > 10	Essentially no support		

Figure 1. Definition of differences in AIC and BIC criteria compared to the best fitting model

Sources: Burnham and Anderson (2004)[11], Raftery (1995)[12]

Using the updated DBL data, seven fully parametric functional forms were fitted to the nivolumab and placebo arms, including the generalised F function, which has increased flexibility versus the standard parametric models. These are further described in the Appendix 1, along with the rationale for considering the generalised F function. The statistical fit of seven fully parametric functional forms have been established.

For the updated DBL, the generalised F distribution has the lowest AIC and BIC in both arms (Table 2 and Table 3). For the nivolumab arm, generalised F has the lowest AIC and BIC, with an increase in AIC of [redacted] and BIC of [redacted] for the second-lowest fitting distribution (log-normal). For the placebo arm, second lowest Gompertz has an increase of [redacted] for AIC and [redacted] for BIC compared to the best fitting distribution (generalized F), which is "essentially no support" for the model in terms of AIC[11] and "very strong" evidence of difference in the model per BIC versus generalized F[12].).

Though the Gompertz [the ERG's previous preference] is the second-best fitting curve per AIC and BIC for placebo, and the third best-fitting curve for nivolumab, it is important to reiterate the difference in AIC points versus generalised F ([redacted] for the placebo arm, [redacted] for the nivolumab arm) means there is "essentially no support" for evidence for the Gompertz on this data cut as based on AIC. Log normal was the second best fitting model for the nivolumab arm but also had large differences in AIC versus Generalized F as previously described. Further, it is worth noting that lognormal had AIC/BIC differences of < 3 compared to the Gompertz curve, indicating no significant differences between the two curves.[11]

Overall, evaluation of the AIC and BIC indicate that the generalised F model has substantially better fit than the next best-fitting model in both arms.

Table 2. Nivolumab DFS: AIC and BIC values for parametric models based on the updated DBL (11 months minimum FU)

Extrapolation model	DFS			
	AIC		BIC	
	Value	Difference to base case	Value	Difference to base case
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised F [base case]	[redacted]		[redacted]	

Table 3. Placebo DFS: AIC and BIC values for parametric models based on the updated DBL (11 months minimum FU)

Extrapolation model	DFS			
	AIC		BIC	
	Value	Difference to base case	Value	Difference to base case
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised F [base case]	[redacted]		[redacted]	

In summary, evaluating fully parametric curves using AIC and BIC, there is very strong evidence that generalised F is the best fit to the available trial data. Visual fit of the seven fully parametric functional forms compared to KM data are presented below (*Figure 2 and *Figure 3). In addition, there is strong evidence that Gompertz and all other models are poorly fitting for the placebo arm per BIC),[12] with essentially no support for fit for Gompertz or other models in terms of AIC for either treatment arm[11] (
Table 2 and Table 3).

[redacted]**Figure 2. Investigator-assessed DFS for nivolumab: Standard statistical models overlaid upon Kaplan-Meier data (short-term fit to 5 years).**

[redacted]**Figure 3. Investigator-assessed DFS for placebo: Standard statistical models overlaid upon Kaplan-Meier (short-term fit to 5 years)**

		Hazard profiles: expectations A further reason the company did not utilise a fully parametric Gompertz modelling approach for the original DBL was in the shape of the hazard profiles. The updated DBL further indicates that the shape of the Gompertz placebo hazard profile remains an issue. Expectations for hazard profiles are explored in this section. Clinical expert feedback to the company stated patients are not followed-up or unlikely to recur after 5 years disease-free, instead being subject to general population mortality only.[7,13] This should be apparent regardless of treatment (nivolumab or placebo). Within the model, after 5 years disease-free in either arm, patients are assumed to no longer recur or have disease-related deaths and transition to long-term all-cause mortality. Clinical advice to the company further stated that the shape and hazards of both the placebo arm and the nivolumab arm should be expected broadly align to that of Sternberg et al., i.e. reaching general population lifetables at 5 years and not before. This evidence all points to a 5 year timepoint for curves to reach general population lifetables in both arms. A timepoint of 5 years or later for reaching lifetables is also reflected in data from the literature, with the hazards from the 'deferred treatment' arm from Sternberg et al. (with a population similar though not exactly aligned to the CheckMate 274 trial) converging towards lifetables over time (Figure 4). It should be noted there are limitations in evaluating the smoothed hazards from published literature (lack of individual patient data, limited data published). Nevertheless, the trends remain relevant.

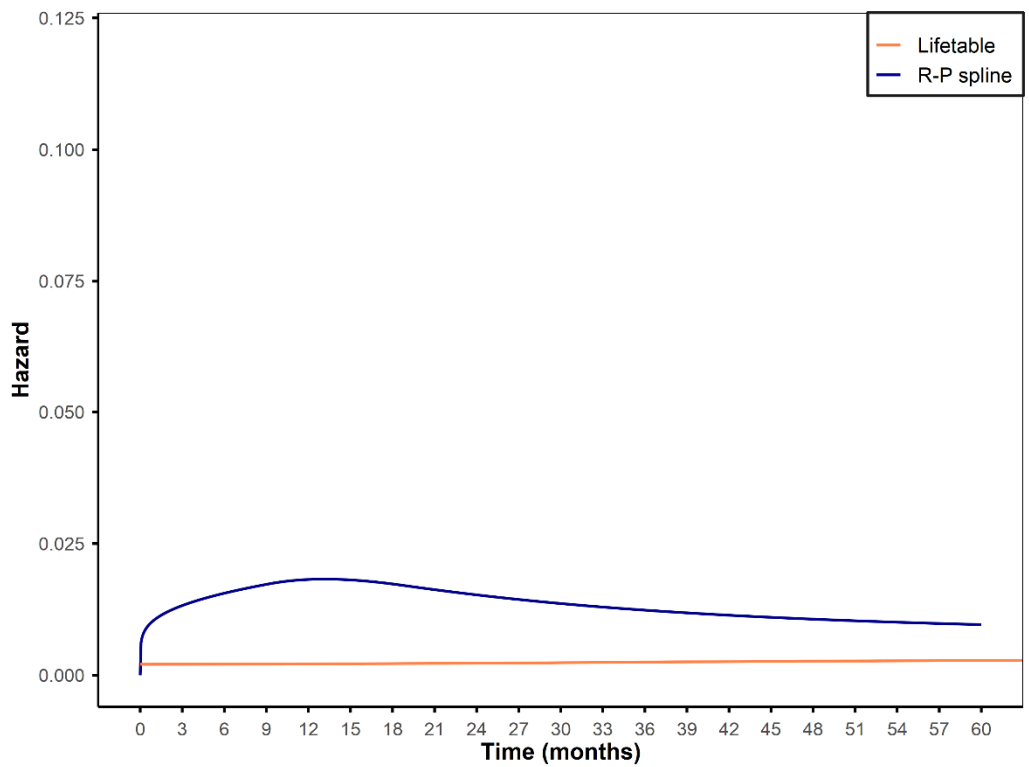


Figure 4. Smoothed hazard estimates of PFS Sternberg et al deferred arm against lifetable hazard. (R-P: Royston Palmer). R-P spline represent Sternberg et al. deferred arm PFS

Hazard profiles: updated DBL

Utilising the updated DBL, the Gompertz model does not sufficiently capture the initial spike and decrease in hazards over the first 12 months (approximately) in both the nivolumab and placebo arms (*Figure 5). The data from CheckMate 274 indicates an increase and subsequent decrease in hazards over the first 9 months, and

		the Gompertz model is not flexible enough to capture this change in hazard profile. Conversely, the generalised F model can capture this initial increase and subsequent decrease due to its increased flexibility. Additionally, hazards for placebo using a Gompertz model reach the general population level by approximately 42 months (*Figure 5). This is not replicated by the generalised F hazard profile in the placebo arm, nor Gompertz or generalised F in the nivolumab arm (*Figure 5). This 42 months point for the Gompertz model is in contrast to the clinical advice to the company and wider literature,[7,13,14] which indicates a 5-year (60 month) timepoint. In the Gompertz model for the placebo arm, from approximately 42 to 60 months, hazards drop below that of the general population (i.e. less risk of death than the general population). In this case, between 42 and 60 months, patients in the placebo arm are effectively 'better-off' than the general population. It is not feasible that this would occur in clinical practice. In addition, this feature was not replicated in the nivolumab Gompertz or generalised F hazard profile, nor the placebo generalised F profile, where in all cases the general population level is only reached at approximately 5 years, and hazards never fall below general population lifetables (*Figure 5). As previously described within the 'Hazard profiles - expectations' section, clinical advice to the company that patients have extremely low risks of recurrence after 5 years disease-free; and expectations of a similar hazard profile shape in both arms. Additionally, data from the wider literature (Sternberg et al., deferred treatment arm) indicates that hazards would not be expected to cross lifetables before 5 years (Figure 4). In contrast to the Gompertz model, the generalised F model hazards approach general population mortality from around 5 years in both arms, consistent with clinical advice and wider literature.

[redacted]Figure 5. Investigator-assessed DFS for nivolumab (left) and placebo (right) (CheckMate 274, updated DBL [11 months minimum FU]): Smoothed hazard function estimates for trial data (R-P spline), Gompertz, and generalised F model.

In summary, the hazard profiles for generalised F in the nivolumab and placebo arms are the most appropriate to capture trial hazards, clinical expert opinion, and wider literature in similar populations.

Validation of DFS generalised F survival estimates

DFS estimates may be validated against published literature, and against clinician estimates.[7] To achieve this, an expert elicitation exercise was undertaken with two clinicians. Two clinicians estimated DFS at 5 years for the KM curves from CheckMate 274, taking into account the study population and available CheckMate 274 KM data from the updated DBL (11 month minimum FU), as opposed to any extrapolated curves themselves. The estimates from the two clinicians can be used to determine a range for 5-year DFS.

Considering the DFS estimates for the KM data for the placebo arm of CheckMate 274, the generalised F functional form aligns closely with the trial data, data from Sternberg et al.[15], and is within 5-year estimates from clinicians (Table 4). Conversely, the Gompertz in the placebo arm exceeds the upper range of estimates (clinician estimates and data from Sternberg et al. [15]) both at 5 years and at 10 years.

Table 4. DFS estimates for the placebo arm

	1 year	2 year	3 year	5 year	10 year
Placebo arm					
CheckMate 274	46.9%	38.7%	34.8%	-	-
Sternberg[15]	50.1%	37.1%	34.5%	31.8%	25.7%
Generalised F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clinician estimates	-	-	-	[redacted]	-
Nivolumab arm					
CheckMate 274	63.5%	48.2%	44.2%		
Generalised F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinician estimates	-	-	-	[redacted]	-

Note: generalized F and Gompertz data in this table incorporate long-term disease-free status (i.e. general population mortality) from 5 years.

Clinicians were not provided any extrapolated/fitted curves to determine their estimates.

In summary, DFS estimates generated by generalised F functions validate well with both literature data and clinician estimates for both placebo and nivolumab arms, whilst the Gompertz curve exceeds clinical expert and literature expectations at 5 years and 10 years.

Impact on cost-effectiveness

Finally, the impact of utilising the updated DBL inputs including the generalised F approach for DFS, on cost-effectiveness outcomes has been established for the updated DBL, as shown in Table 5.

Table 5. Results using generalised F and updated DBL inputs

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,756

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.

		Note: Analysis includes updated DBL data (time on treatment, death on recurrence), using Janssen age-dependent utility data (unchanged from original company submission), updated PAS, generalised F base case Based on the clinical advice to the company, the underlying shape of the hazards profile in the longer term (~3 years onwards) the nivolumab and placebo arms are expected to align with that of the deferred chemotherapy arm within Sternberg et al.[15] Given this, a scenario has been undertaken utilising the hazards from Sternberg et al. to extrapolate trial data up to 5 years; as opposed to any standard survival modelling approaches. This scenario is explored in Appendix 3. In brief, the total and incremental life years align between the two models, with [redacted] life years for nivolumab in the Sternberg-adjusted scenario, versus [redacted] in Table 3; and [redacted] life years for BSC in the Sternberg-adjusted scenario, versus [redacted] in Table 5. *Summary and conclusion* In conclusion, a fully parametric generalised F distribution has the best statistical fit to the data for the updated DBL, with a substantial difference to the next best fitting fully parametric functional forms. In addition, the generalised F profiles (in both arms) have hazard profiles which validate well with clinical expert opinion, the wider literature and the available trial. As such, it is the most appropriate curve to use in the economic modelling. **Based on updated DBL analysis, the company has adopted a fully parametric generalised F distribution in both treatment arms.**
Issue 3: **Use of utility data from Janssen et al.**	No	**The company has updated their submission to use age-dependent utility data from Ara and Brazier.** The original company submission used utility data for the general population from Janssen et al.,[16] as this data was published more recently than the study by Ara and Brazier.[17] However, the ERG highlighted that despite being published more recently, Janssen et al.[16] uses older utility data (collected in 1998-2008) than the Ara

and Brazier study.[17] Therefore, the company has adopted the ERG's preferred approach: to use utility values from Ara and Brazier.

The difference in general population utility values between the two studies makes minimal difference to cost-effectiveness results (Table 6). The increased granularity of health state utility values in Ara and Brazier mean quality-adjusted life year (QALY) gain is slightly reduced compared to using Janssen et al data ([redacted] vs [redacted]), which means the incremental cost-effectiveness ratio (ICER) for the base case (using Ara and Brazier values) is slightly higher. For completeness and face validity, the company will adopt the Ara and Brazier values as the base case, in addition to the other changes incorporated in the cost-effectiveness analysis as described in Issue 2 above.

Table 6. Base case results (using Ara and Brazier) and scenario analysis using Janssen et al.[16] utilities

Technologies	Total costs (£)	Total Lys	Total QALYs	Inc. costs (£)	Inc. Lys	Inc. QALYs	ICER (£/QALY)
Base case*: using general population utility values from Ara and Brazier[17] (and updated DBL inputs)							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,030
Scenario: using general population utility values from Janssen et al.[16]							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,756

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; Lys: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.

*Base case includes: updated DBL data (time on treatment, death on recurrence), generalised F base case, Ara and Brazier age-dependent utility values, updated PAS

Issue 4: **The average age of patients in the UK is likely to be older than those recruited to CheckMate 274**	No	**The mean age derived from CheckMate 274 is the most relevant available age for the population of interest.** *The CheckMate 274 trial age is the most appropriate available age* The mean age derived from the CheckMate 274 trial is used in the model as it is reflective of the population that nivolumab is indicated and licensed for: MIUC patients at high risk of recurrence after undergoing radical resection of invasive urothelial carcinoma. MIUC includes both cancer that originated in the bladder or in the upper urinary tract, both of which were included in the CheckMate 274 trial. The trial also covered patients who received neoadjuvant therapy, whereas the sources cited by ERG are more heterogenous in terms of patient population and previous treatment. UK clinicians agree there is no major discordance between the mean age for MIUC patients in the CheckMate 274 trial versus UK clinical practice.[7] There are considerations to be made in terms of baseline characteristics of patients and how applicable they are to the population of interest. For example, expert clinicians suggest that the mean age of all bladder cancer patients is higher than the age of patients undergoing RC. The mean age of all bladder cancer patients may be approximately 75 years old,[7] but patients who are older are likely to go down a 'bladder sparing' route, and as such, patients who have undergone a RC will be younger. CheckMate 274 only includes patients post-RC, who are therefore likely to be younger than the total population of bladder cancer patients. *Alternative sources for age* A summary of main details for sources of age is presented in Table 7. **Table 7. Summary of studies reporting age in bladder cancer patients**

Study	Patients included and % MIUC	Age reported	Further notes

		CheckMate 274	High risk MIUC post-resection (100%); either with or without neoadjuvant treatment	Mean: 65.6 Median: 67.0	
		Pang et al.[18] [ERG source]	Mixed population including MIUC (37.6%) undergoing cystectomy	Median: 70 Interquartile range: 64 to 76 For entire heterogenous population	No description of neoadjuvant treatment, or risk of recurrence for MIUC
		Jeffries et al.[19] [ERG source]	Mixed population including MIUC (46%) undergoing cystectomy	Median: 69 for entire heterogenous population	No description of neoadjuvant treatment, or high risk of recurrence. Includes patients with cancer originating outside the urinary tract
		Analysis Radical Cystectomies[20] [ERG source]	Mixed population including MIUC (43.8%) undergoing cystectomy	Median: 69-70 for entire heterogenous population	No description of neoadjuvant treatment, or high risk of recurrence. Includes patients with cancer originating outside the urinary tract
		John et al.[4] [Alternative source]	MIUC patients only, undergoing cystectomy	Median: 67 with neoadjuvant chemotherapy Median: 70 without neoadjuvant chemotherapy	No description of risk of recurrence

Alternative sources of age suggested by the ERG

The study by Pang et al.[18] presents results of a heterogeneous population that is not analogous to the CheckMate 274 trial study as it includes a mixed patient population comprising patients undergoing RC for high-risk non–muscle-invasive bladder cancer (HR-NMIBC) and patients with MIUC. A total of 33% of patients in the Pang et al. study were HR-NMIBC patients, and 37.6% were MIUC patients. The patients are not exclusively at high-risk of recurrence. The CheckMate 274 trial includes only MIUC patients at a high-risk of

		recurrence. Since the population in Pang et al. does not align with that of the CheckMate 274 trial[7] and since it did not provide an age estimate for MIUC patients only, it is unreasonable to use the median age from the Pang study of 70 (interquartile range: 64-76) to extrapolate for the MIUC population in the model. The study by Jefferies at al.[19] also presents results for a heterogenous population that is not aligned to that included in the CheckMate 274 trial.. The population in Jeffries et al. includes a mixed patient cohort, where only 46% of the cohort are undergoing a RC for MIUC, without a distinction for high-risk of recurrence, as well as cancer cases originated out of the urinary tract. Additionally, the age estimate (median 69 years) is based on a combination of patients including cancer originated out of the urinary tract. Finally, it does not present the baseline characteristics data for each cancer type. In the Analyses of Radical Cystectomies performed between January 1st and December 31st 2019,[20] a similar proportion of patients with MIUC (43.8%) was reported to the Jefferies study.[19] Again, the median age reported of 69-70 (min 27; max 100) was indicative of the whole patient population, including patients with cancers that originated outside of the urothelial tract. ERG sources are heterogenous populations, including MIUC with other populations such as NMIBC, or patients with cancer originating outside urinary tract. None of the sources suggested by the ERG provide age for MIUC patients only, and therefore it is not possible to leverage these studies to evaluate an MIUC cohort only. The population of interest is MIUC only. Therefore none of the ERG studies are aligned to the indicated population for which this submission is based. A final note should be made that none of the ERG studies distinguish patients by those who received neoadjuvant chemotherapy. Only MIUC patients at high risk of recurrence were included within the CheckMate 274 trial, some of which had received neoadjuvant chemotherapy. Therefore, the baseline characteristics of the patients from the trial are deemed more representative of the indicated population than any alternative sources suggested by the ERG.

		Alternative source for age: John et al.[4] A total of 44.3% of patients in the CheckMate 274 trial received neoadjuvant chemotherapy (based on CSR data). Data from John et al.[4] reports a median age of 67 years for MIUC exclusive patients who received neoadjuvant chemotherapy and RC. The median age of patients that did not receive neoadjuvant chemotherapy prior to RC was 70. This suggests that patients receiving neoadjuvant chemotherapy could be younger than those who do not, therefore neoadjuvant chemotherapy use needs to be considered when estimating the age. While this cohort is not indicative of patients at high risk of recurrence, it does include MIUC exclusive patients and provides estimates of median age between 67 and 70 years old. Based on these two median ages from John et al.[4] (67 with neoadjuvant chemotherapy, 70 without neoadjuvant chemotherapy), and CheckMate 274 proportions of patients who received neoadjuvant chemotherapy ([redacted]% received, [redacted]% did not receive), a median age representing CheckMate 274 patients can be calculated: [redacted] years (noting that this is a median value, and equivalent mean value is unknown). *Conclusion and impact on cost-effectiveness* In conclusion, the age from CheckMate 274 is most appropriate for this decision problem. Use of an older population from an alternative source based on a heterogenous population that is not aligned with the decision problem under consideration is not reasonable as it would introduce bias and uncertainty in the analysis. Moreover, there would be a discrepancy as the model uses the mean age, whereas the age estimate suggested by ERG is based on median and none of the publications report mean age. An exploratory scenario analyses was undertaken using the median of [redacted] for the patients' age based on John et al.[4] and CheckMate 274, and the results are provided below (Table 8). It should be noted that these age estimates are not indicative of the licensed population (high risk of recurrence) and are based on median estimates. **Table 8. Scenario analyses using alternative patients' age**

		<table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total Lys</th><th>Total QALYs</th><th>Inc. costs (£)</th><th>Inc. Lys</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr><tr><td colspan="8">Base case*: using a mean age of 65.6 (representing a median age of 67)</td></tr><tr><td>NIVO</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,030</td></tr><tr><td colspan="8">Scenario: using an age of [redacted] (representation a median weighted between patients that received neoadjuvant chemotherapy and those who did not – CheckMate 274 – and median age values based John et al.[4] estimates)</td></tr><tr><td>NIVO</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£30,066</td></tr><tr><td colspan="8">BSC: best supportive care; ICER, incremental cost-effectiveness ratio; Inc.: incremental; Lys: life years; NIVO: nivolumab; QALYs, quality-adjusted life years. *Base case includes: updated DBL data (time on treatment, death on recurrence), generalised F base case, Ara and Brazier age-dependent utility values, updated PAS</td></tr></table>
Issue 5: **Assumption of an equal proportion of disease-free survival (DFS) events being deaths for nivolumab and placebo**	Yes – the death on recurrence data has been updated using the CheckMate 274 updated DBL (11 months minimum FU). The cost effectiveness analysis for	**The company estimates DFS death events by pooling across arms and using regression, due to data immaturity in CheckMate 274.** The company pools death on recurrence across treatment arms, and calculate this value using regression. Pooling across arms is appropriate due to the small number of events and therefore, the associated uncertainty. At the latest DBL, only [redacted]% of DFS events across both arms were deaths. The number of deaths was also similar between arms ([redacted] in the nivolumab arm and [redacted] in the placebo arm). Thus, this data is considered highly immature, provided by low numbers and similar across treatment arms. Therefore, the company pools this data and uses a regression approach to estimate a rate. The company retains their original approach, but has used data from the updated DBL to inform death upon recurrence. The company have conducted a scenario analysis based on the ERG's approach and using data from the updated DBL. Using arm-specific risks of death upon recurrence based on the number of deaths (as per the ERG's scenario) makes minimal difference to the ICER and cost-effectiveness results (Table 9). The ICER

<table>
<tr>
<td></td>
<td>the updated base case includes this updated death on recurrence.</td>
<td>increases slightly using the treatment-specific approach, since the nivolumab arm has slightly greater number of deaths than the placebo arm, thus incremental life years and QALYs are slightly lower.

Table 9. Base case results and scenario using raw treatment-specific death on recurrence
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total Lys</th><th>Total QALYs</th><th>Inc. costs (£)</th><th>Inc. Lys</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="8">Base case*: using pooled death on recurrence</td></tr>
<tr><td>NIVO</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,030</td></tr>
<tr><td colspan="8">Scenario: using raw treatment-specific death on recurrence based on event rates</td></tr>
<tr><td>NIVO</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,186</td></tr>
<tr><td colspan="8">BSC: best supportive care; ICER, incremental cost-effectiveness ratio; Inc.: incremental; Lys: life years; NIVO: nivolumab; QALYs, quality-adjusted life years. *Base case includes: updated DBL data (time on treatment, death on recurrence), generalised F base case, Ara and Brazier age-dependent utility values, updated PAS</td></tr>
</table>
</td>
</tr>
<tr>
<td>Issue 6:
Patients in the disease-free survival health state have the same utility values as an age- and sex-matched population</td>
<td>No</td>
<td>The company uses general population utility values, rather than using an arbitrary decrement.

Health state utility values calculated from the trial (using the updated DBL and original DBL) exceeded those of the general population for disease free survival. As such, the company capped health state utility at general population values. The ERG suggest an arbitrary utility decrement of 0.02 on the general population values. However, as 0.02 is an arbitrary value, it is impossible to assess appropriateness of this assumption as the true value is unknown. As the decrement value is small, this indicates that the health state utility expected by the ERG is negligibly different from general population values. It also has minimal impact on cost-effectiveness outcomes (Table 10). Reducing health state utility values reduced QALY gain in both arms, and reduces incremental QALY gain, therefore slightly increasing the ICER. Based on the reasons above, the company has not changed their base case on this issue.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>
Table 10. Base case results and scenario using -0.02 to age
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total Lys</th><th>Total QALYs</th><th>Inc. costs (£)</th><th>Inc. Lys</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="8">Base case*: no additional decrements applied to utility values</td></tr>
<tr><td>NIVO</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,030</td></tr>
<tr><td colspan="8">Scenario: using arbitrary -0.02 to health state utilities</td></tr>
<tr><td>NIVO</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£27,754</td></tr>
<tr><td colspan="8">BSC: best supportive care; ICER, incremental cost-effectiveness ratio; Inc.: incremental; Lys: life years; NIVO: nivolumab; QALYs, quality-adjusted life years. *Base case includes: updated DBL data (time on treatment, death on recurrence), generalised F base case, Ara and Brazier age-dependent utility values, updated PAS</td></tr>
</table>
</td>
</tr>
<tr>
<td>Issue 7:
Patients in the long-term disease-free survival (DFS) health state have the same life expectancy as general population</td>
<td>No</td>
<td>
The company assume a mortality rate equivalent to the general population after 5 years, aligning with clinical advice, wider literature, and hazard profiles from CheckMate 274.
Clinical experts confirmed that 99% of recurrence would happen before the 5 year timepoint and it is reasonable to consider that patients will follow the general population mortality trend if they have not recurred after 5 years post-surgery.[7] Patients who reach 5 years following surgery without recurrence would be discharged and no further monitoring would be assumed based on clinical expert opinion and following the NHS guidelines.[6,21,22]

Therefore, the company model substitutes DFS weekly hazards for age- and sex-matched mortality rates from UK life tables[23] from 5 years in both arms of the trial. It is important to consider that general population measures, such as utility or mortality, are estimates of all individuals, rather than solely referring to “healthy” individuals. Therefore, the use of general population utility does not indicate that patients are without comorbidity, only that it is within the limits of that experienced by others of the same age.
</td>
</tr>
</table>

A mortality ratio value of 1.1, as suggested by the ERG, is arbitrary. There is no data in the literature to suggest this or any other relevant value for such a mortality ratio. Furthermore, this is exceptionally close to a mortality ratio of 1; which would indicate the general population mortality. Assessment of the smoothed hazard curves for CheckMate 274 trial data and generalised F (base case) extrapolations indicate that hazards reach that of the general population by 5 years (*Figure 5). If life expectancy after 5 years were to exceed that of the general population, this would not be the case.

Finally, using a mortality ratio of 1.1 has minimal impact on the ICER, and is not in line with clinical advice received by the company.[6] Therefore the company has not changed their base case on this issue. In terms of cost-effectiveness results, using the mortality ratio slightly increases the ICER by reducing life years (LY) and QALY gain (

Table 11).

Table 11. Base case results and scenario using mortality ratio of 1.1 in long-term disease free

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Base case*: using general population mortality in long-term disease free							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,030
Scenario: using general population mortality with ratio of 1.1 in long-term disease free							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,147

		BSC: best supportive care; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years. *Base case includes: updated DBL data (time on treatment, death on recurrence), generalised F base case, Ara and Brazier age-dependent utility values, updated PAS
Issue 8: Uncertainty surrounding the assumed cure point	Yes – evidence from the updated CheckMate 274 updated DBL (11 months minimum FU) has been used to support the assumption of general population mortality at five years	**The company retains a 5-year long-term disease free timepoint, based on CheckMate 274 data, clinical expert opinion, and data from the wider literature.** *Rationale for a 5-year long-term disease-free timepoint* In the original company submission model, patients remaining in the disease-free health state for 5 years were subject to general population mortality and no risk of disease recurrence. This was based on: • CheckMate 274 trial data hazards: for DFS, hazards approach those of the general population by 5 years (*Figure 5). These features are present within the updated DBL, as well as the original DBL used in the original company submission, and indicate that patients who might be expected to experience recurrence would have done so prior to 5 years. A plateau is also observed in the survival curves for DFS (Figure 6), which inform the hazard profiles. • Clinical advice to the company stated recurrence after 5 years is rare (99% of patients recurring before 5 years timepoint), patients revert to background mortality at 5 years and patients are no longer subject to routine follow up after 5 years.[6,7] These indicate that 5 years is the most appropriate timepoint for 'long term disease free' status. • Clinical advice and NHS treatment guidelines state monitoring for patient ceases after 5 years disease-free, based on rarity of recurrence.[6,21,22]

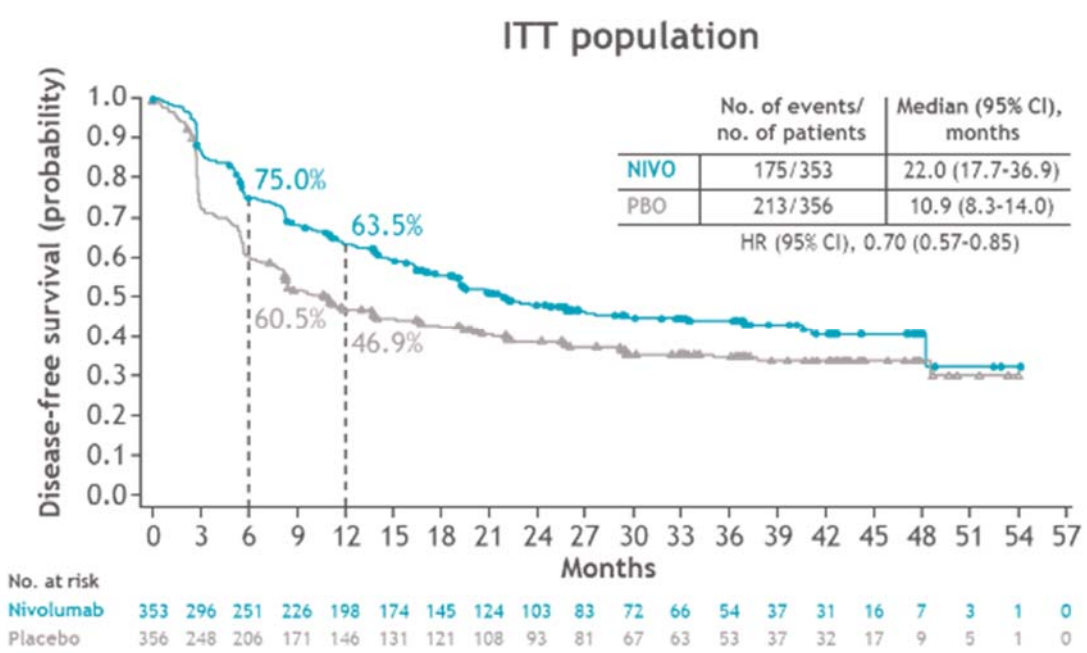


Figure 6. CheckMate 274: Kaplan-Meier plot of disease-free survival (primary definition) receiving nivolumab or placebo, all randomised patients – updated DBL (11 months minimum FU)

Source: Galsky 2021[24]

Furthermore, data in the literature from Sternberg et al.,[15] additionally supports a 5 year 'cure point'. Again, this is based on a visible plateau of survival curves from approximately 4 years, indicating few events after this point (Figure 7). This is also reflected in the hazard profiles (Figure 4, Issue 2). Since the deferred treatment arm of Sternberg et al.[15] partially represents the placebo arm herein, this is further validation for a cure point at approximately 5 years.

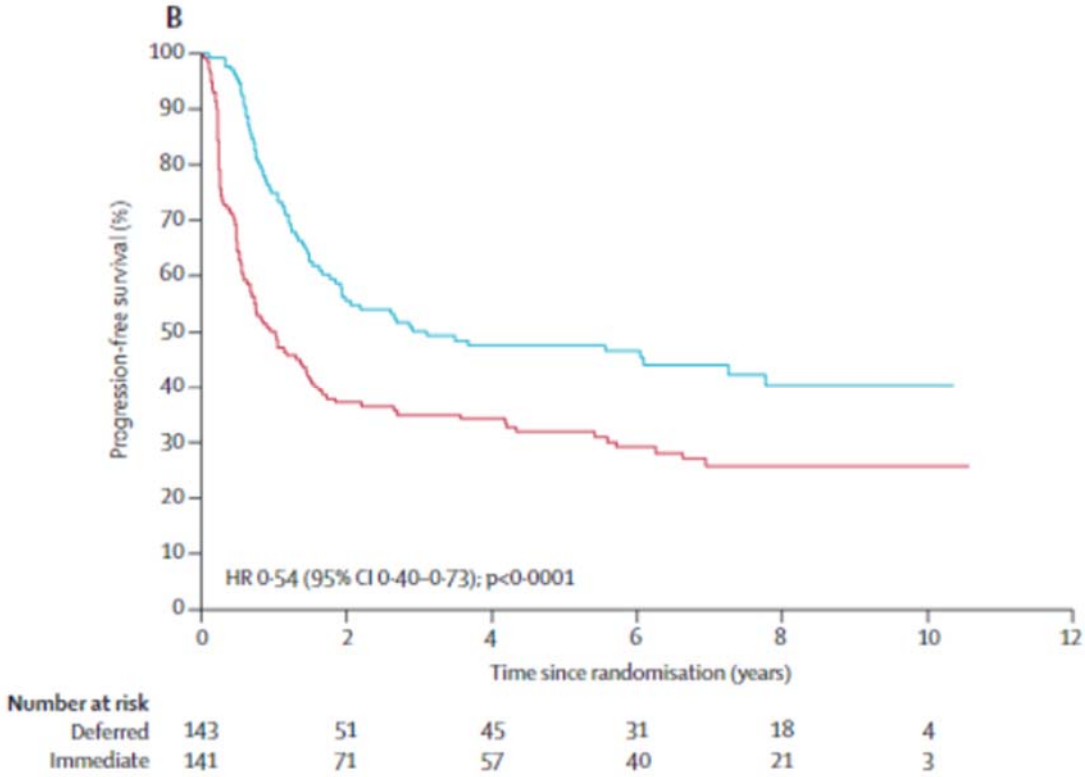


Figure 7. Progression free survival Kaplan-Meier survival curves, Sternberg et al.[15]

Rationale for excluding a 10 year disease-free timepoint

The ERG describe a 'cure point' of 10 years, whereas the company base case uses a 5-year timepoint to determine long-term disease-free survival. The studies which the ERG used to determine that recurrences can occur after 5 years, and to define a 10 year cure point, are of limited relevance to the current indication.

		Hautmann et al.[25] uses a dataset from 1986-2009, considering patients who did not receive neoadjuvant chemotherapy. Clinical advice to the company suggests fewer recurrences would occur in 2021 due to improved practices.[6] Furthermore, by excluding patients who received neoadjuvant chemotherapy, outcomes for the population in Hautmann would be expected to be worse than that of CheckMate 274. Another study, Soria et al.,[26] was used to determine that some patients may experience recurrences after 5 years. However, this study ran from 1998 to 2012 and again excluded patients who received neoadjuvant chemotherapy. This study also included high risk non-MIUC patients refractory to intravesical chemotherapy or immunotherapy. As such, the population evaluated in this study by Soria et al.[26] does not align with that of the CheckMate 274 trial or the current indication, and would be expected to have worse outcomes with more recurrences. Overall, a 5--year cure point remains the most plausible based on clinical advice, clinical guidelines (in terms of surveillance), and published clinical evidence, and therefore the company has not changed the base case on this issue.
Issue 9: The lack of subgroup analysis in the company's submission	Yes	**BMS disagree with the statement as it is inaccurate to say "subgroup analyses were not provided"; clinical data for subgroups are provided.** Clinical subgroup analyses were provided for the co-primary analysis population PD-L1 ≥1% and PD-L1 <1% patient exploratory population (based on original submission and ERG request). In addition, data for these subgroups is also presented for the updated DBL (11 months minimum FU) in Appendix 1. However, the PD-L1 <1% subgroup is not powered to detect differences in outcomes in the CheckMate 274 trial. Moreover, the wide CIs, crossing 1, observed in the efficacy results of the PD-L1 <1% subgroup indicate a less precise estimate and results should be interpreted with caution. The CheckMate 274 trial was designed to detect clinical benefit in intention-to-treat (ITT) and PD-L1 ≥1% patients and met its primary endpoint of DFS in both populations, as outlined in the tabular results in Appendix

		1. Moreover, in an pre-specified, exploratory subgroup analysis of all randomised patients with MIBC (i.e. excludes UTUC patients), irrespective of PD-L1 status, (n = 560), a substantial DFS benefit was also demonstrated. The DFS HR was 0.61 (95% CI: 0.49, 0.77) with median DFS of 25.79 and 9.36 months for the nivolumab and placebo arms, respectively. In UTUC, in the subgroups renal pelvis (n = 96) and ureter (n = 53), the DFS HRs were 1.25 (95% CI: 0.70, 2.25) and 1.54 (95% CI: 0.69, 3.44) respectively, regardless of PD-L1 status. See Appendix 1 for detail. As such, the company considered it inappropriate to conduct economic analyses based on the PD-L1 subgroups, as any such analyses are likely to produce biased and unreliable results, which will not be useful to inform economic model and therefore decision making. The company also sought clinical expert opinion on prognosis by PD-L1 status, and the clinicians noted that PD-L1 status has not been confirmed to be prognostic in MIUC.[6]

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: N/A	N/A	N/A	N/A

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Original company base case analysis (post clarification question response)	August 2020 DBL with initial PAS ([redacted]%)	Change 1: August 2020 DBL with updated PAS ([redacted]%)	**ICER (cost per QALY): £31,534**
Issue 2: The use of semi-parametric models to fit to disease-free survival (DFS) Kaplan-Meier estimates	Semi-parametric approach for DFS based on original DBL (using KM + Weibull curves)	Change 2: Updated DBL (11 months minimum FU) DFS data only, generalised F base case for modelling DFS **Applied cumulatively with:** change 1	**ICER (cost per QALY): £28,187**
		Change 3: Additional parameters updated based on the updated DBL (11 months minimum FU): time on treatment, death on recurrence data from CheckMate 274. **Applied cumulatively with:** change 1 and 2	**ICER (cost per QALY): £26,756**

Issue 3: Use of utility data from Janssen et al.	Using general population utility values from Janssen et al.	Change 4: Using general population utility values from Ara and Brazier in addition to the settings above **Applied cumulatively with:** change 1, 2 and 3 generalised F	**ICER (cost per QALY): £27,030**
Company base case post-technical engagement	The model before technical engagement used the original DBL inputs, semi parametric survival modelling and Janssen general population utility	The post technical engagement model is updated to include the updated DBL data, generalised F base case for modelling DFS and updated time on treatment, death on recurrence data from CheckMate 274. In addition, the model uses general population utility values from Ara and Brazier. Aligning to cumulative changes 1, 2, 3 and 4	**ICER (cost per QALY): £27,030**

Sensitivity analyses around revised base case

Sensitivity and scenario analysis are explored in Appendix 3

References

1. Bristol Myers Squibb. Erratum to Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2021.
2. British National Formulary. Nivolumab solution for infusion. 2021. Available at: https://bnf.nice.org.uk/medicinal-forms/nivolumab.html [Accessed 31 January 2021].
3. Bristol Myers Squibb. Clinical Protocol CA209274: A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. Revised Protocol Number 5. 2019.
4. John JB, Varughese MA, Cooper N, et al. Treatment Allocation and Survival in Patients Diagnosed with Nonmetastatic Muscle-invasive Bladder Cancer: An Analysis of a National Patient Cohort in England. European urology focus. 2020.
5. Metry A, Holmes G, Leaviss J, et al. Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2021.
6. Bristol Myers Squibb. Advisory board: Nivolumab for post-resection adjuvant treatment of high-risk muscle invasive urothelial cancer. 2021.
7. Bristol Myers Squibb. Clinician insights [Personal Communication] 2022.
8. Witjes JA, Bruins HM, Cathomas R, et al. EAU Guidelines in Muscle-invasive and Metastatic Bladder Cancer. 2021. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Muscle-Invasive-and-Metastatic-Bladder-Cancer-2021.pdf [Accessed 7 April 2021].
9. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA: A Cancer Journal for Clinicians. 2021;71(1):7-33.
10. Rouprêt M, Babjuk M, Burger M, et al. European Association of Urology (EAU) Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma. 2021. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Upper-Urinary-Tract-Urothelial-Carcinoma-2021.pdf [Accessed 10 January 2022].
11. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. Sociological Methods & Research. 2004;33(2):261-304.
12. Raftery AE. Bayesian Model Selection in Social Research. Sociological Methodology. 1995;25:111-63.
13. Bristol Myers Squibb. Clinical expert consultation. 2021.
14. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol. 2015;16(1):76-86.
15. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. The Lancet Oncology. 2015;16(1):76-86.
16. Janssen B, Szende A. Population Norms for the EQ-5D. In: Janssen B, Szende A, Cabases J, editors. Self-Reported Population Health: An International Perspective based on EQ-5D. Dordrecht: Springer Netherlands; 2014. p. 19-30.

17. Ara R, Brazier JE. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. Value in Health. 2010;13(5):509-18.
18. Pang KH, Thomas F, Novara G, et al. The Impact of Centralised Services on Metric Reflecting High-quality Performance: Outcomes from 1110 Consecutive Radical Cystectomies at a Single Centre. European urology focus. 2021;7(3):554-65.
19. Jefferies ER, Cresswell J, McGrath JS, et al. Open radical cystectomy in England: the current standard of care - an analysis of the British Association of Urological Surgeons (BAUS) cystectomy audit and Hospital Episodes Statistics (HES) data. BJU Int. 2018;121(6):880-5.
20. The British Association of Urological Surgeons, Section of Oncology,. Analyses of Radical Cystectomies performed between January 1st and December 31st 2019. 2020. Available at: https://www.baus.org.uk/_userfiles/pages/files/publications/audit/CystectomyFinalAnalyses2019.pdf [Accessed 15 December 2021].
21. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management [NG2]. UK: NICE, 2015.
22. Yoo SH, Kim H, Kwak C, et al. Late Recurrence of Bladder Cancer following Radical Cystectomy: Characteristics and Outcomes. Urol Int. 2019;103(3):291-6.
23. Office of National Statistics. National life tables: UK. 2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables/current [Accessed 10 January 2022].
24. Galsky MD, Witjes JA, Gschwend JE, et al. Disease-free survival with longer follow-up from the Phase 3 CheckMate 274 trial of adjuvant nivolumab in patients who underwent surgery for high-risk muscle-invasive urothelial carcinoma. 2021. Available at: https://suo-abstracts.secure-platform.com/a/gallery/rounds/12/details/1592 [Accessed 9 December 2021].
25. Hautmann RE, de Petriconi RC, Pfeiffer C, et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol. 2012;61(5):1039-47.
26. Soria F, Moschini M, Wirth GJ, et al. Characterization of Late Recurrence After Radical Cystectomy in a Large Multicenter Cohort of Bladder Cancer Patients. Urology. 2017;106:119-24.

Introduction

Thank you for your questions regarding the company's documentation provided at technical engagement for 'nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]'. Please find responses below.

Updated survival analysis:

1. Please provide a figure showing the KM functions for both nivolumab and placebo with the fitted survival functions for the generalised-F, lognormal and Gompertz models overlaid for both arms (similar to ERG Report Figure 15).

Requested figure provided below:

2. Please clarify how "Figure 4. Smoothed hazard estimates of PFS Sternberg et al deferred arm against lifetable hazard. (R-P: Royston Palmer). R-P spline represent Sternberg et al. deferred arm PFS" has been produced. Is it reproduced from a publication, constructed from pseudo-IPD, or something other?

Figure 4 within the technical engagement response form was generated using data published within the Sternberg et al. (2015) publication.[1] This contains a figure of the relevant PFS data (deferred arm) which was digitised to generate a survival curve. The number at risk for PFS for the deferred arm was also available from the publication.

Together, the digitised PFS curve and number at risk data were used to generate pseudo IPD. Then, in turn, smoothed hazard estimates were fitted to this data which were plotted on Figure 4 of the technical engagement response.

3. Please supply 95% confidence intervals for the 5 and 10 year survival proportions from Sternberg.

At five years (survival of 0.318), 95% confidence intervals are from 0.242 to 0.396. These are published within the Sternberg study.[1]

At ten years, equivalent data is not published. Using the pseudo IPD generated (as described in question 2), confidence intervals have been estimated for 10 years: [redacted] to [redacted].

Updated ITC analysis:

4. Please clarify if the ITC analysis was changed in any other ways apart from updating to the latest database lock.

There were no additional changes to the ITC analysis apart from updating to the latest database lock. Of note, one subject was reclassified from cisplatin refuser to cisplatin ineligible between the two database locks. The updates to the sample size along with the updated ITC results are included in the ITC appendix (Appendix 2).

References

1. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. The Lancet Oncology. 2015;16(1):76-86.

Introduction

Thank you for your questions regarding the company's documentation provided at technical engagement for 'nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]'. Please find responses below.

Updated survival analysis:

1. **Request - An updated version of Figure 5 from the TE response which also includes the B-spline and Kernel Smoothed versions of the smoothed hazards (as presented in Figures 4 and 5 from the clarification response) in addition to the R-P splines.**

Requested figure provided below, nivolumab (left), and placebo (right):

2. **Some explanation of the differences in methodology between the smoothers which explains the differences between the results - Plot of the observed ratio of smoothed hazards for each of the smoothing methods**

Kernel smoothed: Estimates the hazard function from right censored data using kernel-based methods. These are convolutional, where the observations far from each point of prediction are down-weighted by the shape of the kernel. For truncated kernels (non-Gaussian), observations outside of the width of the kernel will have no influence, consequently they tend to be highly logical. This can bring them 'closer' to the data but also causes them to break down near the boundary of the observed domain, as the kernel must be progressively narrowed or truncated to prevent inclusion of terminal signals in the data (i.e implicit zeros beyond the observed domain). The results can also be sensitive to the (dynamic) kernel size, as noise features may be preserved with narrow kernels.

Bspline: The influence of each of the spline components in a B-spline is present over a wider range of the domain, and boundary effects are "carried forward" from the spline portions approaching the boundary in the absence of additional data. The penalty function defining the smoothed fit necessarily gives additional weight to periods of dense observation, which can leave the tail driven by "knots" determined by earlier periods.

Royston-Palmer (RP) spline: Uses a fully parametric maximum likelihood approach to fitting a natural cubic spline to the data. This method allows for extrapolation, and is dependent on the assumed functional form implicit in the use of cubic splines upon the log cumulative hazard function.

The requested plots of the observed ratio (relative to lifetables) of smoothed hazards for each of the smoothing methods are provided below:

Nivolumab arm:

Placebo arm:

3. **A revised copy of the combined KM plot for both arms of the updated DBL, as per our last request, with the generalised F and Gompertz survival predictions but omitting the lognormal. (We can manage without this but it would be clearer in our response to include this requested version).**

Requested figure provided below

[redacted]

4. **Can the company confirm the increase in the risk of death between that estimated from its preferred Gen-F distribution and the life tables at 60 months.**

This question has been interpreted as comparing the hazards of the generalised F DFS curves at 60 months for placebo and nivolumab, in comparison to lifetable hazards at 60 months (based on CheckMate 274 data, using the Ederer I method[1]). Please also note that the generalised F DFS distributions denote the risk of leaving DFS (either due to recurrence or death). Results are provided below:

Model	Hazard at 60 months
Generalised F – Nivolumab arm	[redacted]
Generalised F – Placebo arm	[redacted]
Lifetable	0.00279

References

1. Cho H, Howlader N, Mariotto A, et al. Estimating relative survival for cancer patients from the SEER Program using expected rates based on Ederer I versus Ederer II method. 2011 Contract No.: Technical Report #2011-01.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of nivolumab is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical 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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 17 January 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating urothelial cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	James Catto
2. Name of organisation	Sheffield Teaching Hospitals NHS FT, University of Sheffield and NIHR
3. Job title or position	Professor, Honorary Consultant
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in nivolumab of people with urothelial cancer? ☒ A specialist in the clinical evidence base for urothelial cancer or technology? ☐ Other (please specify):
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 did not submit one, I do not 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. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for urothelial cancer?	Main outcomes are survival and quality of life.

(For example, to stop progression, to improve mobility, to cure urothelial cancer, or prevent progression or disability)	Survival in this context mean disease specific survival (rather than overall survival).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	• In this context, an absolute improvement in disease-specific (such as recurrence free) survival of 5% would be a clinically meaningful and significant improvement.
10. In your view, is there an unmet need for patients and healthcare professionals in urothelial cancer (specifically resected high-risk invasive urothelial cancer)?	• Yes, this is an important area of unmet need. • Survival from bladder cancer has not improved for 30 years. We can (relatively) clearly identify patients at high risk of cancer recurrence after radical cystectomy using their pathology. Recurrence in this context is usually a lethal event. For example, within 1100 cystectomies from our unit in Sheffield [published in Pang et al. Eur Urol Focus 2021 May;7(3):554-565], cancer was present at the resection margin in 7.7%, locally advanced (T3+) cancer was seen in 33.1% and lymph node metastases were present in 14.3%. Death from bladder cancer occurred in 56%, 51-76% and 52-64% of these patients, respectively. These mortality figures are even higher for those who have this pathology after neoadjuvant chemotherapy. • There is currently no standard of care for these patients. No RCTs have shown significant benefits of adjuvant chemotherapy on disease specific or overall mortality. Hence, rates of adjuvant use are very variable and mostly confined to node positive cancers in patients who did not receive neoadjuvant cisplatin. Consequently, patients at highest risk of recurrence mostly receive no adjuvant treatment.

11. How is urothelial cancer (specifically resected high-risk invasive urothelial cancer) currently treated in the NHS? • Are any clinical guidelines used in urothelial cancer, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	• This application applies to muscle invasive bladder cancer. The care of this disease is described within the NICE Bladder Cancer guidelines NG2. • Pathway: Patients with this cancer are diagnosed at all NHS hospitals and mostly treated within NHS Cancer centres. Patterns of practice are similar in England, Scotland, Wales and N. Ireland. Suitable treatment options are 1. Radical Surgery (cystectomy), 2. Radical Radiotherapy (±chemotherapy), 3. Palliation (supportive care ± chemotherapy). NHSE data suggest around 40-50% of patients receive option #3, the reminder are split between options #1 and #2. Between 30-50% of patients receiving surgery and radiotherapy also receive neoadjuvant chemotherapy. The pathway is well defined and is described within the NICE Bladder Cancer guidelines NG2. • Impact: The need for Nivolumab would be identified either at the network MDT or in clinics after surgery. Suitable patients would then need referral to medical oncology for discussion/treatment. This is not always standard care (given the inconsistent use of adjuvant chemotherapy) and so this would be a new referral pathway. But there are relatively few suitable patients, and they can be clearly identified, so this should be possible.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	• There is no standard of care for adjuvant treatment after Cystectomy. As such, this would be a new standard of care. • Nivolumab is administered as an intravenous infusion over 30 minutes, within the medical oncology (secondary care) outpatient setting. There is clinic/phone/blood monitoring needed before and after administration. • No new investment is needed – beyond funding of the drug.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• As stated, there is no standard of care. Consequently, Nivolumab would deliver clinically meaningful benefits to suitable patients. These improvements would be fewer patients developing cancer recurrence. In real terms, this translates into fewer needing chemotherapy, fewer needing admission to hospital for pain relief or relief of a complications from recurrence, and fewer deaths from cancer. • Many cancer recurrence events reduce HRQOL. For example, compared to BC patients cured from their cancers, surveys show that participants living with advanced disease have lower HRQOL (e.g. 70% report one or more problem in EQ5D, 20-30% report social distress using SD16 and 43% report a lack of energy (and numerous other symptoms) [Br J Cancer 2018 May;118(11):1518-1528]).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• Suitable patients are those with high-risk features after radical cystectomy. • Of these, tumours with high PDL1 expression benefit most. • Selection to patients who have already had cisplatin based neoadjuvant chemotherapy would also make sense. Those who are naive to chemotherapy could receive adjuvant cisplatin as the first line approach.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	• Nivolumab is used in many malignancies in various contexts. As such, this should be easy to use.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• Yes. • Clear indications for use, clear regimens (12 months), and cessation guidelines. • Regarding extra testing, if PDL1 expression is used to identify those with most benefit then this would be extra.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, would nivolumab regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	• Whilst one would expect QOL improvements, the trial report from Checkmate 274 showed no differences between Nivolumab and Placebo, over time, using EQ5D and QLQ-C30. • Neither instrument is particularly sensitive to changes in bladder cancer QOL and so it is possible there were differences, but these were not reflecting overall or cancer specific QOL. • Regardless, evidence suggests Nivolumab is better tolerated, with fewer side effects and is easier to administer than cisplatin-based chemotherapy.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of urothelial cancer? • Does the use of the technology address any particular unmet need of the patient population?	• Yes. Given that these patients mostly receive no adjuvant treatment, Nivolumab would represent a significant innovation. • Yes, this is an unmet need – see answers above.
19. How do any side effects or adverse effects of the technology affect the management of urothelial cancer	• Immune related adverse events are common, mostly mild and easily managed. Severe immune related adverse events occur rarely and need

(specifically resected high-risk invasive urothelial cancer) and the patient's quality of life?	prompt appropriate treatment. Given the widespread dissemination of immune therapy, these should be of minimal impact to services.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• Yes the critical trial does reflect UK practice. Centres from the UK recruited patients into the phase 3 registration study. • Most important outcomes are recurrence rates – and was the primary outcome within Checkmate 274. • Surrogates were not used.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None
22. How do data on real-world experience compare with the trial data?	Real world data show that immune therapies are well tolerated and popular with patients. There are no real-world data of Nivolumab in this setting, but experience in the 1st line metastatic setting is encouraging.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering urothelial cancer (specifically resected high-risk invasive urothelial cancer) and nivolumab? Please explain if you think any groups of people with urothelial cancer (specifically resected high-risk invasive urothelial cancer) are particularly disadvantaged.	Bladder cancer is more common in older patients, in men, in smokers, in manual workers and those of higher social deprivation. Nivolumab will improve outcomes within this population. Those of higher social deprivation and those who do not engage in healthcare are areas of need.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which nivolumab is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

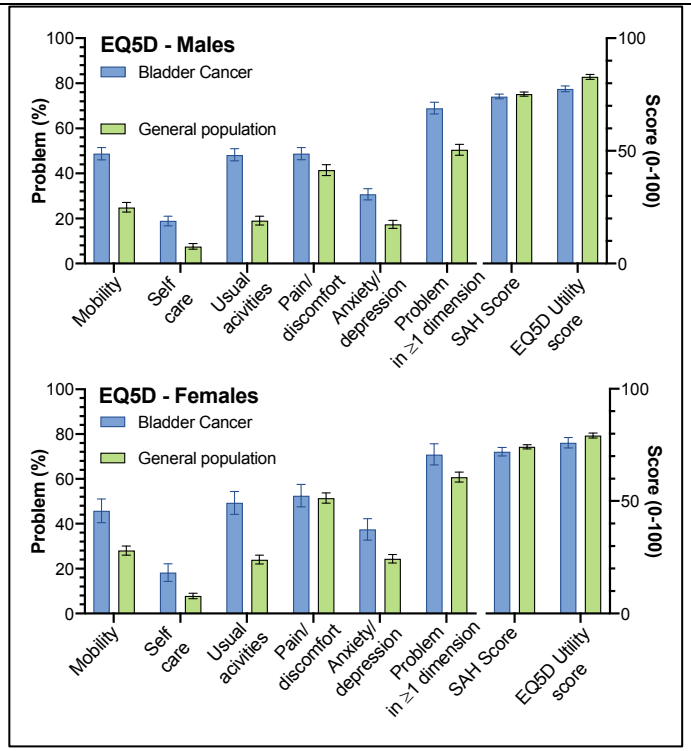
Table 2 Issues arising from technical engagement

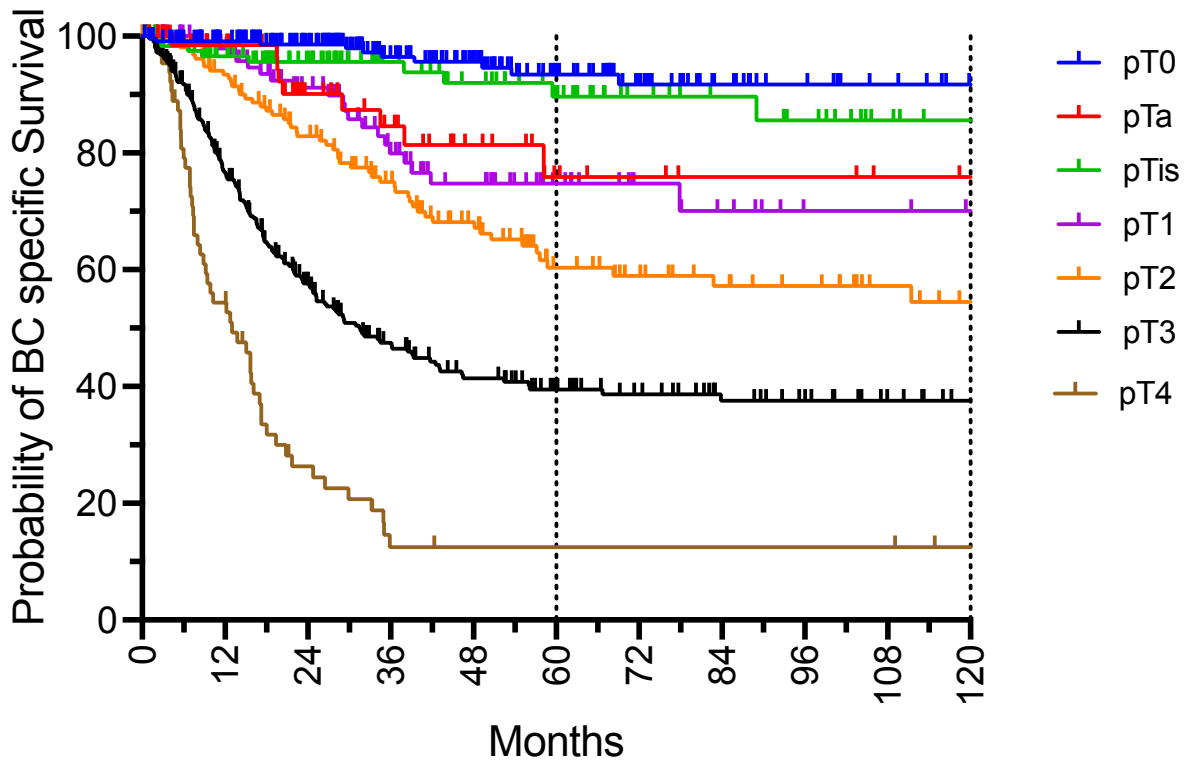
Issue 1: **Exclusion of cisplatin-based adjuvant chemotherapy as a comparator** **How often is cisplatin-based adjuvant chemotherapy used in clinical practice in this population?**	• I would agree that Cisplatin should not be used as a comparator in this evaluation: 1. There are no RCTs that have shown benefits of adjuvant chemotherapy on disease specific or overall mortality. The best RCT (EORTC Lancet Oncol. 2015 Jan;16(1):76-86) failed to recruit and was underpowered for a meaningful analysis. 2. Consequently, guidelines do not recommend adjuvant chemotherapy in this context (see table 4 in ID2694 technical engagement document). For example, NICE NG2 states 'consider' in the context of high-risk disease in patient who have not had neoadjuvant chemotherapy. 3. As such, rates of adjuvant therapy use are very variable and mostly confined to node positive cancers. Many/most patients at highest risk of recurrence mostly receive no treatment.

Clinical expert statement

Issue 2: **The use of semi-parametric models to fit to disease-free survival (DFS) Kaplan-Meier estimates**	• This is beyond my expertise.
Issue 3: **Use of utility (quality of life) data from Janssen et al.** **How appropriate is this source to inform quality of life in this population?**	• The source data do look appropriate. I have recently been part of a cross sectional survey recording HRQOL in 1,900 bladder cancer patients in Yorkshire (see Eur Urol. 2021 May;79(5):621-63). Our findings are broadly compatible with these Utility data – albeit that we only see relative differences rather than absolute raw numbers (to allow comparison) in the company's submission. It is known that these patients do have a poor quality of life and that this appears worse than for other pelvic cancers. In this context, the EQ5D and QLQC30 data presented appear typical to those seen in this population. • That improvements in HRQOL are only seen in the PDL1 positive cohort is interesting and supports that the stratified/targeted use of Nivolumab is most sensible.
Issue 4: **The average age of patients in the UK is likely to be older than those recruited to CheckMate 274** **From your experience, what is the average age of people with resected high-risk invasive urothelial cancer?**	• The average age in Checkmate 274 is 65.3-65.9 years. • This is younger than the average age for a new bladder cancer diagnosis in the UK (which is over 75 years according to CRUK data). • However, within the UK/NHS, the average age for patients undergoing Radical Cystectomy is younger. For example, within the iROC RCT (ISRCTN13680280 and NCT03049410: which recruited from 9 NHS cancer centres) the average age was 69 years (± st. dev. 8.2).

Issue 5: **Assumption of an equal proportion of disease-free survival (DFS) events being deaths for nivolumab and placebo**	I can not comment on this.
Issue 6: **Patients in the disease-free survival health state have the same utility values as an age- and sex-matched population** **How would you describe the quality of life for a person with resected high-risk urothelial cancer who are disease-free?**	• In general, patients living beyond BC have a *marginally* worse HRQOL than the general population (see Eur Urol. 2021 May;79(5):621-63 and figure below). • Some aspects of HRQOL are more similar (such as generic HRQOL (EQ5D) and cancer specific HRQOL (EORTC QLQ C30)), whilst others differ greatly (Cystectomy specific HRQOL (EORCT BLM30 and FACT-BI) report more issues with sexual problems/sexual bother & loss of function and money worries), compared to the general population. These are surgery and prior comornidity related differences. • Within the iROC trial, we saw HRQOL measures mostly returned to baseline by 3 or 6 months after treatment. • Therefore, I would agree that HRQOL in patients who are disease free is similar to that in the same population prior to diagnosis (i.e., baseline). However, bladder cancer affects older, smokers, less affluent and more co-morbid persons than typical in the general population, and so this baseline HRQOL may be marginally worse than average in age matched persons.

	
Issue 7: **Patients in the long-term disease-free survival (DFS) health state have the same life expectancy as general population**	• Most cancer recurrences occur within 5 years of radical cystectomy. • After this time, survival matches that of the general population/normal life expectancy. • For example, we reported outcomes from the last 1,100 Cystectomies in Sheffield (Eur Urol Focus. 2021 May;7(3):554-565 and figure below). After 5 years, Bladder Cancer recurrences rates are low and so patient survival matches that of the life expectancy

How is life expectancy impacted when people are in a long-term disease free state?	
Issue 8: Uncertainty surrounding the assumed cure point **Is there any timepoint without disease recurrence**	• Please see above. • There is no fixed time around which certainty (of no recurrence) reaches 100%. • However, we (NHS care and regional guidelines) discharge patients from further follow up at 5 years after surgery - given that most recurrences have occurred by then. • Thus, I would use a 5 year timepoint to define cure.

after which a person with this condition can be assumed to be cured?	
Issue 9: **The lack of subgroup analysis in the company's submission**	• One would expect sub-group analysis regarding high risk features. • The NEJM paper (Bajorin et al.) does present a plot (figure 2) of various sub-analyses. For most the errors bars cross the 1.0 HR mark, and so do not provide statistical support for selective Nivolumab use. Exceptions are high PDL1 expression, prior neoadjuvant chemotherapy, bladder location and normal renal function (all favour Nivolumab). • As such, I would expect these analyses, with the above caveats.
Are there any important issues that have been missed in ERG report?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- ***This is a new treatment in an area of unmet clinical need. This offers hope to patients and is a logical step in those failing chemotherapy.***
- ***Bladder cancer is a relatively underfunded and under supported disease. Patient outcomes are poor (lack of survival improvements and poor HRQOL) and so new approaches are needed.***
- ***NICE approval of Nivolumab would offer meaningful improvements to outcomes in patients at high risk of treatment failure.***
- ***Depending upon cost, Nivolumab use could/should be targeted to patients at greatest benefit (high risk pathological features and prior cisplatin)***

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of nivolumab is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical 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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 17 January 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating urothelial cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Syed A Hussain
2. Name of organisation	University of Sheffield (nominated by BMS)
3. Job title or position	**Professor of Medical Oncology and Honorary Consultant** Member NCRI-Bladder and Renal CSG Chair NCRI-Advanced Bladder cancer sub-group
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in nivolumab of people with urothelial cancer? ☒ A specialist in the clinical evidence base for urothelial cancer or technology? ☐ Other (please specify):
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 did not submit one, I do not 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)	☐

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for urothelial cancer? (For example, to stop progression, to improve mobility, to cure urothelial cancer, or prevent progression or disability)	Treatment for organ confined Muscle invasive bladder cancer comprises of neo-adjuvant chemotherapy followed by radical curative cystectomy or organ preservation. Patients undergoing cystectomy and with persistent muscle invasive disease remain at high risk of early disease relapse and poor outcome with early death. The main aim at this stage is to improve disease control, thus improving cure rate that is likely to lead to improved survival.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in disease control by 6 months or more is likely to significantly improve patient outcome in this setting of high risk muscle invasive bladder cancer. Improvement of this magnitude is likely to impact on survival
10. In your view, is there an unmet need for patients and healthcare professionals in urothelial cancer (specifically resected high-risk invasive urothelial cancer)?	There remains an unmet need as outcome for patients after disease relapse and progression in high -risk urothelial cancer is poor with limited prognosis and survival in the range of 14-15 months.
11. How is urothelial cancer (specifically resected high-risk invasive urothelial cancer) currently treated in the NHS? • Are any clinical guidelines used in urothelial cancer, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	• NICE guidelines are routinely followed for these patients. • In UK , majority of Patient receive cisplatin based neo-adjuvant chemotherapy. This patient group would not be offered adjuvant chemotherapy • Patient did not receive neo-adjuvant chemotherapy (for whatever reason) and is not suitable for cisplatin based chemotherapy post-cystectomy. This patient would not be offered adjuvant chemotherapy. • Patient did not receive neo-adjuvant chemotherapy , for patient or clinician reason, and is suitable for cisplatin post-cystectomy. For this group of patients, cisplatin based chemotherapy can be offered. and is recommended in the NICE guideline. This technology is likely to provide treatment opportunities to these patients in adjuvant setting after neo-adjuvant chemotherapy and persistent high risk disease , thus improving their disease control rate and delays their disease progression significantly.

	Results of the CheckMate-274 trial indicate an additional value of adjuvant nivolumab in patients with high-risk UC previously treated with cystectomy with or without neoadjuvant cisplatin-based chemotherapy.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will bring the use of immune check point inhibitor Nivolumab earlier in the treatment pathway by bringing it into adjuvant setting. This should be used in the secondary care in specialist hospital settings. As immune check point inhibitors are already being used in advanced setting in urothelial cancers and other cancers, no new changes or investments in facilities or infrastructure is required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes based on the clinical trial data, CheckMate-274 revealed clinically and statistically significant difference in median DFS between the nivolumab and placebo groups (20.8 vs 10.8 months; HR 0.70; *P* < .001). The significant improvement in PFS is likely to translate in improvement in overall survival. Overall Nivolumab is generally well tolerated and hence this technology is likely to increase health related quality of life. Given the recent U.S. Food and Drug Administration approval of nivolumab on August 19, 2021, wider use of nivolumab worldwide in patients with high-risk muscle-invasive UC following cystectomy is anticipated

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Subgroups data have to be interpreted carefully. The trial met its primary end point with significant improvement in DFS in intention to treat population. Results of the CheckMate-274 trial indicate an additional value of adjuvant nivolumab in patients with high-risk UC previously treated with cystectomy with or without neoadjuvant cisplatin-based chemotherapy 1) In upper tract urothelial cancer subgroup, the technology was not any different to placebo. 2) In biomarker positive patients the Hazard ratio was more favourable to Nivolumab in analysis within subset of patients.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Immune check point inhibitors are used routinely in NHS. Management of toxicities with this class of drugs has improved nationally with better education of clinicians and patients. There are no practical implications or requirements of additional tests for its use.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, would nivolumab regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of urothelial cancer? • Does the use of the technology address any particular unmet need of the patient population?	Yes; Moving Immune check point inhibitor from advanced metastatic setting into earlier setting as adjuvant treatment, where Improvement in DFS is likely to translate into improvement in OS and higher percentage of patients achieving cure is likely to be a "step change 'in the management of urothelial cancer. The clinical gains is likely to impact on improvement in QOL
19. How do any side effects or adverse effects of the technology affect the management of urothelial cancer (specifically resected high-risk invasive urothelial cancer) and the patient's quality of life?	There were no new safety signals to report
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Patients undergoing cystectomy within UK are not very different to the population in the clinical trials. Median age in a recent national neoadjuvant trial NEOBLADE was 68. (Hussain et al ASCO GU 2020 presentation) Upper tract cancers in UK directly proceed to nephroureterctomy and receive adjuvant chemotherapy with Platinum based chemotherapy in adjuvant setting . Further follow-up and reporting of mature OS data from this trial is awaited
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	In real world we do not use adjuvant immune check point inhibitors. In patients who have not received cisplatin based neo-adjuvant chemotherapy for any reason are considered for cisplatin based adjuvant chemotherapy if post cystectomy histology confirm high risk MIBC.

23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering urothelial cancer (specifically resected high-risk invasive urothelial cancer) and nivolumab? Please explain if you think any groups of people with urothelial cancer (specifically resected high-risk invasive urothelial cancer) are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which nivolumab is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Nothing to add.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: **Exclusion of cisplatin-based adjuvant chemotherapy as a comparator** **How often is cisplatin-based adjuvant chemotherapy used in clinical practice in this population?**	In patients who did not receive neo-adjuvant chemotherapy but post cystectomy has high risk MIBC and patient is fit for cisplatin based adjuvant chemotherapy, in that setting chemotherapy can be used as a comparator. These numbers will be small and approximately 10-15 % of cases, as most patients receive neo-adjuvant chemotherapy in UK if they are fit and eligible for cisplatin based chemotherapy. Patients who have received cisplatin based neo-adjuvant chemotherapy will not be offered adjuvant chemotherapy , so in that setting, cisplatin based adjuvant treatment cannot be used as a comparator. Similarly patients who did not receive neo-adjuvant chemotherapy and are not suitable for cisplatin based adjuvant chemotherapy because of impaired renal functions or other co-morbidities, again chemotherapy cannot be used as a comparator in this setting. Patients with upper tract urothelial cancers do not receive neo-adjuvant chemotherapy outside of clinical trials in UK. We offer adjuvant chemotherapy with platinum based chemotherapy based on POUT trial results. For this group of patients comparator arm of adjuvant chemotherapy should be considered.

Issue 2: **The use of semi-parametric models to fit to disease-free survival (DFS) Kaplan-Meier estimates**	No
Issue 3: **Use of utility (quality of life) data from Janssen et al.** **How appropriate is this source to inform quality of life in this population?**	This is reasonable in my opinion.
Issue 4: **The average age of patients in the UK is likely to be older than those recruited to CheckMate 274** **From your experience, what is the average age of people with resected**	CheckMate 274 is trial of patients undergoing radical cystectomy. In clinical trials often the patient population is carefully selected in terms of fitness and meeting strict eligibility check-list and therefore are often younger patient population compared to real world setting. Patient undergoing cystectomy in clinical trials or in real world are selected after careful evaluation of their fitness as these are complex surgeries associated with morbidity and mortality. In UK almost 40-50% of patient undergo organ preservation and are likely to be older and with worse performance status compared to patients undergoing cystectomy. In the recently reported Neoadjuvant trial in UK, NEOBLADE , median age was 68 years (Hussain et al ASCO GU 2020 presentation). The average age for this group of patients with resected high risk urothelial cancers will be around 68-69 years but they will be fit patients with minimal competing co-

high-risk invasive urothelial cancer?	morbidities for them to be undergoing radical curative Cystectomy in the first instance. In view of that I do feel the clinical trials data is applicable to our patient population in UK.
Issue 5: **Assumption of an equal proportion of disease-free survival (DFS) events being deaths for nivolumab and placebo**	Further follow-up and reporting of mature OS data from this trial is awaited . The clinically and statistically significant improvement in DFS is likely to translate into improvement in OS.
Issue 6: **Patients in the disease-free survival health state have the same utility values as an age- and sex-matched population** **How would you describe the quality of life for a person with resected high-risk urothelial cancer who are disease-free?**	The impact of radical surgery on patients QOL are well documented. There will be treatment related toxicities as well. These are short lived and patient adapt to surgical changes with stoma or neo-bladder with the passage of time. We routinely see these patients enjoying a fully functional life style and good quality of life.
Issue 7: **Patients in the long-term disease-free**	Patients who are disease free from urothelial cancers after 5 years, the relapse rate remains extremely low in those case. Most clinicians discharge patients from hospital follow up after 5 years.

survival (DFS) health state have the same life expectancy as general population **How is life expectancy impacted when people are in a long-term disease free state?**	
Issue 8: **Uncertainty surrounding the assumed cure point** **Is there any timepoint without disease recurrence after which a person with this condition can be assumed to be cured?**	Patients who are disease free from urothelial cancers after 5 years, the relapse rate remains extremely low in those case. Most clinicians discharge patients from hospital follow up after 5 years. At the same time there is never "NO" risk of death from bladder cancer, for these patients, though other competing risk factors for mortality with increasing age may overtake the risk from bladder cancer. In UK most patients will have received neo-adjuvant chemotherapy as standard of care if they are fit for cisplatin based chemotherapy and will receive nivolumab if they have high risk disease post cystectomy.
Issue 9: **The lack of subgroup analysis in the company's submission**	PDL1 status, in urothelial cancer has been shown to be a prognostic marker and not a useful predictive biomarker. We do not routinely check PDL1 status in this population in the UK for immune checkpoint inhibitor treatment in most cases (except in 1st line setting in Cisplatin ineligible patient population). Trial meets primary end point in ITT. Sub-group data has to be interpreted with caution, but at the same time it is worth highlighting, In upper tract urothelial cancer subgroup, the technology was not any different to placebo

Are there any important issues that have been missed in ERG report?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Clinically and statistically significant improvement in disease free survival in intention to treat population

Important addition to patient treatment in high risk urothelial cancer that is likely to be a game changer.

PDL1 is not a useful predictive biomarker

Moving Immune check point inhibitor from advanced metastatic setting into earlier setting as adjuvant treatment, where Improvement in DFS is likely to translate into improvement in OS and higher percentage of patients achieving cure is likely to be a "step change 'in the management of urothelial cancer. The clinical gains is likely to impact on improvement in QOL

AS GU oncologists, we hope this drug will be made available to our patients in UK based on exciting clinical trials data discussed above.

Professor Syed A Hussain, MBBS, MSc, MD, FRCP, Professor of Medical Oncology, University of Sheffield, & Sheffield Teaching Hospitals, Sheffield, South Yorkshire, United Kingdom.
Member: NCRI Bladder and renal group
Chair: NCRI Advanced Bladder cancer sub-group

Conflicts of interest:
Grants: CR UK, MRC/NIHR, Boehringer Ingelheim, Roche, Janssen- Cilag, Pierre Fabre.
Consulting fee: Pierre Fabre, Bayer, Janssen Oncology, Roche, Merck, Bristol-Myers Squibb, AstraZeneca, Pfizer, Astellas and GSK.
Support for attending meetings and/or travel: Janssen- Cilag, Bayer, Boehringer Ingelheim, Pierre Fabre, Pfizer, Roche, Bristol-Myers Squibb, AstraZeneca and MSD Oncology.

Thank you for your time.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Thank you for agreeing to give us your views on nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with urothelial cancer or caring for a patient with urothelial cancer. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 17 January 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with urothelial cancer or caring for a patient with urothelial cancer

Table 1 About you, urothelial cancer , current treatments and equality

1. Your name	Kevin Gorman
2. Are you (please tick all that apply)	☑ A patient with urothelial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with urothelial cancer? ☑ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Action Bladder Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☑ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☑ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☑ I am drawing from personal experience ☑ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: As a patient trustee of a leading bladder cancer charity, I have regular

	feedback from fellow patients we support, and their carers, through patient support groups, our helpline and our patient surveys. ☑ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with urothelial cancer? **If you are a carer (for someone with urothelial cancer) please share your experience of caring for them**	Bladder cancer patient. TURBT diagnosis of urothelial cancer followed by radical cystectomy and urinary diversion (urostomy). Currently under regular review for recurrence or metastasis. Depending on outcome, I could become a candidate for the proposed treatment.
7a. What do you think of the current treatments and care available for urothelial cancer (specifically resected high-risk invasive urothelial cancer) on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Patients struggle to come to terms with the very poor outcomes when they are told their bladder cancer is high risk. In addition to coming to terms with the very poor outlook they must also endure the adverse side effects of currently available treatments, leaving patients both emotionally and physically exhausted. Family members and carers struggle between providing optimistic support and hoping that the ordeal they are forced to witness gets no worse, or lasts too long, giving rise in many cases to feelings of guilt at their own mixed emotions. Our patient groups, survey responses and incoming queries all reflect similar experiences for patients with this condition. Of significant concern to UC patients is the lack of any progress in new treatment options over very many years, especially compared with most other forms of cancer. These views are shared by the vast majority of UC cancer patients we deal with, either through support groups, our helpline, or surveys.
8. If there are disadvantages for patients of current	Cisplatin based chemo can be particularly unpleasant, causing a significant number

NHS treatments for urothelial cancer (for example, how nivolumab is given or taken, side effects of treatment, and any others) please describe these	of patients to either reject it or drop out of treatment.
9a. If there are advantages of nivolumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nivolumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	We are not aware of particular disadvantages in receiving nivolumab over chemo.The most important advantage of nivolumab is the knowledge that it can extend life, and may in some cases potentially prevent recurrence. The treatment provides hope, when there is currently very little.
10. If there are disadvantages of nivolumab over current treatments on the NHS please describe these. For example, are there any risks with nivolumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None known
11. Are there any groups of patients who might benefit more from nivolumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	None known
12. Are there any potential equality issues that should be taken into account when considering urothelial cancer and nivolumab? Please explain if you think	None known

any groups of people with urothelial cancer are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	This group of patients is relatively small, and the data sets available to the committee are therefore quite limited. This has perhaps inevitably led to several differences between the company and the evidence review group on how best to interpret the data, and how to derive quality of life years. Whilst we recognise and accept the need for NICE to use cost comparators to support decisions, we hope the committee bears in mind that this small group of patients is heavily skewed in one direction, ie towards early death. They also do not, currently, have any good treatment options. This treatment offers real hope for a group of very poorly served patients.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: **Exclusion of cisplatin-based adjuvant chemotherapy as a comparator** **How often is cisplatin-based adjuvant chemotherapy used in clinical practice in this population?**	We agree with the company that including this comparator would not be meaningful - the numbers are low, data is difficult to ascertain, and the dropout rate is quite high.

Patient expert statement

Issue 2: **The use of semi-parametric models to fit to disease-free survival (DFS) Kaplan-Meier estimates**	It is not really feasible for patients to comment meaningfully on the applicability of one modelling tool over another - we are not medical scientists or statisticians. Obviously, we prefer the company's chosen interpretation, selected on their assessment of best fit to the available data, to that of the ERG, as the former is more likely to make the treatment affordable. Where there is doubt, as here, we hope the committee will balance their judgement in favour of UC patients who have been so poorly served for so long. We hope the committee will only deviate from the company model if they are certain it is wrong, and the ERG Gompertz model is right.
Issue 3: **Use of utility (quality of life) data from Janssen et al.** **How appropriate is this source to inform quality of life in this population?**	Both models are predictors based on a small dataset, and it is difficult to see why Janssen should be seen as less valid. Neither model says much about the experience of life quality.
Issue 4: **The average age of patients in the UK is likely to be older than those recruited to CheckMate 274 (resected high-risk invasive urothelial cancer)** **<u>we consider patient perspectives may</u>**	It is difficult for us to objectively determine average age, but our impression is that advanced bladder cancers mostly affect men in their mid 60s onwards. However, we are experiencing a rising number of younger patients seeking support, both men and women, some as young as early 40s. For example, we are receiving more queries on how to obtain financial support through loss of income.

particularly help to address this issue **From your experience, what is the average age of people with resected high-risk invasive urothelial cancer?**	
Issue 5: **Assumption of an equal proportion of disease-free survival (DFS) events being deaths for nivolumab and placebo**	
Issue 6: **Patients in the disease-free survival health state have the same utility values (quality of life) as an age- and sex-matched population** **we consider patient perspectives may particularly help to**	We do not understand the ERG position. One of their references (57) includes this in the summary: *"HRQOL following BC appears to be relatively independent of disease stage, treatment, and multimodal care…… **Age and other illnesses appear to be more important** in determining this quality of life than the treatments received"* The other (58) was a comparison between different types of radical surgery, and in part concluded *"Post-operative QOL may **improve**, but urinary and sexual dysfunction remains inferior to the general population"* From a patient perspective, loss of function (or acquiring a disability or dysfunction) does not of itself lead to a loss in quality of life. It is perfectly possible to have a high quality of life with a disability (the disability paradox). As a patient with resected high-risk urothelial cancer who is disease-free (so far as I'm aware), I can assure the committee that I regard my quality of life to be excellent, allowing me to travel the world, engage in my chosen

address this issue **How would you describe the quality of life for a person with resected high-risk urothelial cancer who are disease-free?**	hobbies, exercise regularly, and generally thoroughly enjoy life. I know plenty of other UC stomates who would agree.
Issue 7: **Patients in the long-term disease-free survival (DFS) health state have the same life expectancy as general population** **we consider patient perspectives may particularly help to address this issue** **How is life expectancy impacted when people are in a long-term disease free state?**	Strongly agree. See response to issue 6. The key phrase here is "long term disease free state". The ERG contends that it is possible that patients in this group have a reduced life expectancy, and have suggested a possible reduction to model a negative cost impact. There is no evidence for this assumption.
Issue 8: **Uncertainty surrounding the**	Five years as a "cure point" is as good as any. The clinical advice quoted is that the chance of recurrence is not zero after 5 years. This is true of most if not all

assumed cure point **we consider patient perspectives may particularly help to address this issue** **Is there any timepoint without disease recurrence after which a person with this condition can be assumed to be cured?**	cancers, and clinicians are usually wary of pronouncing any cancer patient "cured". Whilst it is possible that the risk of recurrence after 5 years may be higher than with some other cancers, there is little evidence to show that any particular alternative has significance. Subjectively, disease free for five years seems worth celebrating as a meaningful turning point.
Issue 9: **The lack of subgroup analysis in the company's submission**	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Current treatments for this group of patients are not very effective, leading to particularly poor outcomes. This has not changed for 30 years or so.
- Diagnosis of high risk invasive urothelial cancer is devastating for patients and carers, given the very poor outcomes at present.
- Nivolomab offers real hope for this poorly served group of patients, offering much better outcomes without significantly worse adverse effects than current treatments.
- The committee is faced with conflicting interpretations of data which could lead to different conclusions on affordability. We hope, where reasonable doubt exits, the committee will accept the baseline submission by the company seeking approval. This would be to the great benefit of a poorly served group of patients.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Thank you for agreeing to give us your views on nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with urothelial cancer or caring for a patient with urothelial cancer. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 17 January 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with urothelial cancer or caring for a patient with urothelial cancer

Table 1 About you, urothelial cancer, current treatments and equality

1. Your name	Lydia Makaroff
2. Are you (please tick all that apply)	☐ A patient with urothelial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with urothelial cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Fight Bladder Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Supporting patients & carers with bladder cancer ☒ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with urothelial cancer? **If you are a carer (for someone with urothelial cancer) please share your experience of caring for them**	Quotes from patients: "It has been 2 years since I had my radical cystectomy. My health is unpredictable at best. I've struggled with stomach-ache and cramps, diarrhoea, vomiting, breathlessness, phantom pain where things were removed. I have an itchy rash spreading over the area around my stomach. I have good days, bad days, and OK days. "Five years ago, this month was when I got my BC diagnosis. Now here it is five years later, no cancer, and millions of fabulous, unbelievably wonderful memories later. When I look back, losing my bladder was such a tiny, tiny price to pay for all of that! I've been here to see the grandchildren grow, watch them enjoy their sports, dance recitals, graduate high school, and the littlest one (now almost 6) actually knows who I am instead of learning who I "was". The aches and pains that I have now from older age are amazing because I'm here to complain about them!" "Four years ago, I was hooked up to the Da Vinci robot having my bladder and bits removed. I hoped I had made the right decision, and every day I've had since has made me sure that I did. 1,460 bonus days without cancer so far. I'd had hundreds of opportunities to live life, enjoy watching the grans grow up, learn new things, and try to pay it forward. What a tiny, tiny price to pay for all of that!" From carers: "My Dad was diagnosed with bladder cancer in 2006. We'd never heard of anyone having bladder cancer before. I can remember him phoning to say he was on his

	way home, and then walking into the kitchen and telling us he had cancer, and extremely aggressive cancer at that. We decided as a family to go straight for the RC (we just wanted it out of his body) and just weeks later we dropped him off at the hospital for his 14-hour surgery. My Dad was a very fit and healthy 70-year-old, and had no side-effects from the chemo, and it wasn't long before he was back doing his bits of gardening for people. Apart from chronic constipation, and breaking his shoulder in two, he's kept reasonably fit and well. That was until he developed stomach pain. During a phone call from the hospital, we were told my dad, once again, has cancer. Sadly, nothing can be done, and it's a case of just keeping him as comfy as possible."
7a. What do you think of the current treatments and care available for urothelial cancer (specifically resected high-risk invasive urothelial cancer) on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	From patients: "Nearly 3 years on from radical cystectomy and becoming a 'bag lady' for life, and another "all clear". I don't share this to be insensitive to those who aren't dealing with such happy news, but to hopefully encourage anyone facing the daunting treatment. The new normal can, with a bit of luck, be a happy and healthy one." "6 years ago, I had my radical cystectomy, learned how to deal with a stoma, spent 16 days in hospital - had cannulas and drips in both arms for quite a few days and getting out of bed without help was impossible with drips in both arms. Eventually got out of hospital (there were days when I never thought I would), cried when I got to my brother's (stayed with him for 2 weeks). Got back to my home having not been there for a month and never looked back. Been clear of cancer and been fine ever since." "Two years ago, I was a jabbering mess sat waiting for my operation. Spent 7 days in hospital, home for Christmas and the next few weeks were very hard, but I managed to get back to work full time within 6 weeks. Not going to lie, it was tough but now I am happy with my lot, my life has not changed that much living with a bag, and I am grateful for it every day as it saved my life. Just waiting for results of my annual CT scan now (the waiting is always the worst)."

8. If there are disadvantages for patients of current NHS treatments for urothelial cancer (for example, how ~~nivolumab~~ current treatments are given or taken, side effects of treatment, and any others) please describe these	From patients: "When follow up biopsies showed recurrence of high grade TCC with invasion of the lamina propria, I decided it was time for a radical cystectomy before my high grade cancer became invasive. I did well with the surgery and didn't miss my bladder one bit, but it left me severely incontinent" From carers: "Two years ago, hubby almost died after a massive post-op infection. Since then, he's battled crippling fatigue and whole raft of other problems caused by the chemo he had prior to his radical cystectomy, some of which are now lifelong and mean he was not able to return to his old job."
9a. If there are advantages of nivolumab over current treatments on the NHS, please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nivolumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	The most important advantage is increased disease-free survival. In the CheckMate 274 trial involving people with high-risk muscle-invasive bladder cancer who had undergone radical bladder surgery, disease-free survival was longer with adjuvant nivolumab than with placebo. The median disease-free survival in the intention-to-treat population was 20.8 months (95% confidence interval 16.5 to 27.6) with nivolumab and 10.8 months (95% confidence interval 8.3 to 13.9) with placebo. Health-related quality of life – as assessed by the EORTC-QLQ-C30 global score – did not deteriorate in the nivolumab versus placebo study arms. From carers: "My Dad had 13 infusions so far, every 2 weeks. He has completed 6 months on this now. My oncologist says, after recent scans and general condition of my father, the disease can be considered as stable. Thankfully, he had no major side effects from nivolumab so far. He will continue on the same with scan after next 4 infusions"

	"We had the first infusion. He doesn't have any side effects. The oncologist said that it might take 2 or 3 infusions to see if there is impact onto his functions. Our check point is in 4-months' time. That when we will get some idea if this is an effective treatment."
10. If there are disadvantages of nivolumab over current treatments on the NHS please describe these. For example, are there any risks with nivolumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	In the CheckMate 274 trial, Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 17.9% and 7.2% of patients in the nivolumab and placebo arms, respectively. From a carer: "My Dad has lower back pain and urethral region pain due to the tumours there, but pain meds help on that to some extent."
11. Are there any groups of patients who might benefit more from nivolumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	It appears that the PD-L1 ≥ 1% population benefited more from treatment. It would be interesting to know why this PD-L1 ≥ 1% population has responded more positively to checkpoint inhibitors compared to other bladder clinical trials. However, Fight Bladder Cancer would be very concerned if this treatment was just restricted to just the PD-L1 ≥ 1% population, as this study also demonstrated benefit to the entire population regardless of PD-L1 status.
12. Are there any potential equality issues that should be taken into account when considering urothelial cancer and nivolumab? Please explain if you think any groups of people with urothelial cancer are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Women are often diagnosed much later with bladder cancer, compared to men with bladder cancer. Women are also more likely to die of bladder cancer. These issues should be taken into account when considering this technology.

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Urothelial cancer has come near 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.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: **Exclusion of cisplatin-based adjuvant chemotherapy as a comparator** **How often is cisplatin-based adjuvant chemotherapy used in clinical practice in this population?**	In this population, cisplatin-based adjuvant chemotherapy is rarely used.

Issue 2: **The use of semi-parametric models to fit to disease-free survival (DFS) Kaplan-Meier estimates**	We are unable to comment
Issue 3: **Use of utility (quality of life) data from Janssen et al.** **How appropriate is this source to inform quality of life in this population?**	Unable to comment
Issue 4: **The average age of patients in the UK is likely to be older than those recruited to CheckMate 274 (resected high-risk invasive urothelial cancer)** **we consider patient perspectives may particularly help to address this issue**	In our experience, the average age of patients in the UK is likely to be of a similar age to those recruited to CheckMate 274. The average age of patients that Fight Bladder Cancer supports with resected high-risk invasive urothelial cancer is 62 years old, with a standard deviation of 14 years, and a range of 26 to 93 years.

Patient expert statement

From your experience, what is the average age of people with resected high-risk invasive urothelial cancer?	
Issue 5: **Assumption of an equal proportion of disease-free survival (DFS) events being deaths for nivolumab and placebo**	Unable to comment
Issue 6: **Patients in the disease-free survival health state have the same utility values (quality of life) as an age- and sex-matched population** **<u>we consider patient perspectives may particularly help to address this issue</u>**	The quality of life for a person with resected high-risk urothelial cancer is similar to that of those who are disease-free. Patients say: “Life with a bag isn’t the end of the world. No more pain, surgeries, treatments etc. I’ve had my bag for 6 months. Life is good and I feel good. For the first time since cancer diagnosis early 2013 I feel like I’m finally recovering. It’s an adjustment but not near as bad as your imagination leads you to believe” “As for quality of life, the biggest impact may be to sexual function, however a referral to a sexual dysfunction specialist can help with that. As far as everything else, having this surgery won't change who you are or what you can do.”

Patient expert statement

How would you describe the quality of life for a person with resected high-risk urothelial cancer who are disease-free?	"I had my bladder removal a year ago. I swim 3 times a day, I don't need to get up in night for pee. Down sides? Libido almost zilch but I am 70 after all. After all said and done I'm alive, fit, strong and happy. "When I first diagnosed for 18 months, I was determined to keep my bladder, I couldn't think of any worse than having a bag. But it came back twice and then removal seemed better than constant hospital appointments and treatments. I was alive but not living any kind of life. I had my bladder removal 2 years ago so am a bag lady, and everything is pretty fab now. I have yet to find anything I can't do now that I did before." "I had my bladder removed 13 years ago. Stage 2. You soon adapt to the bag, and it doesn't stop me from doing much at all. We are pretty good at adapting." "I have a urostomy, so I'm a bag man! Since my bladder removal four years ago, I've climbed a small mountain, travelled to the opposite side of the world, and spent time in a very small Campervan touring around north island New Zealand. Having a bag is far better than being in a box !!"
Issue 7: **Patients in the long-term disease-free survival (DFS) health state have the same life expectancy as general population** **<u>we consider patient perspectives may</u>**	We do not have data to answer this question

particularly help to address this issue **How is life expectancy impacted when people are in a long-term disease-free state?**	
Issue 8: Uncertainty surrounding the assumed cure point **we consider patient perspectives may particularly help to address this issue** **Is there any timepoint without disease recurrence after which a person with this condition can be assumed to be cured?**	There is no clear consensus from the patient perspective. Patients say: “5 years free was the point they said not to go back” “I was told that if I was clear for 5 years, I would need no more checks.” “I won’t consider myself completely cancer free until I’ve had 5 full years with no recurrence.” “I'm almost 5 years cancer free post bladder removal, but still at risk for upper tract recurrence.” “Cancer is cancer. You either have it, had it treated, are in treatment, or never had it. I consider myself to actively have cancer until I hit the five-year mark. At that point, I'd consider myself a cancer survivor.” “I was told all clear after 10 years.” “I just say that I have no current evidence of disease (NED). I don't think I'll ever consider myself "cured"” “I was told not to say cancer free, just that it didn’t show up on the pet scan” Carers say: “My husband says rather morbidly “you are cured when you die of something else”. He has a point though!”

Issue 9: **The lack of subgroup analysis in the company's submission**	The study was not powered for subgroup analysis. Fight Bladder Cancer would be very concerned if this treatment was just restricted to just some subgroups, as this study also demonstrated benefit to the entire population.
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The most important advantage of nivolumab is increased disease-free survival from a median of 10.8 months to 20.8 months.
- In this population, cisplatin-based adjuvant chemotherapy is rarely used
- The average age of patients that Fight Bladder Cancer supports with resected high-risk invasive urothelial cancer is 62 years old
- The quality of life for a person with resected high-risk urothelial cancer is similar to that of those who are disease-free
- Fight Bladder Cancer would be very concerned if this treatment was just restricted to just some subgroups, as this study also demonstrated benefit to the entire population.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 17 January 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: **Exclusion of cisplatin-based adjuvant chemotherapy as a comparator**	No	There are three relevant treatment scenarios for bladder cancer in UK. 1. Patient has received neo-adjuvant cisplatin-based chemotherapy. This patient would not be offered adjuvant chemotherapy of any sort, and so, for this group, it is reasonable to exclude it as a comparator. 2. Patient did not receive neo-adjuvant chemotherapy (for whatever reason) and is not suitable for cisplatin post-cystectomy. This patient would not be offered adjuvant chemotherapy of any sort, and so, for this group, it is reasonable to exclude it as a comparator. 3. Patient did not receive neo-adjuvant chemotherapy (for whatever reason) and is suitable for cisplatin post-cystectomy. For this group of patients, it is unreasonable to exclude cisplatin-based chemotherapy as a comparator. This is accepted as standard treatment and is recommended in the NICE guideline. In addition, for patients with UTUC the considerations are different. Neoadjuvant chemotherapy is not considered standard of care in UK and is rarely, if ever, offered. Thus, all patients with muscle invasive disease should be considered for

		adjuvant chemotherapy. Furthermore, the UK POUT trial demonstrated activity for carboplatin in place of cisplatin in patients unsuitable for cisplatin due to impaired renal function. Whilst it is possible that there will be small group of patients unsuitable for cisplatin for reasons other than renal function (eg. heart failure, hearing loss, performance status 2 or worse) following nephroureterectomy, for the great majority of patients undergoing nephroureterectomy, platinum-based chemotherapy would be the standard of care. Thus, for this subgroup, the exclusion of this from the comparator is unreasonable. We appreciate the difficulties in segmenting the patients in the model in this way, but the population in CM-274 appears to have included a significant proportion of patients who did not receive chemotherapy in the neoadjuvant setting who would have been considered suitable to receive it adjuvantly, and so the broad exclusion of this comparator is unreasonable. However, for the subgroups of patients who did received neo-adjuvant chemotherapy, and those with bladder cancer unsuitable for cisplatin, it would be important to know whether the addition of adjuvant nivolumab is effective and cost-effective.
Issue 2: **The use of semi-parametric models to fit to disease-free survival (DFS) Kaplan-Meier estimates**	No	We have no strong views on this issue.
Issue 3: **Use of utility data from Janssen et al.**	Yes/No	The ERG's suggestion to include other sources of utility data seems reasonable, but we note this has minimal impact on the ICER, suggesting that this issue should not be the defining one in making a recommendation in favour or against the technology.

Issue 4: **The average age of patients in the UK is likely to be older than those recruited to CheckMate 274**	Yes/No	We are not sure that this is a reasonable challenge: whilst, in general, the average age of patients entering trials is younger than the 'real-world' population, the ERG does not appear to have considered any actual evidence to support their challenge. Radical cystectomy is a major operation (and radical nephrouretectomy, though less morbid, is not undertaken lightly). The main purpose of such radical treatment is to prolong survival by reducing the risk of recurrent urothelial cancer, and so case selection should already consider the patients' life-expectancy 'but for urothelial cancer'. Thus, even if the ERG's assertion is correct (that the average age in UK is higher), it would not be correct to broadly assume that the life expectancy of these patients undergoing surgery 'but for urothelial cancer' is the same as the general population, as the older patients are likely to be exceptionally fit for age. In the absence of direct evidence to support this uncertainty, we would prefer to stick with the company's submission in this regard.
Issue 5: **Assumption of an equal proportion of disease-free survival (DFS) events being deaths for nivolumab and placebo**	No	This is a curious observation which is not entirely unexpected given the relative immaturity of the CM-274 data on which the observation is based. The availability of immunotherapy at the point of relapse for patients in the placebo arm may, at least in part, explain the lower proportion of deaths in the placebo arm.
Issue 6: **Patients in the disease-free survival health state have the same utility values as an age- and sex-matched population**	No	Whilst many of these patients undoubtedly have negative impacts from permanent changes in urinary and sexual function, the impact of these on global utility are known to be short-lived as patients adapt to survivorship.
Issue 7: **Patients in the long-term disease-free survival (DFS) health state have the same life**	Yes/No	Most clinicians accept that the increased relapse or death from urothelial cancer in patients who have remained alive and recurrence-free for 5 years is so low, that they are generally discharged from follow up for relapse. We note the very small impact of this on the ICER.

expectancy as general population		
Issue 8: **Uncertainty surrounding the assumed cure point**	No	Most clinicians accept that the increased relapse or death from urothelial cancer in patients who have remained alive and recurrence-free for 5 years is so low, that they are generally discharged from follow up for relapse. Nonetheless it is likely there is never a point at which a patient has zero risk of death from urothelial cancer. We note that the data used by the ERG to support their argument are derived from a group of patients who did not undergo neoadjuvant chemotherapy. In UK, it is likely that most patients who might receive adjuvant nivolumab will have received neoadjuvant chemotherapy (for the reasons outlined in answer to issue 1), and so these data are probably not relevant to the specific population under consideration in a UK HTA of adjuvant nivolulumab.
Issue 9: **The lack of subgroup analysis in the company's submission**	Yes/No	With regards to PDL1 status, we agree that this may demonstrate heterogeneity in the ICER. However, PDL1 status is not routinely checked in this population in the UK and other data in advanced urothelial cancer have revealed this not to be a useful predictive marker for immune checkpoint therapy in most situations. Thus, unless PDL1 expression were demonstrated to be a clinically useful predictive biomarker in this treatment setting, it seems irrelevant to the HTA. However, we do note the ERGs passing reference to subgroup analyses by tumour location. We believe this to be a very important subgroup analysis.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Failure to consider UTUC as a separate disease entity.	Please indicate the section(s) of the ERG report that discuss this issue. Discussed in section '**UTUC',** but the issue has broad implications for the analysis.	No	Prior to CM-274, studies of adjuvant treatment in urothelial cancer were conducted either purely in bladder cancer, or purely in UTUC, and so the inclusion of both diseases in the same trial (and thus the same HTA) is clinically puzzling. The diseases are treated differently with different operations. Patterns of relapse differ, as does the underlying biology of the two diseases (particularly with regard to factors which might lead to effectiveness of nivolumab – UTUC may be less likely to respond). It is, therefore, a puzzling *a priori* assumption that this would not be an important source of heterogeneity. Furthermore, the systemic therapy of these two conditions has always been different with little or no use of neoadjuvant chemotherapy in UTUC in the UK. In addition, the results of the POUT trial became available during the conduct of CM-274 and so it is likely that outcomes for patients with UTUC are now better than those seen in the comparator group (as the standard of therapy is no longer BSC).
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Confidential until published

Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal/ Addendum: ERG comments on company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Geoff Holmes, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	21st April 2022

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/39/77.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

1 Introduction

The company submission (CS)[1] was submitted in August 2021. The company's base case deterministic incremental cost-effectiveness ratio (ICER), expressed in terms of cost per quality-adjusted life year (QALY) gained was £32,813 when compared to best supportive care (BSC).

Subsequently, further data relating to the pivotal study, CheckMate 274, have become available. In January 2022, the company submitted its technical engagement (TE) response for the appraisal of nivolumab for treatment of resected high-risk invasive urothelial cancer.[2] The company's response was structured around nine key issues that were raised within the Evidence Review Group (ERG) report with the company presenting additional clinical effectiveness evidence from an updated database lock (DBL) (data cut-off 1st February 2021), which had an additional five months of follow-up and a minimum follow-up period of eleven months. Three sets of changes were made in the company's TE response: (i) an increase in the Patient Access Scheme (PAS) discount, from [redacted] to [redacted]; (ii) alternative distributions used to estimate disease-free survival (DFS), time on treatment, and death on recurrence based on the updated DBL; and (iii) a change in the utility estimates for the general population. Following these combined changes, the company's base case ICER became £27,030. The ERG produced a response to the company's document that was sent to NICE in January 2022.[3]

Following this iteration, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion[4] for nivolumab which the company believes will lead to an anticipated European Medicines Agency licenced indication of *"OPDIVO as monotherapy for the adjuvant treatment of adults with MIUC [Muscle invasive urothelial carcinoma] with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC"*. Previously the company had submitted an ICER for all PD-L1 expression groups combined; the ERG had concerns about this grouping and requested that the company provide ICERs by PD-L1 expression subgroup. Following the CHMP opinion, the company has submitted revised analyses focussing only on a population with a tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (hereafter termed the PD-L1 ≥1% population) with accompanying supporting documentation.

This document provides a commentary on the company's response following the anticipated licence-change (CRFALC) and should be read in conjunction with the ERG report.[5] The CRFALC included an updated version of the executable model.

For clarity, Section 2 provides a summary of the company's changes since the model submitted with the CS and provides information relating to the new analyses of time-to-event data from CheckMate 274 based on the more recent DBL and being restricted to the PD-L1 ≥1% population. Section 3

provides a fuller description of the CRFALC and the ERG's critique of these points. Section 4 presents the results of the company's updated base case and scenario analyses and additional analyses undertaken by the ERG. Overall conclusions are presented in Section 5. All results presented in this document refer to the PD-L1 ≥1% population unless explicitly stated and include the latest PAS discount for nivolumab. A confidential appendix provides the results when PAS for comparator treatments potentially used in the decision problem are incorporated.

In order to aid reading this report, the key limitations in the company's updated base case are summarised in advance of the more detailed critique, along with the approaches undertaken by the ERG to provide ICERs, expressed in terms of cost per QALY gained, that attempt to address these limitations.

1.1 Key limitations within the company's updated base case in the CRFALC

The company's updated base case assumes that based on goodness-of-fit statistics a Generalized gamma distribution is the best model to estimate DFS and that a patient is cured after 5 years residing in the disease-free state. A distinction should be made between those patients who are deemed cured of their urothelial carcinoma (UC) episode, but who have a greater risk of death due to the clinical burden relating to the UC episode, and patients who have the same utility and risk of death as an age- and sex-matched population; this latter group have been denoted by the ERG as 'fully cured'. The company assumes that patients are fully cured at 5 years. This is at odds with the extrapolation of its chosen Generalized gamma distribution which indicates that at 5 years the hazard of death is considerably higher in patients with resected high-risk UC than for an age- and sex-matched population. This discrepancy is further supported by data from a study with similar patients with longer follow-up,[6] and by clinical opinion provided to the ERG suggesting that relapse after 5 years is possible. In order to address this inconsistency, the ERG has explored three alternative assumptions.

1) Using the Generalized gamma distribution preferred by the company, but assuming an increased risk of death, using a standardised mortality rate (SMR) based approach for an additional 5-year period in the disease-free state associated with the clinical burden of people with a history of resected high-risk UC. After 10 years in the disease-free state the patient is assumed to be fully cured.
2) Using a Gompertz distribution to model DFS, noting that before 5 years the risk of death predicted by the Gompertz models becomes similar to that of an age- and sex-matched population and assuming that patients are fully cured at this time point. Note that in this exploratory analysis the model has been amended such that the risk of DFS cannot fall below mortality risk of an age- and sex-matched population.

3) Increasing the time in the disease-free state before which a patient is considered fully cured to 10 years and using the Generalized gamma distribution preferred by the company until this timepoint.

All three of the ERG's exploratory analyses have limitations. The first and third analyses apply arbitrary time points at which the increased risk of death or a DFS event is assumed to cease. The second has the same limitation as the company's base case in that the evidence does not support the assumed full cure at 5 years, but unlike the company's base case, there is not a greater risk of death than the age- and sex-matched population which is instantly removed at 5 years. The ERG notes that neither the company's base case nor any of the ERG's exploratory analyses are ideal in modelling longer-term risk of death or DFS but believes that consideration of the four methods will be informative to the NICE Appraisal Committee.

The company's base case has a further key limitation which is that no ICERs have been provided when a patient could be treated with cisplatin-based adjuvant chemotherapy. Because of this, the ERG highlights that the ICERs presented are applicable only for patients in whom cisplatin-based adjuvant chemotherapy is not appropriate.

1.2 Summary of differences in the company's updated base case and the ERG alternative scenarios

As a reference point, Table 1 summarises key characteristics of the company's updated base case and the three alternative scenarios run by the ERG. Based on the later DBL and focussing on the PD-L1 ≥1% population, the ERG has amended its assumption relating to the proportion of DFS events that are deaths; this is described more fully in Section 3.5.

Further, the CRFALC also includes an analysis where people on BSC receive atezolizumab on progression. This new analysis has been detailed and critiqued (Section 3.11) in this report, assuming the list price of atezolizumab. A confidential appendix provides the ICER when the PAS for atezolizumab is incorporated.

Table 1: Summary of key characteristics of the company's updated base case, and three alternative scenarios run by the ERG

Scenario	Distribution used to model DFS	Time point at which a cure of UC is assumed (years)	Time point when a patient is considered fully cured†	Is a utility decrement applied for disease-free patients compared with age- and sex-matched general population values?	Method for calculating the proportion of DFS events that are deaths
Company's updated base case	Generalized gamma	5	5	No	Pooled from a logistic regression
ERG Alternative Scenario 1	Generalized gamma	5	10	Yes	Pooled from data observed in the CheckMate 274
ERG Alternative Scenario 2	Gompertz	5	5	Yes	Pooled from data observed in the CheckMate 274
ERG Alternative Scenario 3	Generalized gamma	10	10	Yes	Pooled from data observed in the CheckMate 274

†At which point the risk of death and utility are assumed to be equal to the age- and sex-matched general population values
DFS – disease-free survival; ERG – Evidence Review Group; UC – urothelial cancer.

2 Summary of the CRFALC

Following the CRFALC, where only a PD-L1 ≥1% population was considered, and time-to-event data re-analysed, the company's deterministic base case ICER became £11,105 (probabilistic ICER = £11,300). When atezolizumab, at list price was included as a treatment after progression on BSC, nivolumab dominated BSC. Scenario analyses were presented by the company; for brevity, these are not all presented in this document.

Table 2 summarises the company's original base case model, the ERG's preferred analysis at the time of the ERG report and the company's updated base case model as presented in the CRFALC. A more detailed discussion of each issue including an ERG critique and, where appropriate, changes to the ERG base case is provided in Section 3, although a summary of the more mature data from CheckMate 274 following the new DBL is provided in Section 2.1.

Table 2: Summary of company's original base case (CS), ERG preferred analysis (ERG report) and company's updated base-case (CRFALC)

Aspect of model	Company's original base case	ERG preferred analysis after TE	Updated company base case model after CRFALC	Did the assumption change between the original and CRFALC base case?
Amendments relating to key issues presented in ERG Report				
Issue 1: Exclusion of cisplatin-based adjuvant chemotherapy as a comparator	Cisplatin-based adjuvant chemotherapy was excluded from the decision problem	Cisplatin-based adjuvant chemotherapy to be included in the decision problem or recommendations only to apply to those in whom cisplatin-based treatment is not an option	Cisplatin-based adjuvant chemotherapy remains excluded from the decision problem	No
Issue 2: The use of semi-parametric models to fit to DFS Kaplan Meier (KM) estimates	Use of the KM estimates and then Weibull distributions for both nivolumab and BSC	Scenario analyses allowing the Appraisal Committee to see the results from different assumptions	Use of the Generalized gamma distributions for both nivolumab and BSC	Yes
Issue 3: Use of utility data for the general population from Janssen *et al.*[7]	Data sourced from Janssen *et al.*[7]	Data to be sourced from Ara and Brazier[8]	Data sourced from Ara and Brazier[8]	Yes
Issue 4: The average age of patients in the UK is likely to be older than those recruited to CheckMate 274	Company base case uses the mean age from CheckMate 274 ([redacted] years)	Not known, but clinical advice suggests that in English practice the mean patient age would be greater than seen in CheckMate 274	Uses the mean age from CheckMate 274 ([redacted] years). An additional scenario analysis using a higher age ([redacted] years) is provided.	No
Issue 5: Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo	Applied a fixed probability of [redacted], calculated from a logistic regression that a recurrence event is a death for both arms.	Using treatment specific values for each arm.	The method used in the CS, although the value is now [redacted]. An additional scenario analysis was presented using arm-specific proportions.	No, although the probability that an event is a death has changed based on more mature data
Issue 6: Patients in the DFS health state have the same utility values as an age- and sex-matched population	That patients in the DFS state had the same utility values as an age- and sex-matched population	That a decrement be applied to the general population utility to consider the impacts of having had a resected urothelial carcinoma (UC)	That patients in the DFS state have the same utility values as an age- and sex-matched population.	No

Aspect of model	Company's original base case	ERG preferred analysis after TE	Updated company base case model after CRFALC	Did the assumption change between the original and CRFALC base case?
Issue 7: Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population	That patients in the DFS state had the same life expectancy as an age- and sex-matched population	That it is plausible that the life expectancy for people with DFS and resected UC is lower than the general population.	That patients in the DFS state have the same life expectancy as an age- and sex-matched population.	No
Issue 8: Uncertainty surrounding the assumed cure point	Cure point assumed at 5 years	Exploration of longer cure points due to clinical advice stating that recurrence can occur after five years and due to published data also indicating this.	Cure point assumed at 5 years. Scenario analyses run assuming 10 years and 3 years cure points.	No
Issue 9: The lack of ICERs related to subgroup analysis in the company's submission	The company did not provide ICERs conditional on PD-L1 status of the tumour	Analyses to be presented based on whether the PD-L1 status of the tumour was ≥ 1% or not. The ERG notes that the NICE scope stated that these would be considered if evidence allows, and that CheckMate 274 was stratified on this factor	The company provides analyses for the PD-L1 ≥ 1% only	Yes
Other amendments to the CS base case contained in the CRFALC				
Additional issue 1: Change in the PAS	Simple discount of [redacted]	Not Applicable	Simple discount of [redacted]	Yes

2.1 Additional data from CheckMate 274

The CRFALC reports new DFS data, specifically for the PD-L1 ≥ 1% population, from CheckMate 274, an ongoing Phase III, randomised (1:1 ratio), international multi-centre, double blind, placebo-controlled study. The updated DBL provided DFS data with eleven months minimum follow-up. In its updated survival analyses, the company followed the ERG's preferred approach of fitting only the fully parametric survival models to the data instead of considering semi-parametric models which it previously preferred. Six fully parametric models were considered with independent models fitted to data for each arm. The company presented Kaplan-Meier (KM) functions for the nivolumab and placebo arms alongside plots of the predicted survival functions from the fitted models. These are reproduced here as **Figure 1** for the nivolumab arm and **Figure 2** for the placebo arm.

Figure 1: Investigator-assessed DFS for nivolumab: Standard statistical models overlaid upon Kaplan-Meier functions

Figure 2: Investigator-assessed DFS for placebo: Standard statistical models overlaid upon Kaplan-Meier functions

The company also presented Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for the fitted survival models which are reported in

Table 3 (nivolumab) and Table 4 (placebo). The evidence for how well specific models fit the observed data summarised by the company is shown in Figure 3 based on Burnham and Anderson[9] and Raftery.[10]

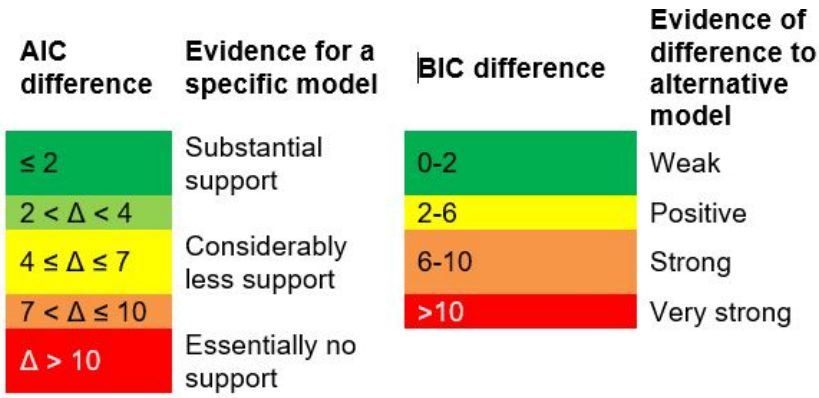
Table 3: Nivolumab DFS: AIC and BIC values for parametric models based on the updated DBL (11 months minimum follow-up)

Extrapolation model	DFS			
	AIC		BIC	
	Value	Difference to base case	Value	Difference to base case
Generalized gamma (base case)	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Placebo DFS: AIC and BIC values for parametric models based on the updated DBL (11 months minimum follow-up)

Extrapolation model	DFS			
	AIC		BIC	
	Value	Difference to base case	Value	Difference to base case
Generalized gamma (base case)	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3: Evidence of support for a model compared to the model with the lowest AIC / BIC value



The company correctly notes that, according to the AIC and BIC statistics, the Generalized gamma model is the model with best fit to the observed data for both arms. For placebo, there is strong evidence that the Generalized gamma is the best fit; however, this is less definitive for nivolumab, with the Gompertz model having AIC and BIC values closer to the Generalized gamma. However, as detailed in Section 3.2, the AIC and BIC statistics may be misleading if the time of events are protocol-driven.

The company chose the Generalized gamma distribution to represent DFS for both treatment groups in its updated economic analysis. Further evidence presented by the company is discussed in the ERG critique in Section 3.2.

3 ERG critique of the CRFALC

This ERG addendum is structured around the nine key issues in the initial ERG report which are detailed in Sections 3.1 to 3.9. Each section summarises the issue as reported by the ERG, new data presented by the company (if any), the view put forward by the company, and any new ICERs generated when using the company's preferred assumptions. Each section also includes the ERG's opinion on the new data / assumptions; the impacts of these assumptions on the ICER are presented in Section 4 alongside the company's preferred ICER and an ICER preferred by the ERG. Section 3 also contains two new issues, which include a model correction made by the ERG and an additional concern relating to the new analysis that includes atezolizumab treatment following progression after BSC treatment.

3.1 Key Issue 1: Exclusion of cisplatin-based adjuvant chemotherapy as a comparator

In the CS, and reiterated in the TE response, the company states that '*Cisplatin is not a relevant comparator of interest for nivolumab in this indication*.' It notes that '*Patients who were eligible and willing to receive adjuvant cisplatin based adjuvant chemotherapy were not eligible per study inclusion criteria.*' that '*cisplatin-eligible patients may not have been willing to be randomized to a placebo arm.*' and that therefore there '*is no evidence available from CheckMate 274 for patients who would have actually received chemotherapy in a non-clinical trial*'. The company provides further evidence from John *et al*.[11] and Witjes *et al*.[12] and from clinical advice to the company all of which support the company's assertion that the proportion of patients likely to receive cisplatin-based adjuvant chemotherapy is low, and that European Association of Urology (EAU) guidelines do not report an '*unequivocal recommendation for the use of adjuvant chemotherapy.*' Critically, the ERG notes that none of these sources suggests that the percentage is zero with the company stating that '*only a minority of patients actually receive adjuvant cisplatin-chemotherapy.*'

The company reiterates the limitations in the indirect treatment comparison (ITC) conducted to assess the relative efficacy of nivolumab and cisplatin-based adjuvant chemotherapy, which was updated for the TE response. The key limitations cited by the company were the considerable heterogeneity of studies, limitations in the evidence base and small sample sizes. EAU guidelines were quoted which state that '*All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases).*[12]' The results from the company's ITC had wide credible intervals which crossed unity. The company reports that '*using the latest data from the updated DBL (11 months minimum FU), the updated hazard ratio (HR) of nivolumab versus placebo from group C (excluding UTUC patients from both arms) was* [redacted] *and the updated HR of nivolumab from group C (UTUC patients removed) versus adjuvant chemotherapy from the two gemcitabine studies and Sternberg pooled was*

[redacted].' The ERG acknowledges the limitations of the ITC but notes that the onus is on the company to show that the evidence indicates nivolumab is more clinically effective than cisplatin-based treatment given the marked difference in acquisition prices. The ITC was not updated in the CRFALC, meaning that the relative efficacy of nivolumab and cisplatin-based adjuvant chemotherapy in those with a PD-L1 tumour expression ≥ 1% is unknown.

The ERG maintains its view that cisplatin-based adjuvant chemotherapy is likely to be an appropriate treatment option for a proportion of patients in accordance with the clinical advice received by the ERG. For these patients, the company declined to present an ICER to support any assumption that nivolumab treatment would represent a cost-effective use of resources. Therefore, the ERG maintains its opinion that based on the current available evidence, that it is likely that cisplatin-based regimens would either dominate nivolumab or that the ICER for nivolumab would be greater than £30,000 per QALY gained. The ERG also stills believes that the ICERs presented in the company submission are applicable only to the comparison of adjuvant nivolumab and BSC.

3.2 Key Issue 2: The use of semi-parametric models to fit to DFS Kaplan Meier (KM) estimates

Having reviewed the evidence presented in the CRFALC, the ERG is satisfied that the Generalized gamma is a reasonable choice of distribution to model the DFS in both treatment arms. However, this is subject to a number of limitations, described in the rest of this section, which means the choice of this distribution over the Gompertz is not as clear-cut as the company concluded.

As in our previous report, the ERG notes the company's statements in the CS that the Gompertz distribution *"does not accurately capture the pattern of the KM data from the trial, in particular the protocol-induced features, such as the 'stepwise' nature of the data, particularly in the first year"*. In addition, the company highlighted *"the complex hazard profiles underlying DFS – chiefly the steepness of the increase at 3 months – [which] were predominantly a protocol-induced feature due to the timing of tumour assessments"*. The Generalized gamma distribution has 3 parameters whilst the Gompertz distribution has 2 parameters. This gives extra flexibility which allows a better fit to the protocol-induced features. The ERG's view is that fitting to the protocol-induced features remains potentially undesirable if these patterns would not be observed in clinical practice. For this reason, the significantly better fit of the Generalized gamma distribution, judged on the basis of AIC and BIC values could be misleading if the true underlying hazard was monotonically decreasing rather than having an increasing hazard which peaks at the time of first tumour assessment and then declining thereafter.

In the CRFALC, the company provided B-spline smoothed and kernel smoothed versions of the hazards for nivolumab (**Figure 4**) and placebo (**Figure 5**). The B-spline versions of smoothed hazard were monotonically decreasing, which may be more clinically plausible and which matched very closely to

the hazard predicted by the Gompertz model for nivolumab, but less well for placebo. However, the hazards using the Gompertz models fall below that estimated from life-tables at approximately [redacted] months in the nivolumab arm, and [redacted] months in the placebo arm, which the ERG believes is implausible.

The ERG comments that the company's preferred Generalized gamma distributions have hazards of a DFS event at 5 years which are higher than the hazard of death estimated from life tables; this is not compatible with the company's assumption that the patient is fully cured at 5 years. This was also observed in the smoothed hazard for progression or death derived from Sternberg *et al.*[6] (progression free survival was assumed to be generalisable to DFS) that is shown in Figure 6.

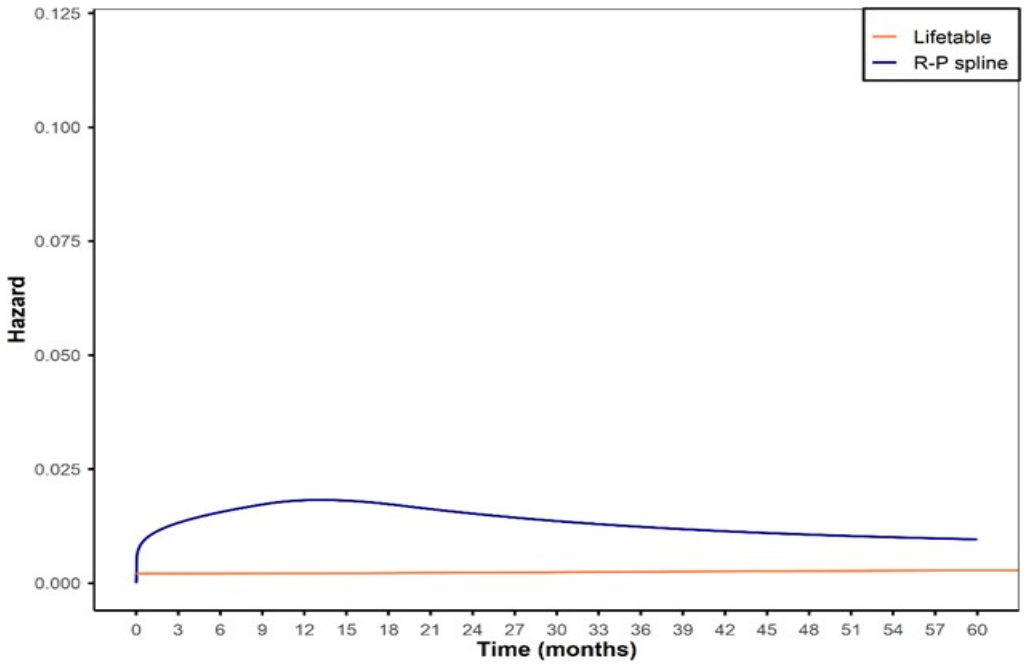
Figure 4: Investigator-assessed DFS for nivolumab (CheckMate 274, updated DBL with 11 months minimum follow up): Smoothed observed hazard function estimates for the trial data together with predictions from the Gompertz and Generalized gamma distribution models

Figure 5: Investigator-assessed DFS for placebo (CheckMate 274, updated DBL with 11 months minimum follow up): Smoothed observed hazard function estimates for

the trial data together with predictions from the Gompertz and Generalized gamma distribution models

[redacted]

Figure 6: Smoothed hazard estimates of PFS from the Sternberg *et al.* deferred arm against life-table hazard (reproduced from Figure 4 of the company's TE response)



For both the nivolumab and placebo arms, the Generalized gamma distributions estimate lower proportions of survivors than the Gompertz distributions as shown in **Figure 7**. This differs from the results generated in the company's TE response, where the generalized F and Gompertz distributions predicted similar estimates of survival for nivolumab, but the generalized F predicted a lower proportion of survivors than the Gompertz for placebo. The differences in the absolute survival difference between the distributions selected at CRFALC and at TE explain the fact that the choice of distribution has much less of an impact on the ICER in the CRFALC than it did with the company's response at TE.

Figure 7: Comparison of KM functions from the updated database lock (11 months minimum follow-up) and fitted survival models using the Generalized gamma and Gompertz distributions

In conclusion, the ERG is satisfied that the Generalized gamma distributions are a reasonable choice for both arms but that the use of this distribution is incompatible with an assumption that patients are fully cured at 5 years. Gompertz distributions are also plausible and would be compatible with this assumption although suggests a cure point at an earlier time point (approximately [redacted] years).

The ERG suggests that the results generated by the Generalized gamma and the Gompertz distributions are informative in exploring the cost-effectiveness of nivolumab; fortunately, there is not a large difference in the ICER using the different distributions.

3.3 Key Issue 3: Use of utility data from Janssen et al

In the CS, the company estimated utility data from Janssen *et al*.[7] The ERG preferred an alternative source, Ara and Brazier[8], which used more recent data, and importantly did not assume that utility remained constant after 75 years of age. In the CRFALC, the company has amended the model to use data from Ara and Brazier.[8]

3.4 Key Issue 4: The average age of patients in the UK is likely to be older than those recruited to CheckMate 274

In the CS, the company modelled a cohort of patients with the mean age as observed in CheckMate 274 ([redacted] years). Clinical advice provided to the ERG suggested that patients seen in clinical practice in England would likely be older than patients enrolled in the RCT. The ERG explored the sensitivity of the ICER to an arbitrarily increased age of 70 years in the ERG report, but did not have an accurate estimate of the true mean age for patients in the decision problem.

In its TE response, the company has stated that '*UK clinicians agree there is no major discordance between the mean age for MIUC patients in the CheckMate 274 trial versus UK clinical practice*.' This advice differs from that provided to the ERG which suggested that the age of patients in English practice will be higher than in CheckMate 274. The company provides a discussion of alternative data sources commenting on the limitation of these publications in accurately estimating the mean age for patients with MIUC at high-risk of recurrence following radical resection of invasive urothelial carcinoma, with a common reason being the heterogeneity of patients included in the studies. The company provides an alternative scenario which calculates a weighted median age of [redacted] years based on data reported from John *et al*.[11] based on the proportions and median ages of patients receiving neo-adjuvant chemotherapy, or not. A small limitation of the analyses in the CRFALC is that the mean age of the PD-L1 ≥ 1% population has been used.

The ERG has considered the comments in the company's TE response and CRFALC, keeping in mind the opinions of the experts providing clinical advice to the ERG. In the ERG base case, the age of the population has been maintained as the mean age of those in CheckMate 274, but an additional sensitivity analysis has been conducted using a mean age of 67 years, which was informed by the median ages in John *et al*.[11] and CheckMate 274.

3.5 Key Issue 5: Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo

The company approach in the CS was to pool data from the nivolumab and BSC arms to calculate the probability that a DFS event was a death and to use the same proportion for both treatment arms. The pooled value was calculated from a logistic regression. The ERG had commented that the '*observed proportion of deaths among DFS events were different between the trial arms:* [redacted] *versus* [redacted] *for nivolumab and placebo respectively*' and that the treatment-specific probabilities should be used. In its TE response, the company undertook an analysis using [redacted] for patients treated with nivolumab and [redacted] for patients treated with BSC. This slightly increased the ICER (from £27,030 to £27,186).

The company maintained the pooled approach in the CRFALC although the proportion of DFS events that were deaths has been recalculated using the updated DBL and the PD-L1 ≥ 1% population. A scenario analysis was performed by the company that showed that using treatment-specific rates resulted in a small decrease in the ICER.

Based on Table 11 of the CRFALC, the proportion of DFS events that were deaths was [redacted] was [redacted]%, individually being [redacted] ([redacted]%) for nivolumab and [redacted] ([redacted]%) for placebo. The more mature data has resulted in a smaller difference between the treatment-specific rates of death, and the ERG is now content to use a pooled estimate for both arms. The ERG has implemented this by assuming that [redacted]% of DFS events are deaths; this differs from the proportion estimated from the logistic regression, but the ERG prefers its simpler approach to that used by the company.

3.6 Key Issue 6: Patients in the DFS health state have the same utility values as an age- and sex-matched population

The company has assumed that the utility for people in the DFS state was equal to that of an age- and sex-matched population as the utility values calculated from CheckMate 274 exceeded those of the general population. However, the advice from ERG's clinical experts indicated that history of having a resected UC would, on average, have a detrimental effect on the patient's health-related quality of life (HRQoL) compared with an average person of the same age and sex without resected UC. The ERG also notes that patients with resected UC are also likely to have other comorbidities as do the general population and that the UC burden would be additional to these.

The company has maintained the approach used in the CS in the CRFALC stating that the 0.02 decrement in utility explored by the ERG was arbitrary. The ERG acknowledges the arbitrary nature of the value but believes this is a more plausible estimate than assuming no decrement which is not aligned with the clinical advice provided to the ERG.

The ERG has maintained the 0.02 utility decrement for patients in the DFS state until the time at which it was assumed that there would be no excess risk of mortality for patients treated with nivolumab compared with an age- and sex-matched population (See Issue 7). This period was assumed to be for a maximum of 10 years in the disease-free state when the Generalized gamma distribution was used, for a maximum of 5 years in the disease-free state when a Gompertz distribution was used and for a maximum of 10 years in the disease-free state when the cure point was assumed to be 10 years.

3.7 Key Issue 7: Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population

The company assumed that the life expectancy for people in the DFS state for at least five years was equal to that of an age- and sex-matched population. The TE response states that '*Clinical experts confirmed that 99% of recurrence would happen before the 5 year timepoint and it is reasonable to consider that patients will follow the general population mortality trend if they have not recurred after 5 years post-surgery.*' The company also states that such patients would be discharged with no further monitoring.

However, data reported by the company in its TE response, and replicated in Figure 6, indicate that the hazard of death remains much higher in those in the deferred treatment arm of Sternberg *et al*. at 5 years. The company states that this was "*a population similar though not exactly aligned to the CheckMate 274 trial*." These data when considered with the increased hazard of death predicted from the Generalized gamma distribution at 5 years compared with life table data (**Figure 4** and **Figure 5**) indicate that there is likely to be a considerable excess of risk of death for people with high-risk resected UC beyond 5 years.

The ERG appreciates that DFS is a composite endpoint that includes both recurrence and death but deems it logical that if the company assumes that the patient is cured of UC then the event must be a death. In order to estimate an SMR that would describe the increased risk of death compared with an age- and sex-matched population, the ERG used values contained within the model accompanying the CRFALC. The average of the hazard of a DFS event in the week before 60 months in the nivolumab and the placebo arm was extracted from the company's model and divided by the extracted hazard of all-cause mortality for the same period. This resulted in an estimated SMR of [redacted]. This was applied in ERG's scenario analysis based on Generalized gamma distributions for a period of 5 years, from year 6 to year 10, at which point the chance of a DFS event was small (see Figure 8 in the discussion of Issue 8). After 10 years residing in the DFS state, it was assumed that patients were fully cured and the hazard of death reverted to that of an age- and sex-matched population.

For the additional scenario analysis using a Gompertz distribution to estimate DFS for both nivolumab and BSC it was assumed that the risk of death was equal to that of an age- and sex-matched population after residing in DFS for five years (or before, if the hazard was assumed to be lower than the general population).

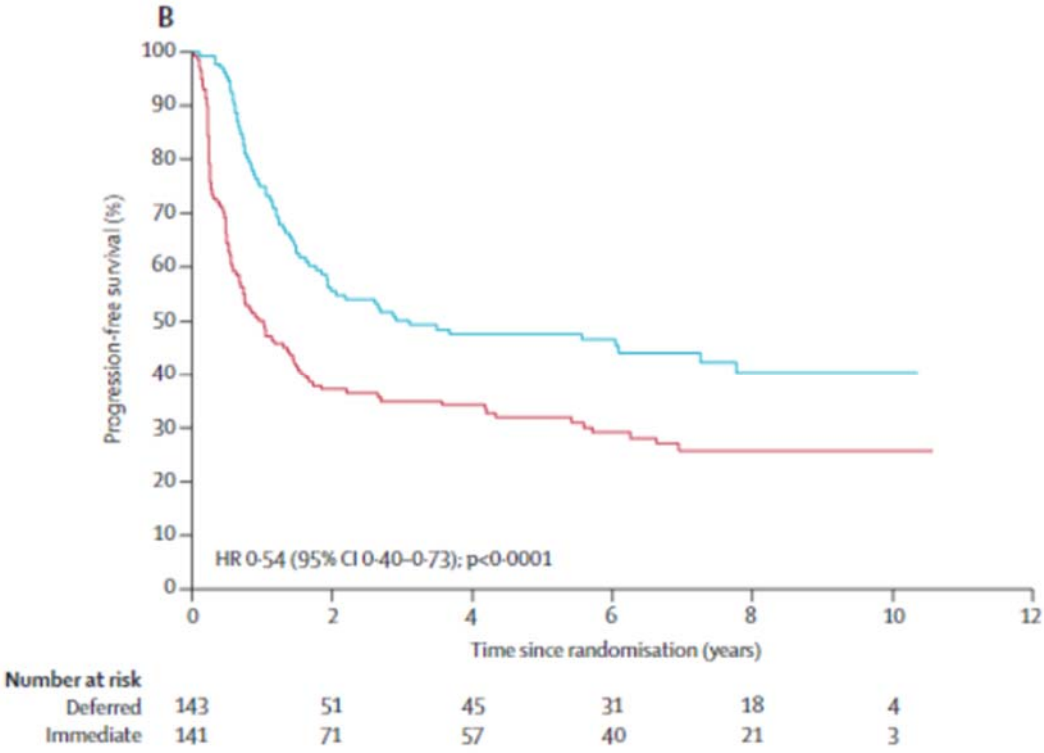
3.8 Key Issue 8: Uncertainty surrounding the assumed cure point

The company assumed that after 5 years residing in the DFS state that patients could not have a recurrence of UC. Clinical advice to the ERG suggests that whilst the recurrence rate diminishes as the time since resected UC increases, it is not zero after 5 years and explored a longer time before a patient was considered cured.

In its TE response, the ERG believes that the company intended to state that based on clinical advice it received that 99% of patients *that recur* do so before 5 years. The company also highlights that these patients do not receive routine follow-up after 5 years based on rarity of recurrence.[13] The company further cites a study by Sternberg *et al*.[6] which compares immediate treatment with deferred treatment which the company states provides '*further validation for a cure point at approximately 5 years*' as there were few events after approximately 4 years. A 10-year cure point was excluded by the company on the basis that the studies that supported this longer time point excluded patients that received neo-adjuvant chemotherapy.[14, 15]

The ERG notes that the data from Sternberg (shown in Figure 8) indicate that events do happen beyond 5 years, as was also indicated by clinical advice provided to both the company and the ERG. As such, the ERG has explored a scenario where the time point at which a patient is considered fully cured is 10 years.

Figure 8: KM plot of DFS events from Sternberg et al. (reproduced from Figure 7 of the company's TE response)



3.9 Key Issue 9: The lack of ICERs related to subgroup analysis in the company's submission

Following the anticipated licence change, this key issue is no longer relevant. As expected, the focus on a PD-L1 ≥1% population rather than the all patients regardless of tumour PD-L1 status, has produced an ICER that is more favourable to nivolumab.

3.10 Key Issue 10: Model correction

Within the company's model there are three ways in which a patient could leave the disease-free state: disease recurrence; death due to disease; or death due to other causes. The probability of the first two are combined in the probability of having a DFS event.

The method used by the company to calculate the probability of having a DFS event multiplied the probability of leaving the disease-free state by (1- probability of all-cause mortality (pACM)). The ERG believes that the following formula is more appropriate:

p(having a DFS event) = p(leaving the disease-free state) - pACM

3.11 Key Issue 11: Overestimation of post-recurrence treatment costs for the BSC arm in the "atezolizumab as subsequent treatment" scenario analysis

Atezolizumab has been recently approved "*as an option for untreated locally advanced or metastatic urothelial cancer in adults whose tumours express PD-L1 at a level of 5% or more and when cisplatin-containing chemotherapy is unsuitable.*"[16] The company considered patients who received nivolumab "*previously treated*" with an anti-PD-1 immunotherapy, hence considered only patients who received BSC eligible for atezolizumab as a subsequent therapy. The company estimated that [redacted] of patients could receive atezolizumab "*aligning to the proportion of PD-L1 ≥ 1% patients who were also PD-L1 ≥ 5% within CheckMate 274*".

In estimating the costs associated with atezolizumab, the company used reported values from TA739 where total acquisition and administration costs of atezolizumab (at list price) were £74,084, equivalent to a weekly cost of £1321 over 12.9 months (the mean time on atezolizumab treatment). However, in the company's model for this STA, subsequent treatment costs were applied for the rest of the patient's life until death (on average 24.7 months when atezolizumab is used in the BSC arm). Applying the costs of subsequent treatments until death was highlighted under Section 4.3.4 of the ERG report and was considered a minor issue, as atezolizumab treatment was not considered in the CS, and thus the impact on the ICER was small because of the relatively low acquisition costs for cisplatin- and carboplatin-containing chemotherapies. When atezolizumab is included, the impact on the ICER on the assumption of treatment until death is more pronounced.

Including subsequent atezolizumab treatment within the BSC arm increased the total costs by [redacted] per patient starting on BSC treatment. This number is significantly higher than that in TA739, and reported in the CRFALC, as the model assumes that patients are treated until death. The ERG highlights an apparent lack of face validity given the estimated cost of £74,084 per patient in TA739, and noting that only [redacted] of patients are anticipated to receive atezolizumab treatment.

4 Additional analyses undertaken by the company and the ERG

4.1 Results of the analyses presented by the company

This section presents the central estimates of cost-effectiveness using the version of the company's model submitted at the CRFALC. As mentioned in Section 2, for brevity many of the scenario analyses within that document are not presented here.

Table 5 presents the central estimate of cost-effectiveness generated using the company's updated model for the comparison of nivolumab versus BSC. The probabilistic estimate of the ICER was similar at £11,300.

Table 5: Company's updated base case deterministic results

Options	LYGs	QALYs	Cost	Inc. LYGs	Inc QALYs	Inc Costs	ICER
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,105**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

The company also presented a scenario analysis where atezolizumab was used a subsequent therapy after recurrence for [redacted] of patients at the BSC arm (CRFALC Section 1.3.3.1) with the remaining patients being split 50:50 between cisplatin and carboplatin regimens as in the original CS. The company recalculated the annual probability of post-recurrence death for patients receiving BSC as 0.30 (instead of the previous 0.42, which was still applied to the nivolumab arm). Post-recurrence treatment costs were also re-estimated, and a weekly cost of £1320.75 was used until death for patients on atezolizumab using the list price. Implications of this cost calculation is critiqued under Section 3.11 of this report. Results of the company's scenario analysis are shown Table 6.

Table 6: Company's updated deterministic results for the atezolizumab as subsequent treatment scenario in the BSC arm (using list price of atezolizumab)

Options	LYGs	QALYs	Cost	Inc. LYGs	Inc QALYs	Inc Costs	ICER
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

4.2 Description of additional exploratory analyses undertaken by the ERG

In all exploratory and additional sensitivity analyses, the ERG has used the model provided by the company with the CRFALC. The exploratory analyses are linked to the key issues identified in the ERG

report. As stated, the ERG provides three alternative scenario analyses for the Appraisal Committee to consider, noting that all of these have limitations.

ERG exploratory analysis 1: Exclusion of cisplatin-based adjuvant chemotherapy as a comparator

The ERG could not formally assess the ICER when cisplatin-based adjuvant chemotherapy was a comparator, although believes it likely based on the ITC conducted by the company that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY gained. An additional uncertainty associated with the CRFALC is that the ITC was not revised for a PD-L1 ≥ 1% population.

ERG exploratory analysis 2: Use of alternative DFS survival functions

The ERG undertook three alternative scenario analyses (ASA). For ASA 1 and ASA 3, the ERG used the Generalized gamma distribution preferred by the company, in ASA 2, the ERG explores the use of a Gompertz distribution. In ASA 1, an increased risk of death was applied between years 6 and 10 in DFS whereas in ASA 3 the cure point was extended to 10 years. In ASA 2, the ERG uses the age- and sex-matched risk of death after 5 years in DFS. In all models, distributions are amended such that the risk of a DFS event is never lower than the age- and sex-matched population value.

ERG exploratory analysis 3: Use of utility data from Janssen *et al.*

The company has changed its assumption to that preferred by the ERG and thus no further analyses are required.

ERG exploratory analysis 4: The average age of patients in the UK is likely to be older than those recruited to CheckMate 274

The company has provided additional analyses which means that the ERG has maintained the age of patients to those in CheckMate 274 but has run an additional scenario analysis using a mean age of 67 years. An additional uncertainty associated with the CRFALC is that the age of the PD-L1 ≥ 1% population has not been used in the company's model, but the ERG believes this would be favourable to nivolumab treatment if undertaken as the mean age of the PD-L1 subgroup is lower than that of ITT population of CheckMate 274 (65.2 and 65.6 respectively).

ERG exploratory analysis 5: Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo

Following access to more mature data the ERG is content to pool the probability of deaths between arms. However, the ERG's preferred analysis assumes that [redacted]% of DFS events are deaths, based on the observed data from CheckMate 274 rather than the results of the logistic regression.

ERG exploratory analysis 6: Patients in the DFS health state have the same utility values as an age- and sex-matched population

Based on clinical advice, the ERG maintains an exploratory decrement of 0.02 in the first 5 years residing in the disease-free state for each of the three alternative scenario analyses. As detailed in Section 3.7, this was further applied until a patient was considered fully cured. The additional periods associated with utility decrements beyond five years, were five years in ASA 1 and ASA 3 and zero years in ASA 2.

ERG exploratory analysis 7: Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population

The ERG applies a SMR of [redacted] to the age- and sex-matched general population for the period of 5 to 10 years residing in the disease-free state in ASA 1. For ASA 2 and ASA 3 the age- and sex-matched general population was used after 5 and 10 years residing in the disease-free state respectively. Note, the ERG report after TE erroneously stated the use of an SMR of [redacted] applied for a period of 5 years for both ASA 2 and ASA 3.

ERG exploratory analysis 8: Uncertainty surrounding the assumed cure point

For ASA 1 and ASA 2 the cure point of 5 years was used, as preferred by the company. For ASA 3 the cure point was extended to 10 years.

ERG exploratory analysis 9: The lack of ICERs related to subgroup analysis in the company's submission

Following the anticipated change in license, this key issue no longer applies to the results in the CRFALC.

All of the ERG's alternative ICERs combine ERG exploratory analyses 5, 6 and 7. The generated ICERs are assumed to apply only to those people in whom cisplatin-based chemotherapy would not be an option (see Issue 1).

4.3 Description of additional scenario analyses undertaken by the ERG

ERG scenario analysis regarding the atezolizumab as a subsequent treatment

In this analysis, the ERG calculated the weekly cost needed to be applied in order that the acquisition and administration costs associated with atezolizumab over a mean survival of 24.7 months equalled the £74,084 value reported in TA739. This resulted in a weekly cost of £690.57 for patients on atezolizumab. This mounted to an average weekly cost of £670.86 for all patients in the BSC arm. The post-recurrence weekly treatment cost for the nivolumab arm remained £279.21.

4.4 Results of exploratory analyses undertaken by the ERG

Table 7 presents the deterministic results of the ERG's alternative scenario analyses; probabilistic results are similar and are not reported. All ICERs calculated were below £20,000 per QALY gained. The largest change in the ICER occurs in ASA 1 which increased the ICER by less than £2500. In this scenario, patients were assumed fully cured at 10 years with an SMR of [redacted] applied between years 6 and 10 of the disease-free state and assuming a utility decrement of 0.02 for the first 10 years of a patient being disease-free. ASA 2 and ASA 3 changed the ICER by less than £800.

Table 7: Deterministic results of the ERG's additional scenario analyses

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,105**
Company's updated base case (error corrected as per key issue 10)							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,034**
ERG ASA 1 ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,474**
ERG ASA 2 ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,827**
ERG ASA 3 ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,931**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
† Assumed applicable only to those in whom cisplatin-based chemotherapy would not be an option (see Issue 1)

After applying the ERG's corrections regarding the post-recurrence weekly costs for including atezolizumab as a subsequent treatment for [redacted] of patients in the BSC arm, The ERG carried out all the analyses for the atezolizumab scenario using its list price and these are reported in Table 8. All results suggest that nivolumab dominates BSC.

Table 8: Deterministic results of the ERG's additional scenario analyses when atezolizumab is used as a subsequent treatment (list price)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's scenario results							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
Company's updated base case (errors corrected as per key issues 10 and 11)							
BSC	[redacted]	[redacted]	[redacted]				

Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
ERG ASA 1 ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
ERG ASA 2 ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
ERG ASA 3 ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**

5 Overall conclusions

The model submitted by the company was implemented to a good standard, although the ERG preferred alternative assumptions to those used by the company. The ERG believes that the Generalized gamma distributions were an appropriate choice. However, the ERG does not believe that these distributions were compatible with the company's assumption that patients were fully cured after 5 years of being in DFS. The ERG also questions the use of Generalized gamma distribution if the true hazard of DFS was in fact monotonically decreasing with the increase in the hazard observed at 3 months being an artefact of the time of first tumour assessment; in this instance the Generalized gamma distribution would not represent the true hazards despite the better goodness-of-fit to the observed data. For this reason, the ERG believes that Gompertz distributions should also be considered, although these imply a cure point at approximately [redacted] years.

The ERG provides alternative scenarios that may be informative to the Appraisal Committee. The first (ASA 1) explicitly considers that the hazard of death is not the same as the age- and sex-matched general population after 5 years of being disease-free. The second, ASA 2, uses Gompertz distributions rather than the Generalized gamma distributions, whilst the third (ASA 3) extends the time point of being fully cured to 10 years. All three analyses apply a utility decrement of 0.02 until a patient is considered fully cured.

ASA 1 and ASA 2 increase the ICER compared to the company's base case by between £700 and £2000, whereas ASA 3 decreases the ICER by less than £200. All ICER values were below £14,000. All three analyses have limitations. ASA 1 assumes arbitrarily that patients are fully cured at 10 years, as does ASA 3, although they differ as an SMR is applied in ASA 1, whereas the cure point is explicitly set to a longer duration in ASA 3. ASA 2 has the same limitation as the company's base case in that external data does not support a cure point at 5 years, although it has the advantage over the company's base case that the distributions chosen for both arms have a hazard of a DFS event at 60 months similar to the hazard of death estimated for general population at that time. Including atezolizumab as a post-recurrence treatment for the BSC arm led to nivolumab dominating BSC at the list price of atezolizumab.

The ERG highlights that the ICERs produced are applicable only to patients in whom cisplatin-based regimens are not appropriate; the ERG believes it likely that the cisplatin-based chemotherapy would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 based on the ITC conducted by the company.

6 References

1. Bristol-Myers Squibb. Company evidence submission for nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]; 2021.
2. Bristol Myers Squibb. Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]. Technical Engagement response; 2021.
3. Metry A HG, Stevenson M. Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal/ Addendum: ERG comments on company's technical engagement response.
4. (EMA) EMA. Opdivo (nivolumab) Committee for Medicinal Products for Human Use (CHMP) opinion. 2022. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/opdivo-7 (Accessed Accessed 9 March 2022).
5. Metry A, Holmes G, Leaviss J, Martyn-St James M, Clowes M, Aning J*, et al.* Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal.: School of Health and Related Research (ScHARR); 2021.
6. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M*, et al.* Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol* 2015;16:76-86.
7. Janssen B SA. Population Norms for the EQ-5D. In: Szende A JBCJ, editor. *Self-Reported Population Health: An International Perspective based on EQ-5D*Dordrecht: Springer Netherlands; 2014:19-30.
8. Ara R, Brazier J. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010;13:509-18.
9. Burnham KP, Anderson DR. Model selection and multi-model inference [electronic resource] : a practical information-theoretic approach. 2nd edn: New York ; London: Springer; 2002.
10. Raftery A. Bayesian Model Selection in Social Research. *Sociological Methodology,* 1995;25:111-63.
11. John JB VM, Cooper N, Wong K, Hounsome L, Treece S, McGrath JS, Harden S. Treatment Allocation and Survival in Patients Diagnosed with Nonmetastatic Muscle-invasive Bladder Cancer: An Analysis of a National Patient Cohort in England. *Eur Urol Focus* 2021 Mar;7:359-65.
12. Witjes JA, Bruins HM, Cathomas R, Compérat E, Cowan NC, Gakis G*, et al.* EAU Guidelines in Muscle-invasive and Metastatic Bladder Cancer: European Association of Urology (EAU); 2021.
13. Health NIf, and Care Excellence. Bladder cancer: diagnosis and management [NG2]. UK: NICE; 2015.
14. Hautmann RE, de Petriconi RC, Pfeiffer C, Volkmer BG. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. *Eur Urol* 2012;61:1039-47.
15. Soria F, Moschini M, Wirth GJ, Gust KM, Klatte T, Briganti A*, et al.* Characterization of Late Recurrence After Radical Cystectomy in a Large Multicenter Cohort of Bladder Cancer Patients. *Urology* 2017;106:119-24.
16. Excellence NIfHaC. Final appraisal document – Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable. 2021.

18 March 2022

Single Technology Appraisal

Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]

Dear Jasdeep,

The original NICE submission was targeted toward all patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC, and was based on the overall ITT population of the CheckMate 274 trial August 2020 database lock (DBL; 5.9 months minimum follow up [FU]). Subsequently, outcome data from an additional DBL, referred to as updated DBL (11 months minimum FU), with 5 additional months FU (data cut off 1 February 2021) were presented for the ITT population at technical engagement. Following CHMP positive opinion (24 February 2022),[1] there has been a change in relation to the licensed indication population where the wording of the licence is reflective of patients with tumour cell PD-L1 expression level ≥ 1%, henceforth referred to as PD-L1 ≥ 1% population.

In light of this, an addendum for ID2694 has been prepared for the PD-L1 ≥ 1% population, in line with the anticipated EMA licenced indication *"OPDIVO as monotherapy for the adjuvant treatment of adults with MIUC with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC",*[1] which includes an updated economic model and two additional documents, as detailed below.

- Survival analysis appendix including:
    - clinical efficacy data and *de novo* analysis of disease-free survival (DFS) reflecting the PD-L1 ≥1% population of CheckMate 274, utilising data from the updated DBL (11 months minimum FU)
    - updated responses to questions from the clarification stage in relation to the PD-L1 ≥ 1% population, highlighted by the ERG in an email from G. Kenny to F. Toron, 14 February 2022[2]
- Cost-effectiveness appendix incorporating the changes in DFS estimates and time on treatment data from the updated DBL (11 months minimum FU) for both nivolumab and BSC to reflect the PD-L1 ≥ 1% patient population.

Considering the updated expected label, all the necessary inputs and analyses to inform decision making for this population have been provided in these documents. Robust survival and economic analysis has been undertaken and the resulting new base case ICER for nivolumab versus BSC (with patient access scheme) is £11,105 per QALY (detailed in the survival and cost-effectiveness appendices), which is well below a willingness to pay threshold of £30,000 per QALY. Extensive sensitivity analyses show nivolumab to be cost-effective in all scenarios, with consistently low ICERs ranging from nivolumab dominating BSC, to an ICER of £12,455 per QALY versus BSC, demonstrating that nivolumab represents a cost-effective use of NHS resources.

In conclusion, the majority of MIUC patients with PD-L1 ≥ 1% at high risk of recurrence after radical resection currently receive no adjuvant treatment on the NHS and the standard of care after surgery is BSC, in the form of regular routine surveillance. Therefore, MIUC patients with PD-L1 ≥ 1% have a significant unmet need for adjuvant treatment options that reduce the risk of recurrence and thus improve survival. Nivolumab is the first and only treatment to demonstrate superior efficacy to placebo in this setting.

The introduction of nivolumab for adjuvant treatment of high-risk MIUC patients with PD-L1 ≥ 1% would therefore represent a significant advance in the management of these patients. Moreover, nivolumab is highly cost effective, presenting a low base case ICER which is robust when tested through extensive sensitivity analysis. We therefore strongly believe nivolumab should be accepted for routine commissioning for the adjuvant treatment of adults with MIUC with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.

Yours sincerely,

Farah Toron
Senior manager, Health Economics & Outcomes Research
Bristol-Myers Squibb Pharmaceuticals Limited

18 March 2022

References

1. European Medicines Agency (EMA). Opdivo (nivolumab) Committee for Medicinal Products for Human Use (CHMP) opinion. 2022. Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/opdivo-7 [Accessed 9 March 2022].
2. Kenny G. RE: Brief Call - ID2694 - Nivolumab Adj Bladder [Internet]. Email to: Farah Toron. 2022 Feb 14 [cited 9 Mar 2022].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: Addendum

Nivolumab for treating resected high-risk invasive urothelial cancer

ID2694

Appendix: Survival analyses

March 2022

Table of Contents

Tables

Figures

Abbreviations

AFT	accelerated failure time
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CI	confidence interval
DBL	database lock
DFS	disease-free survival
DMFS	distant metastasis-free survival
DSU	Decision Support Unit
ERG	evidence review group
FU	follow up
HR	hazard ratio
HRQoL	heath-related quality of life
ITT	intention to treat
KM	Kaplan-Meier
LRDFS	locoregional disease-free survival
MIUC	muscle-invasive urothelial cancer
NMIBC	non-muscle invasive bladder cancer
NUTRFS	non-urothelial tract recurrence-free survival
PD-L1	programmed death-ligand 1
PFS2	progression-free survival on next line systemic therapy
PH	proportional hazards
PLD	patient-level data
Q-Q plot	quantile-quantile plot
R-P	Royston-Parmar
TSD	technical support document

1 Introduction

1.1 Context

This report documents the analysis of disease-free survival (DFS) for all randomised patients with tumour cell programmed death-ligand 1 expression level ≥ 1% (termed herein as PD-L1 ≥ 1%), the co-primary analysis population of the CheckMate 274 study, utilising data from the updated database lock (DBL; 11 months minimum follow up [FU]).

1.2 Objectives

The objectives of this study were:

- To capture DFS outcomes for patients with resected high-risk muscle invasive urothelial carcinoma (MIUC) and PD-L1 ≥ 1% treated with nivolumab therapy or placebo based on available patient-level data (PLD) from the updated DBL (11 months minimum FU) from the CheckMate 274 trial.

- To assess the appropriateness of each extrapolation and select the most appropriate model, reflecting the approaches outlined by the NICE DSU (TSD 14[1] and TSD 21[2]) and Bagust and Beale (2014).[3]

2 Methodology

In order to provide a robust and transparent assessment of DFS for the PD-L1 ≥ 1% population, all DFS analyses were undertaken from scratch. The survival modelling approach was selected based on methodologies suggested by the NICE DSU (TSD 14[1] and TSD 21[2]) and Bagust and Beale (2014)[3].

2.1 Patient Level Data Source

2.1.1 Trial arms

The population of all randomised patients with tumour cell PD-L1 ≥ 1% in the CheckMate 274 trial constituted 282 patients with resected MIUC: 140 patients in the nivolumab arm and 142 in the placebo arm. All survival analyses were performed using PLD from the updated DBL (11 months minimum FU).[4]

2.1.2 Lifetable data

General population mortality rates were used where relative survival was analysed, or where general population survival was plotted as a reference outcome. In the initial analysis, general population mortality was estimated as an expected outcome for matched patients in the CheckMate 274 trial according to age at baseline, sex and country, using country-specific lifetables.[5-18]

In the final analysis, the baseline hazards were assumed to come from the UK population (age- and sex- matched to CheckMate 274 patients).[19]

2.1.3 Outcome definition

The primary outcome in CheckMate 274 was DFS, defined as the time between randomisation and the date of first recurrence or death from any cause. Recurrence was determined by investigator assessment and defined as:

- *Local, urothelial tract*: any high- and intermediate-risk non-muscle invasive bladder cancer (NMIBC) and any new invasive urothelial carcinoma in the lower or upper urothelial tract (defined as T2 or greater), including lesions thought to be a second urothelial carcinoma primary
- *Local, non-urothelial tract*: Any recurrence in pelvic soft tissue or involving pelvic nodes below the aortic bifurcation
- *Distant*: Any non-local recurrence
- Low-risk NMIBC was not reported as a DFS event

In the primary definition of DFS, people who remained alive and without recurrence at data cut-off were censored on the date of the last evaluable disease assessment. People who began a subsequent therapy or developed a second primary cancer without recurrence before data cut-off were censored at the last disease assessment date prior to the start of the subsequent therapy or development of the second primary cancer. The secondary definition of DFS was per the primary definition, except that people were not censored for starting subsequent therapy. The primary definition of DFS was used in this analysis in line with the clinical study report.

The following definitions were added during analysis:

- *Time to death or last observation:* The time between randomisation and either the date of death (if observed) or the date of the last observation of the patient (censored).

2.2 Methods of extrapolation

2.2.1 Overview of approach

In order to provide a robust and transparent assessment, the methodologies suggested by the NICE DSU[1,2] and Bagust and Beale (2014)[3] were applied. The model selection algorithm was used to select a suitable model (Figure 1). An overview of the approach is detailed below:

- Characterise the available data from CheckMate 274
- Describe trends in the available data
- Assess viability of accelerated failure time (AFT) and proportional hazards (PH) models
- Assess suitability of standard statistical models
- If standard statistical models are not indicated:
    - Consider other flexible standard parametric models as per TSD 14[1]
- Assess appropriateness of parametric models of extrapolation on the basis of:

- Goodness-of-fit statistics (Akaike Information Criterion [AIC]/ Bayesian Information Criterion [BIC])
- Non-parametric or smoothed representations of PLD
- Examination of log-cumulative hazard plots
- Assessment of clinical validity
- Consideration of external data (e.g., within-class in similar indications)

- Select most plausible models, and other valid models for sensitivity analysis.

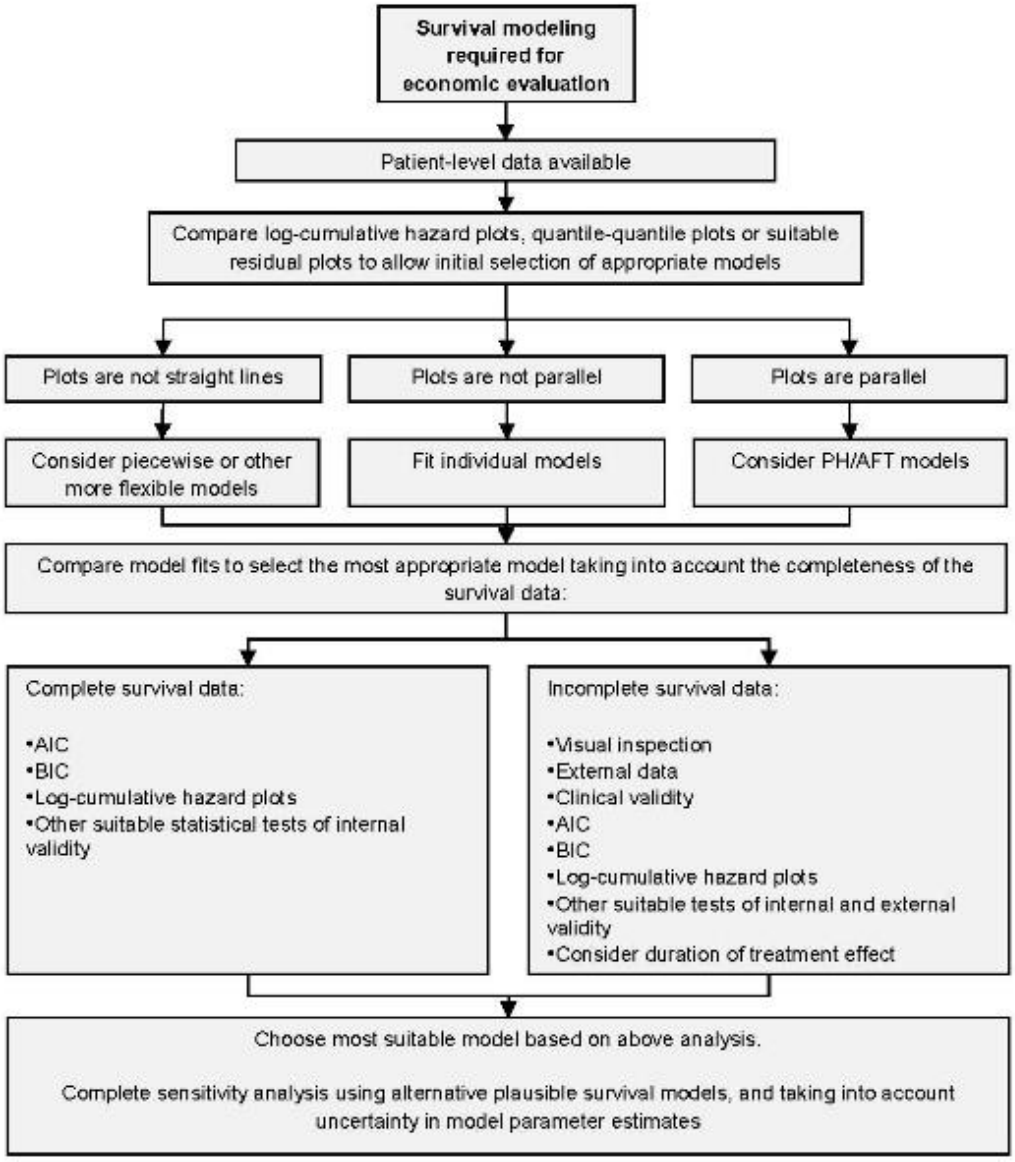


Figure 1. Survival model selection process algorithm

AFT: accelerated failure time; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; PH: proportional hazards.

Source: NICE DSU Document 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data.[1]

Matched general-population survival

A matched general-population survival curve was estimated using recent nationality, sex, and age-specific lifetables. Based upon their exact age at randomisation, each patient was modelled as receiving piecewise-constant hazard of death to maximum age represented in their lifetable:

$$h_{LT_i}(t) = \ln\left(1 - q_{LT_i}(floor\left(t + age_{baseline_i}\right)\right)$$

Where $h_{LT_i}(t)$ is the instantaneous hazard of death per lifetable in units of 1/year for patient, i, $age_{baseline_i}$ is the age of the patient at randomisation, and $q_{LT_i}(x)$ is the annual probability of death from the lifetable stratum of patient i. The cumulative hazard due to lifetable:

$$H_{LT_i}(t) = \int_0^t h_{LT_i}(\tau)d\tau$$

was then converted to survival probability:

$$S_{LT_i}(t) = \exp\left(-H_{LT_i}(t)\right)$$

The mean survival probability across all patients within the original population was taken as the final matched general-population survival curve:

$$S_{LT}(t) = \frac{1}{n}\sum_{i=1}^{n} S_{LT_i}(t)$$

Where n is the total number of patients at risk at t=0.

2.2.2 Selection of models from hazard profiles of available data

TSD 14[1] indicates that the selection of models should be based on the shape of hazard profiles over time. The trends in the survival data were analysed using the nonparametric plots as described in Ishak et al (2013).[20] Smoothed estimates of event hazards experienced over the follow-up were produced by three independent estimators:

- Kernel-smoothing of the cumulative hazard function using the “R” package *muhaz*
- Formation of a flexible parametric Royston-Parmar spline model of cumulative hazard using the “R” package *flexsurv*
- B-spline smoothing of the hazard function using the “R” package *bshazard*

2.2.3 Standard statistical models

Within TSD 14,[1] six statistical survival time distribution models are nominated as being necessary to consider prior to undertaking other alternative survival modelling methods. These six models are:

1. Exponential
2. Weibull
3. Gompertz
4. Log-logistic
5. Lognormal
6. Generalised Gamma

Fitting of these probability distributions to survival data for the purpose of extrapolation is performed under the assumption that all times, until the nominated event within the modelled population, are drawn from the same, optionally conditional, distribution. For a cohort-level marginal model of survival times, the unexplained, natural variance of survival time and the variance due to heterogeneity of the modelled population are incorporated into a single distribution.

The hazard profiles given by the nominated models can be grouped as follows:

- The average hazard over the whole cohort is constant (exponential model)
- The average hazard over the whole cohort increases or decreases proportional to a function of time (Weibull, Gompertz model [both degenerate to an exponential model when the coefficient of proportionality is 0])
- The average hazard over the whole cohort increases to a peak, then decreases long term (log-logistic, lognormal model)

The generalised gamma model can describe any of these profiles, and can degenerate to exponential, Weibull or lognormal models, depending upon its parameter values.

Use of these models also implies that no abrupt changes in circumstances arise, i.e., treatment effects are maintained or changed smoothly with respect to time, and changes in risk factors with respect to time are smooth and consistent across the population.

Parametric survival functions were fitted to PLD using the R statistics environment, version 4.0.2 (2020-06-22), using the parametric survival fitting package *flexsurv* (version 1.1.1). The functional forms of the fitted models are described in Table 1.

Table 1. Functional forms of parametric survival equations

Distribution	Survival Function	Hazard Function
Exponential	$e^{-\lambda t}$	λ
Weibull	$e^{-\left(\frac{t}{\lambda}\right)^{k}}$	$\frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1}$
Log-logistic	$\frac{1}{1+\left(\frac{t}{\alpha}\right)^{\beta}}$	$\frac{(\beta / \alpha)(t / \alpha)^{\alpha-1}}{1+(t / \alpha)^{\beta}}$
Lognormal	$\frac{1}{2}-\frac{1}{2} erf\left(\frac{\ln t-\mu}{\sqrt{2}\sigma}\right)$	$\frac{\frac{1}{\sigma t} erf\left(\frac{\ln t}{\sigma}\right)}{erf\left(\frac{-\ln t}{\sigma}\right)}$
Gompertz	$e^{\frac{\lambda}{\theta}(1-e^{\theta t})}$	$\lambda e^{\theta t}$
Generalised gamma function	$1-\Gamma_{(\lambda t)^{\theta}}(\rho)$ Where $\Gamma_{(\lambda t)}(\rho)=\frac{1}{\Gamma(\rho)}\int_{0}^{\lambda t} u^{\rho-1}e^{-u}\,du$ Is the incomplete gamma function	$\frac{\theta\lambda^{\rho\theta}t^{\rho\theta-1}\exp\{-(\lambda t)^{\theta}\}}{\Gamma(\rho)}/S(t)$

t = time
e = Euler's number
erf = Error Function
$\Gamma(\ )$ = Gamma Function
$\ln(\ )$ = natural logarithm
Other parameters are distribution specific.

2.2.4 Alternative models

Following NICE guidance in TSD 14,[1] if standard parametric approaches do not capture survival trends appropriately, per the methodological process given in TSD 14,[1], piecewise modelling and other alternative survival modelling methods such as those demonstrated by Royston and Parmar[21] and Jackson et al.[22] should be considered. However, we also note that during the NICE review process, the evidence review group (ERG) has previously indicated a preference for a standard model to characterise DFS in order to smooth protocol induced artifacts. In addition, the ERG further noted that when the economic model applies all-cause mortality after a fixed amount of time (e.g. five years) the extrapolation becomes irrelevant. This would support the decision not to use the alternate models such as piecewise models.

2.2.5 Assessment of a proportional hazards and single accelerated failure time model assumptions

Complementary log-log plots of DFS from CheckMate 274 were plotted simultaneously to assess the appropriateness of a PH assumption. Plots of Schoenfeld residuals were assessed for systematic patterns that would suggest that the hazard ratio (HR) in the Cox model is

correlated with time and, therefore, whether the PH assumption is violated. The Schoenfeld residuals test was also performed to test for zero slope (indicative of no relationship with time) on the scaled residuals of the Cox model. A single AFT model may be appropriate if the quantiles in a quantile-quantile (Q-Q) plot follow a linear trend. This checks that the survival time accelerates (or decelerates) by a constant factor when comparing two groups of a key explanatory variable.

TSD 14[1] also indicates that a PH assumption may not be necessary when individual PLD are available (which is the case for this submission) and if a PH model is to be assumed, then extensive justification should be provided.

2.3 Assessment of fit

In the analysis of CheckMate 274 data, assessment of extrapolations was undertaken on the basis of the following criteria:

- Goodness-of-fit statistics
- Visual inspection of the parametric fit over the observed period
- Consideration of the log cumulative hazard plots
- Plausibility of the hazard profile

Goodness-of-fit was evaluated using the AIC and BIC. Minimisation of these measures indicates goodness-of-fit whilst penalising overfitting, therefore a smaller value demonstrates a more appropriate fit.

It is worth noting that while the above goodness of fit methods for validating the extrapolation of progression and death events are appropriate, they are also necessarily constrained by derivation from observed data, which is limited by a relatively short duration of follow-up.

The log cumulative hazard plots were examined to identify how closely the curve fits adhere to the hazard profile of the observed data. The assessment was made visually as with the time-to-event curves. Each model provided a prediction of the hazard through the observed time with an indication to its direction in the extrapolated period.

Final model selection was ultimately at the analysts' discretion, as there were no *a-priori* specified models. The models were selected following the above criteria – i.e., by examining log cumulative hazard plots, by analysing statistical goodness of fit, and using visual inspection of the fits. To evaluate the sensitivity of model predictions to economic analysis, a number of alternative models were selected to form scenario analyses.

2.4 General statistical considerations

All analyses were undertaken on an x64-based laptop running Windows 10 Pro (v1909+), within the "R" statistical software environment version 4.0.2 (2020-06-22) as provided by CRAN (https://cran.r-project.org/). Relevant external statistical packages used were:

- survival (v3.2-7)) (R base)

- flexsurv (v1.1.1) (https://CRAN.R-project.org/package=flexsurv)
- muhaz (v 1.6.2.1) (https://CRAN.R-project.org/package=muhaz)
- bshazard (v 1.1) (https://CRAN.R-project.org/package=bshazard)

3 Results of analysis from CheckMate 274

3.1 Safety and health-related quality of life (HRQoL)

Outcomes from an updated DBL of CheckMate 274 are available reflecting 11 months minimum FU (data cut-off on 1 February 2021), and expanding upon the 5.9 month minimum FU from an older DBL (August 2020). DFS, non-urothelial tract recurrence-free survival (NUTRFS) and distant metastasis-free survival (DMFS) outcomes were updated in the intention to treat (ITT) population, presented at technical engagement, and the PD-L1 ≥ 1% population, presented in Appendix 1. Safety and HRQoL endpoints were not analysed as part of the updated DBL (11 months minimum FU), as 85% of events of disease recurrence or death in each trial population had been observed (348 events in the intention-to-treat population and 137 in the group of patients with a PD-L1 ≥ 1%), representing a significant portion of the overall study population. The previous DBL (August 2020) demonstrated that the overall safety profile of nivolumab monotherapy was manageable, no new observed safety signals were observed, and the HRQoL of patients was sustained. Safety and HRQoL endpoints will be analysed again at the next planned DBL.

3.2 Investigator-assessed DFS

3.2.1 Data description

Investigator-assessed DFS, hereafter reported as DFS, as observed in the CheckMate 274 tumour cell PD-L1 ≥ 1% population at the updated DBL (11 months minimum FU) is summarised in Table 2 and the KM plots for nivolumab and placebo containing the number at risk are shown in Figure 2.

Table 2. Observed DFS – CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Endpoint	Nivolumab (N=140)	Placebo (N=142)
DFS*		
Events, n (%)	56 (40.0)	85 (59.9)
Median, months (95% CI)	N.A. (22.1, N.E.)	8.4 (5.6, 20.0)
HR (% CI)	0.53 (0.38, 0.75)	
CI: Confidence Interval; DFS: Disease Free Survival; HR: Hazard Ratio; N.A.: not reached, N.E.: not estimable * primary definition, includes censoring for subsequent treatment Source: Galsky 2021[23]		

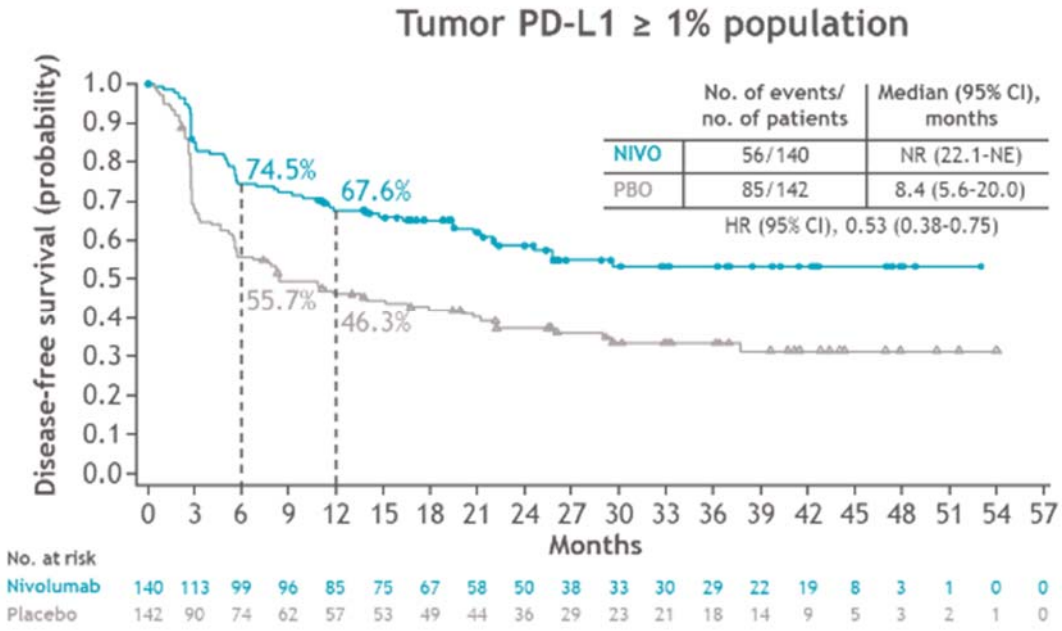


Figure 2. KM plot of DFS (primary definition) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

The key features of the KM estimates of DFS from the CheckMate 274 trial are: the initial drop at around three months, which is more pronounced in the placebo arm (grey line, Figure 2); the tendency towards low hazards in the second half of the data, and the level of censoring throughout each arm, shown in Figure 2. This can also be visualised from the cumulative hazard plot in Figure 3.

The initial drop in both arms in the early part of the data may be explained by the trial protocol, as the first tumour assessment occurred at 3 months and thus cumulative recurrence in that first 3-months from high-risk or non-responding patients would be captured at this first assessment. The drop is more pronounced in the placebo arm, implying that nivolumab may prevent early recurrence in a proportion of patients who may otherwise have experienced tumour growth or death from disease.

Figure 3. DFS, cumulative hazard function - CheckMate 274, PD-L1 ≥ 1% population - updated DBL 11 months minimum FU)

DBL: Database Lock; DFS: Disease-free survival; PD-L1: programmed death-ligand 1

A visual inspection of the smoothed underlying hazard plots for the nivolumab and placebo arms (Figure 4 and Figure 5) indicate that DFS for both treatments has a time dependent

hazard with an early single inflexion point (R-P spline and kernel smoothed curves – red and dark blue lines) correlating with the time of first tumour assessment shown by the KM data. A stabilising low hazard, seen in all three splines, indicates that long-term remission may be possible for a proportion of patients (e.g. the excess risk from the disease becomes negligible towards the end of the trial data, with the hazard profile meeting the lifetable hazard at around 50 months). It is also notable that there is substantial right censoring in both arms from early in the DFS curve (Figure 2), indicating that not all features of the underlying hazard profiles are clear due to limited FU.

Figure 4. Investigator-assessed DFS for nivolumab, KM curve and smoothed hazard function estimates for nivolumab - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

DBL: Database Lock; DFS: Disease-free survival; PD-L1: programmed death-ligand 1; R-P: Royston-Parmar

Figure 5. DFS for placebo, KM curve and smoothed hazard function estimates for placebo - CheckMate 274, PD-L1 ≥ 1% population - updated DBL 11 months minimum FU)

DBL: Database Lock; DFS: Disease-free survival; PD-L1: programmed death-ligand 1; R-P: Royston-Parmar

3.2.2 Assessment of proportional hazards or single accelerated failure model

In order to determine the most suitable model for the event time distribution under consideration, i.e. DFS (Figure 2), firstly the assumption of PH or single AFT models was assessed. This can be achieved through comparing log-cumulative hazard plots (for both PH models and single AFT models), quantile-quantile plots (for single AFT models) and suitable residual plots (for PH models).

Initially, curves were generated for log cumulative hazard plots for both arms (*Figure 6) and used to inform whether PH or single AFT models were suitable. In relation to the single AFT model assumption, there is no clear indication of a constant horizontal spacing in the complimentary log-log plot, which in turn indicates that a single AFT model is not suitable or there is a lack of a single AFT between two event time distributions. In terms of PH, a constant vertical spacing of the logarithm of cumulative hazard was present, and considered indicative of a potentially constant PH between the two event time distributions.

In summary, the log cumulative hazard plots (*Figure 6) indicate that single AFT models are not appropriate, while PH models cannot be completely ruled out.

Figure 6. DFS, log cumulative hazards - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

DFS: disease-free survival

In order to explore the appropriateness of AFT models further, a quantile-quantile relationship (or Q-Q plot) for both the trials arms was utilised, showing that the quantiles are not on or close to the linear trendline (Figure 7). Moreover, if there is no systematic deviation from the relation on a Q-Q plot, then one expects only random noise to cause deviation from the straight line; however, the Q-Q plot shows deviations that are not random. It is also acknowledged that the Q-Q plot shown in Figure 7 uses the step function as they are from the KM survival curves, meaning there is discretisation noise, so crossing counts are expected to be lower. However, in contrast, there are many crossings on the Q-Q plot.

In summary, the deviations from the linear trendline and many observed crossings on the Q-Q plot mean an assumption of an accelerating factor or a single AFT model to represent event time distribution is not appropriate.

Figure 7. Q-Q plot providing quantiles of event times of DFS, placebo arm compared with nivolumab arm - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

In relation to the assessment of PH assumption, Schoenfeld residual plots of DFS were used to further assess whether PH assumption would be appropriate. The Schoenfeld residuals test is used to show independence between residuals and time, and hence it is used to test for PH assumption. Weighted Schoenfeld residuals are presented in Figure 8, where the x-axis represents time and the y-axis represents the coefficient estimate for treatment effect or the treatment arm covariate. The red dots represent the residuals for each individual, the solid line is a smoothing-spline fit to the plot, and the dashed lines represent the 95% confidence interval (CI).

The Schoenfeld residuals test is analogous to testing whether the slope of scaled residuals on time is zero or not. If the slope is not zero, then the PH assumption has been violated. In the Schoenfeld residuals plot for the PD-L1 ≥1 % population DFS, shown in Figure 8, the slope is almost 0 and therefore, the PH assumption is not violated. Furthermore, the residuals (red dots) are spaced equally from the horizontal line towards the right-hand side of the plot and the non-significant p-value ~0.27 also indicate that the PH assumption may not be violated. However, it is also important to note that the red dots are not equally spaced from the horizontal line on the left side of the plot for around the first 3 months, indicating that a PH assumption may not be appropriate throughout. It is, therefore, not possible to conclude that

PH are evident based on the Schoenfeld residuals test. Furthermore, NICE TSD14[1] guidance suggests that applying a PH assumption would require a thorough and extensive justification. This is intuitive given that a PH assumption implies that the relationship between two treatments can be quantified to a single factor and this factor would be applied throughout the whole time horizon. Finally, NICE TSD14[1] guidance suggests assuming PH may not be necessary when individual PLD are available, which is the case for this submission.

Figure 8. Investigator-assessed DFS, Schoenfeld residuals plot - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

DFS: disease-free survival

In summary, the results of the Schoenfeld residuals test and NICE TSD14[1] guidance suggest that applying PH may not be valid. Therefore, with inconclusive evidence to support a joint modelling approach and as supported by NICE TSD14[1] , independent models will be used for selecting the base case curve for use in the economic model. Scenario analyses applying a PH assumption where appropriate is explored in the economic evaluation.

3.2.3 Standard parametric models

Subsequently, due to the uncertainty surrounding PH assumption, unsuitability of single AFT modelling, and adherence to NICE TSD14[1], independent modelling was deemed the most appropriate approach for determining the base case. Consequently, the next step in the model selection process was to assess whether any of the standard parametric models, suggested by the NICE DSU[1,2] and Bagust and Beale (2014),[3] capture the survival trends of the DFS data of the CheckMate 274 PD-L1 ≥ 1% population (updated DBL [11 months minimum FU]).

3.2.3.1 Independent modelling (preferred approach for base case analysis)

There are several facets to selecting an optimal survival model, including visual fit, statistical fit (AIC/BIC), and hazard profiles.

All six standard parametric models were employed to determine the most suitable distribution for both arms independently. AIC and BIC were calculated for all six parametric distributions which were used independently to describe DFS in both treatment arms, shown in 3. In both arms, the generalised gamma distribution had the lowest AIC/BICs followed by the Gompertz; a difference of [redacted] in AIC and [redacted] in BIC between generalised gamma and Gompertz in the nivolumab arm and a difference of [redacted] in AIC and [redacted] in BIC between generalised gamma and Gompertz in the placebo arm indicate that generalised gamma is the best statistical fit.[24,25]

Table 3. Measure of goodness of fit for parametric models with independent modelling using the standard parametric distributions for observed DFS, CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

	Nivolumab	Placebo

	AIC	BIC	AIC	BIC
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; PH: proportional hazards				

Separate survival curves were subsequently plotted, showing the model predicted DFS for the nivolumab arm (Figure 9 and Figure 10) and placebo arm (Figure 11 and Figure 12).

[redacted]

Figure 9. DFS for nivolumab, standard statistical models overlaid upon KM (short-term fit) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DFS: Disease free survival

[redacted]

Figure 10. DFS for nivolumab, standard statistical models overlaid upon KM (long-term projections) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DFS: Disease free survival

[redacted]

Figure 11. DFS for placebo, standard statistical models overlaid upon KM (short-term fit) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DFS: Disease free survival

[redacted]

Figure 12. DFS for placebo, standard statistical models overlaid upon KM (Long-term projections) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DFS: Disease free survival

In both the nivolumab and placebo arm, visual inspection (Figure 9 and Figure 11) shows that each of these models, except the Gompertz (light blue curve) and generalised gamma (red curve), overestimates DFS in the early part of the data and underestimates it in the latter part and; thus, providing a poor fit. Therefore, the exponential, Weibull, lognormal and log-logistic curves are not considered further due to their poor fit to the data. It is also noted that even though the Gompertz model fails to converge to a mean value in the long term, it cannot be rejected for this reason as general population mortality is applied from 5 years in the economic model.

However despite the Gompertz model providing a good visual fit, as well as ensuring the tail of data is captured well, it is penalised in the early time points where there are more observations. In terms of likelihood calculations, this is reflected in the higher AIC for Gompertz than generalised gamma as noted above.

Furthermore, the hazard profile of the Gompertz model (pink curve; Figure 13 and Figure 14) for the event time distributions of both arms represent monotonically decreasing hazards, similar to the Bspline (green curve). However, the Gompertz model cannot replicate the single inflection point in the early timepoints of KM data similar to the Bspline. Conversely, the generalised gamma (red curve) is within the CI in the early time points and captures the tail of the data (Figure 9 and Figure 11). The hazard profiles of generalised gamma (Figure 13 and Figure 14) matches with smooth hazard profiles of observed KM data (Figure 2) similar to the R-P spline and kernel smoothed curves (blue and purple curves Figure 13 and Figure 14), which capture the observed time dependent hazard profile. Due to the flexibility of generalised gamma distribution, the model is able to capture changing hazards with time and therefore capture the inflexion observed in the KM data.

Figure 13. DFS hazard profiles for nivolumab, standard smoothed spline models with the hazard profiles predicted from generalised gamma and Gompertz models (with independent modelling approach) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Figure 14. DFS hazard profiles for placebo, standard smoothed spline models with the hazard profiles predicted from generalised gamma and Gompertz models (with

independent modelling approach) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

In summary, with an independent modelling approach, generalised gamma is preferred to describe the event distribution in both the placebo and nivolumab arms as a base case for economic modelling, due to having a good visual fit, lowest AIC/BIC, and good fit to the KM hazard profile.

3.2.3.2 Joint modelling - exploring the PH assumption

For completeness, a joint modelling approach with PH assumption was also explored for scenario analysis in the economic modelling. With joint modelling approach, a constant PH is assumed when the parametric model is either exponential, Weibull or Gompertz distribution.

Visual inspection of model fits, Figure 15 and Figure 16, shows that all parametric models, except the Gompertz, poorly fit to the observed event distribution. In addition, the goodness of fit statistics (Table 4) indicates that, of the three PH models (Gompertz, exponential, and Weibull), the Gompertz has the best fit to the data.

[redacted]

Figure 15. DFS for nivolumab, standard statistical models with a PH assumption overlaid upon KM (short-term fit) with joint modelling approach - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DFS: Disease free survival

[redacted]

Figure 16. DFS for placebo, standard statistical models with a PH assumption overlaid upon KM (short-term fit) with joint modelling approach - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DFS: Disease free survival

Table 4. Measure of goodness of fit for parametric models with joint modelling using the parametric distributions that hold a PH assumption for observed DFS, CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU).

	Assumption	Joint models	
		AIC	BIC
Gompertz	PH	[redacted]	[redacted]
Weibull	PH	[redacted]	[redacted]
Exponential	PH	[redacted]	[redacted]

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; PH: proportional hazards

In summary, if using a PH approach, the Gompertz curve would be the most appropriate for the scenario analyses.

3.2.4 Comparison of the generalised gamma independent model to the Gompertz PH assumption

As noted above the appropriate curve to use in the base case analysis is independent modelling with a generalised gamma function. If exploring PH modelling as a scenario, then the appropriate curve to use in the PH modelling scenario would be the Gompertz curve. For completeness, a comparative visual description of the fit of these two models to the observed data are presented in Figure 17 for nivolumab and Figure 18 for placebo. As the figures demonstrate, the Gompertz distribution (red curves) do not fit the early time points of the data well, for example the Gompertz model in the nivolumab arm is outside the 95% confidence interval at the start of the curve (Figure 17). Furthermore, the Gompertz is heavily penalised at early time points because of the high number of observations. It is not possible to compare the AIC/BIC as both models use a different number of parameters (joint models will have a reduced number of parameters), nevertheless a crude comparison shows that the sum of AIC/BICs for two arms for the independent generalised gamma model is lower than the AIC/BIC obtained for the joined Gompertz model. To be specific, the AIC and BIC for joined Gompertz model are [redacted] and [redacted] (Table 4), while that for independent generalised gamma are [redacted] and [redacted] respectively (using sum of the individual AIC and BICs of two arms shown in 3).

Figure 17. DFS for nivolumab, generalised gamma model using independent modelling compared to Gompertz joint model overlaid on the KM curve - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

DFS: Disease free survival

Figure 18. DFS for placebo, generalised gamma model using independent modelling compared to Gompertz joint model overlaid on the KM curve - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

DFS: Disease free survival

In conclusion, a generalised gamma independent model remains the most appropriate, and preferred, model for the economic base case.

Note: For completeness and transparency, the visual fits and table of goodness of fits for joint models with single AFT models (log normal, log logistic, and generalised gamma) are given

in Section 7: Appendix 2. Please note these models are not appropriate to inform the economic analysis as illustrated in Section 3.2.2.

3.2.5 Other non-standard models

In keeping with NICE TSD 14 [1] and the model selection algorithm (Figure 1), the six nominated standard models were considered. Moreover, as stated within the ERG report, the ERG prefer a standard parametric model that smooths out the artefacts which will be more likely to describe the underlying hazard profiles.

3.2.6 Remission state

Inspection of the DFS hazards from the trial clearly indicates a trend towards general population mortality rates – with treatment with placebo potentially already crossing matched life-table hazards by the end of the trial data – which supports an assumption that patients who had not experienced disease recurrence by the time of maximum follow-up in the trial (around 4 years) would be at negligible ongoing risk from the disease. Given the immaturity of the data, it was not considered appropriate to fit a mixture-cure model to estimate a 'cured' population fraction or to use the trial data to specify exactly the time at which remission could be assumed in the remaining population. However, the observed trajectory of DFS hazards towards general population level and the time it takes for them to reach that level are in line with clinical expert opinion and UK clinical practice.

Clinician feedback indicated that recurrence after 5 years is rare and patients who reach 5 years following surgery without recurrence would be discharged and no longer monitored as recurrence beyond this point is uncommon.[26,27] It was therefore considered reasonable, given evidence from the CheckMate 274 trial and supporting clinical evidence, to assume zero excess risk from the disease 5 years after beginning treatment. Long-term remission was applied to DFS models by substituting trial DFS weekly hazards for age- and sex-matched mortality rates from UK life tables[12] from 5 years in both arms of the trial. Although not explicitly evaluated in a scenario, deterministic sensitivity analysis evaluated the sensitivity of the model to a 20% increase and 20% decrease in lifetable general population mortality (see CE appendix for full details).

3.2.7 Summary of investigator-assessed DFS

Time-to event models were formed based upon data from CheckMate 274 in order to inform state occupancy of a semi-Markov cost-utility model. A summary of the findings are described below:

- The log cumulative hazard plot and Q-Q plot of the observed DFS showed that a single AFT model is not valid.
- Inspection of the log cumulative hazard plot and Schoenfeld plot suggested a PH assumption may be an option, however it was not conclusive that PH should be applied throughout the time horizon.
- Given NICE TSD 14[1] guidance and inconclusive conclusion decision on the suitability of the PH assumption, independent modelling was selected.

- Visual fit, hazard profiles and goodness of fit statistics, such as AIC/BIC, indicated that the generalised gamma is the most suitable model to predict the event time distribution in both arms (using independent models).
- External expert opinion and smoothed hazard comparison of trial data with lifetable hazards were used to apply remission for those who have not recurred by 5 years.
- Independent modelling with generalised gamma as the parametric distribution was chosen as the base case. Other scenario analyses are explored in the economic modelling using; all other five distributions for the independent modelling, and the Gompertz model using the PH assumption.

4 Conclusion

In summary, this document outlines the analysis and process followed to identify the appropriate method and curve for use in the base case economic model, that is independent modelling using a generalised gamma function. This curve was identified following NICE DSU[1,2] guidance, assessment of visual fits, cumulative log hazard plots, hazard profiles and statistical goodness of fit measures. An alternative approach would be to model DFS based on a PH assumption using a Gompertz curve. However as noted in this document, this approach has limitations when compared to the chosen base case (i.e. independent modelling using the generalised gamma) and is presented for completeness.

5 References

1. National Institute for Health and Care Excellence. NICE DSU Technical Support Document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. Available at: https://nicedsu.sites.sheffield.ac.uk/tsds/flexible-methods-for-survival-analysis-tsd [Accessed 28 February 2022].
2. Rutherford MJ, Lambert PC, Sweeting MJ, et al. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. 2020. Available at: http://nicedsu.org.uk/wp-content/uploads/2020/11/NICE-DSU-Flex-Surv-TSD-21_Final_alt_text.pdf [Accessed 14 January 2021].
3. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making. 2014;34(3):343-51.
4. Bristol Myers Squibb. Erratum to Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2021.
5. Australian Bureau of Statistics. Life tables. 2019. Available at: https://www.abs.gov.au/statistics/people/population/life-tables/2016-2018#data-download [Accessed 10 January 2022].
6. Centers for Disease Control and Prevention: National Center for Health Statistics. U.S. State Life Tables, 2017. 2019. Available at: https://www.cdc.gov/nchs/nvss/life-expectancy.htm#data [Accessed 23 April 2021].
7. Central Statistics Office. Irish life tables 2010-2012. 2015. Available at: https://www.cso.ie/en/releasesandpublications/er/ilt/irishlifetablesno162010-2012/ [Accessed 23 April 2021].
8. Economic Commission for Latin America and the Caribbean (ECLAC). Life Tables. Demographic Observatory, Latin America and the Caribbean (LC/PUB.2017/20-P). Santiago: United Nations,. 2017. Available at: https://www.lifetable.de/cgi-bin/country.php?code=col [Accessed 10 January 2022].
9. INDEC: Instituto Nacional de Estadistica y Censos. Tablas abreviadas de mortalidad por sexo y edad 2008-2010. : total del país y provincias. 2013. Available at: https://www.indec.gob.ar/ftp/cuadros/publicaciones/tablas_mortalidad_2008_2010.pdf [Accessed 10 February 2022].
10. Instituto Brasileiro de Geografia e Estatística. IBGE; Diretoria de Pesquisas (DPE); Coordenação de População e Indicadores Sociais (COPIS): TÁBUA COMPLETA DE MORTALIDADE 2017. . Available at: www.ibge.gov.br/ [Accessed 10 January 2022].
11. Instituto Nacional de Estadistica. Tablas de mortalidad. Resultados. 2020. Available at: https://www.ine.es/dyngs/INEbase/operacion.htm?c=Estadistica_C&cid=1254736177004&menu=resultados&secc=1254736195384&idp=1254735573002 [Accessed 10 January 2022].
12. Office of National Statistics. National life tables: UK. 2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables/current [Accessed 10 January 2022].
13. STATBEL - Statistics Belgium. Evolution de l'espérance de vie à la naissance en Belgique, selon le sexe, 1885-2019. Available at: https://statbel.fgov.be/fr/themes/population/mortalite-et-esperance-de-vie/tables-de-mortalite-et-esperance-de-vie#figures [Accessed 10 January 2022].
14. STATcube - Statistical Database of Statistics Austria. STATcube of STATISTICS AUSTRIA. Available at:

https://statcube.at/statistik.at/ext/statcube/jsf/tableView/tableView.xhtml [Accessed 10 January 2022].
15. Statistics Canada. Life tables, Canada, provinces and territories, catalogue no. 84-537-X. Available at: https://www150.statcan.gc.ca/n1/en/catalogue/84-537-X [Accessed 23 April 2021].
16. Statistikdatabasen. Life table by sex and age. Year 1960 - 2020. Available at: www.statistikdatabasen.scb.se/pxweb/en/ssd/START__BE__BE0101__BE0101I/LivslangdEttariga/ [Accessed 10 January 2022].
17. University of California BU. Human Mortality Database. Available at: www.mortality.orgwww.mortality.org [Accessed 10 January 2022].
18. World Health Organisation. Global Health Observatory data repository,. Available at: https://apps.who.int/gho/data/?theme=main%26vid=60340 [Accessed 10 January 2022].
19. Office of National Statistics. Cancer registration statistics, England. 2019. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 19 February 2021].
20. Ishak KJ, Kreif N, Benedict A, et al. Overview of Parametric Survival Analysis for Health-Economic Applications. PharmacoEconomics. 2013;31(8):663-75.
21. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175-97.
22. Jackson C, Sharples L, Thompson S. Survival Models in Health Economic Evaluations: Balancing Fit and Parsimony to Improve Prediction. The International Journal of Biostatistics. 2010;6.
23. Galsky MD, Witjes JA, Gschwend JE, et al. Disease-free survival with longer follow-up from the Phase 3 CheckMate 274 trial of adjuvant nivolumab in patients who underwent surgery for high-risk muscle-invasive urothelial carcinoma. 2021. Available at: https://suo-abstracts.secure-platform.com/a/gallery/rounds/12/details/1592 [Accessed 9 December 2021].
24. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. Sociological Methods & Research. 2004;33(2):261-304.
25. Raftery AE. Bayesian Model Selection in Social Research. Sociological Methodology. 1995;25:111-63.
26. Bristol Myers Squibb. Advisory board: Nivolumab for post-resection adjuvant treatment of high-risk muscle invasive urothelial cancer. 2021.
27. Yoo SH, Kim H, Kwak C, et al. Late Recurrence of Bladder Cancer following Radical Cystectomy: Characteristics and Outcomes. Urol Int. 2019;103(3):291-6.
28. Bristol Myers Squibb. Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2020.
29. Bristol Myers Squibb. Data on file. BMS-REF-NIVO-0150: Complementary Analysis: Study CA209274. Indication: Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2022.
30. Bristol Myers Squibb. CheckMate 274: Updated DBL (11 months minimum FU). Data on file. 2021.
31. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. New England Journal of Medicine. 2021;384(22):2102-14.
32. Bajorin DF, Witjes JA, Gschwend J, et al. First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab versus placebo in patients who underwent radical

surgery for high-risk muscle-invasive urothelial carcinoma. Journal of Clinical Oncology. 2021;39(6_suppl).
33. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol. 2015;16(1):76-86.

6 Appendix 1: Clinical effectiveness

6.1 Patient disposition and baseline characteristics

6.1.1 Patient disposition

A total of 709 patients were randomised in the study, 353 to the nivolumab arm and 356 to the placebo arm. Of the 282 randomised patients with tumour cell PD-L1 ≥ 1%, 140 were randomised to the nivolumab arm and 142 to the placebo arm.[28] A summary of the patient disposition is provided in Table 5.

At the updated DBL (11 months minimum FU), [redacted]% of patients with tumour cell PD-L1 ≥ 1% in the nivolumab arm and [redacted]% placebo arm had discontinued treatment during the treatment period. The most common reason for treatment discontinuation in both treatment arms was disease recurrence ([redacted] [[redacted]%] patients in the nivolumab arm and [redacted] [[redacted]%] patients in the placebo arm; Table 5).[29]

Table 5. Patient disposition - CheckMate 274, all treated patients – updated DBL (minimum 11 months FU)

	All randomised patients		All randomised patients with tumour PD-L1 expression ≥ 1%	
	Nivolumab	Placebo	Nivolumab	Placebo
Number of patients (intention-to-treat), N	353†	356†	140	142
Number of treated patients, n (%)	351 (99.4)†	348 (97.8)†	[redacted]	[redacted]
Continuation in the treatment period, n (%)[a]				
Ongoing treatment	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Completed treatment	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Discontinued treatment	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Reasons for discontinuation of the treatment period, n (%)[a]				
Disease recurrence	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Study drug toxicity	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Death	[redacted]‡	[redacted]‡	[redacted]	[redacted]
AE unrelated to study drug	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Patient requested to discontinue study treatment	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Patient withdrew consent	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Lost to follow-up	[redacted]‡	[redacted]‡	NR	NR
Maximum clinical benefit	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Patient no longer meets study criteria	[redacted]‡	[redacted]‡	NR	NR
Administrative reason by sponsor	[redacted]‡	[redacted]‡	NR	NR
Other	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Continuation in the study, n (%)[a]				
Patients who continued the study	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Patients who discontinued the study	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Reason for not continuing in the study, n (%)[a]				
Death	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Patient withdrew consent	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Lost to follow-up	[redacted]‡	[redacted]‡	[redacted]	[redacted]
Other	[redacted]‡	[redacted]‡	[redacted]	[redacted]

[a]Percentages based on patients entering treatment period

AE: adverse event; NR: not reported

Source: BMS 2022 (data on file)[29], ‡BMS 2021[30], and †Bajorin, 2021[31]

6.1.2 Baseline characteristics

Baseline characteristics were balanced across the two treatment arms (Table 6), and in the group of patients with a PD-L1 expression level of 1% or more.[31] The median age for all randomised patients with tumour PD-L1 expression ≥ 1% for the nivolumab and placebo arms was [redacted] (range: 34-92) and [redacted] (range: 45-84), respectively, and the majority of patients were

white and male ([redacted]% each).[28] Almost all PD-L1 > 1% patients had a baseline ECOG PS of 0 or 1, with just [redacted]% having ECOG PS 2 ([redacted]% nivolumab arm, [redacted]% placebo arm).[28] The predominant tumour type in both arms was urinary bladder, [redacted]% of all randomised patients with tumour PD-L1 expression.[28] Of all randomised patients with tumour PD-L1 expression [redacted]%, [redacted]%, and [redacted]% had Stage pT2, Stage pT3, and Stage pT4a disease at the time of resection, respectively.[28] Overall, [redacted]% of all randomised patients with tumour PD-L1 expression had received prior neo-adjuvant cisplatin. Of all randomised patients [redacted]% and [redacted]% had tumour cell PD-L1 expression < 1% and ≥ 1%, respectively; [redacted]% of the patients were indeterminate. The majority of all randomised patients were enrolled in Europe (48.2% and 48.0%), with [redacted]% and [redacted]% of patients from Great Britain, in the nivolumab and placebo arms, respectively.[28,32]

Table 6. Baseline characteristics - CheckMate 274 – August 2020 DBL

Baseline characteristic		All randomised patients		All randomised patients with tumour PD-L1 expression ≥ 1%	
		Nivolumab	Placebo	Nivolumab	Placebo
Cohort size (N)		353†	356†	140	142
Age	Median (range), years	[redacted] (30-92†)	[redacted] (42-88†)	[redacted](34-92†)	[redacted](45-84†)
	Mean (range), years	65.3 (30-92)†	65.9 (42-88)†	64.4 (34–92)†	65.9 (45–84)†
Sex, n (%)	Female	88 (24.9)†	81 (22.8)†	39 (27.9)†	30 (21.1)†
	Male	265 (75.1)†	275 (77.2)†	101 (72.1)†	112 (78.9)†
Race	White	264 (74.8)†	272 (76.4)†	104 (74.3)†	109 (76.8)†
	Black or African American	2 (0.6)†	3 (0.8)†	0	2 (1.4)†
	Asian	80 (22.7)†	75 (21.1)†	33 (23.6)†	28 (19.7)†
	Other or not reported	7 (2.0)†	6 (1.7)†	2 (1.4)†	3 (2.1)†
ECOG PS,[a] n (%)	0	224 (63.5)†	221 (62.1)†	86 (61.4)†	85 (59.9)†
	1	122 (34.6)†	125 (35.1)†	51 (36.4)†	53 (37.3)†
	2[b]	7 (2.0)†	9 (2.5)†	3 (2.1)†	4 (2.8)†
Tumour site, n (%)	Urinary bladder	279 (79.0)†	281 (78.9)†	113 (80.7)†	117 (82.4)†
	Renal pelvis	44 (12.5)†	52 (14.6)†	19 (13.6)†	14 (9.9)†
	Ureter	30 (8.5)†	23 (6.5)†	8 (5.7)†	11 (7.7)†
Minor histological variants present, n (%)	Yes	145 (41.1)†	141 (39.6)†	[redacted]	[redacted]
	No	208 (58.9)†	215 (60.4)†	[redacted]	[redacted]
Received neo-adjuvant cisplatin, n (%)	Yes	153 (43.3)†	155 (43.5)†	57 (40.7)†	61 (43.0)†
	No	200 (56.7)†	201 (56.5)†	[redacted]	[redacted]

Baseline characteristic		All randomised patients		All randomised patients with tumour PD-L1 expression ≥ 1%	
		Nivolumab	Placebo	Nivolumab	Placebo
PD-L1 expression status, n (%)	< 1%	210 (59.5)†	209 (58.7)†	[redacted]	[redacted]
	≥ 1% and < 5%	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 5% and < 10%	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 10%	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 5%	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 1%	139 (39.4)†	141 (39.6)†	[redacted]	[redacted]
	Other	4 (1.1)†	6 (1.7)†	[redacted]	[redacted]
Pathologic T stage at resection,[c,d] n (%)	pT0–2	80 (22.7)†	86 (24.2)†	[redacted]	[redacted]
	pT3	206 (58.4)†	204 (57.3)†	87 (62.1)†	83 (58.5)†
	pT4a	57 (16.1)†	62 (17.4)†	23 (16.4)†	27 (19.0)†
	Other	9 (2.5)†	3 (0.8)†	[redacted]	[redacted]
Nodal status at resection,[d] n (%)	N+	167 (47.3)†	168 (47.2)†	[redacted]	[redacted]
	N0/x with < 10 nodes removed	94 (26.6)†	99 (27.8)†	38 (27.1)†	38 (26.8)†
	N0 with ≥ 10 nodes removed	91 (25.8)†	88 (24.7)†	42 (30.0)†	38 (26.8)†

[a]Not reported for 1 patient in the placebo arm; [b]ECOG PS of 2 was permitted only for patients who did not receive cisplatin-based neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy. [c]The T staging included patients with N+, N0, or NX. [d]Not reported for 1 patient in each arm.

ECOG PS: Eastern Cooperative Oncology Group performance status; PD-L1: programmed death-ligand 1

Source: CSR[28], †Bajorin, 2021[31]

6.2 Clinical effectiveness results

6.2.1 Clinical efficacy results

Reported outcomes for all randomised patients with tumour cell PD-L1 ≥ 1% from the updated DBL (11 months minimum FU) are shown in Table 7, and Figure 19 to Figure 21.

Table 7. Clinical efficacy - CheckMate 274, all randomised patients with tumour cell PD-L1 ≥ 1% - updated DBL (11 months minimum FU)

Endpoint	Nivolumab (N = 140)	Placebo (N = 142)
DFS (Primary definition) [1]		
Events, n (%)	56 (40.0)*	85 (59.9)*
Median, months (95% CI)	N.A. (22.1, N.E.)*	8.4 (5.6, 20.0)*
Hazard Ratio (% CI)	0.53 (0.38, 0.75)*	
6 months, % (95% CI)	74.5* ([redacted])	55.7* ([redacted])
12 months, % (95% CI)	67.6* ([redacted])	46.3* ([redacted])
NUTRFS (secondary endpoint)		
Events, n (%)	55 (39.3)*	82 (57.7)*
Median, months (95% CI)	N.A. (25.8, N.E.)*	10.8 (5.7, 20.7)*
Hazard Ratio (95% CI)	0.54 (0.39, 0.77)*	
6 months, % (95% CI)	75.3* ([redacted])	56.7* ([redacted])
12 months, % (95% CI)	69.2* ([redacted])	47.1* ([redacted])
Time to recurrence (exploratory endpoint)		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI)	[redacted]	
6 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	[redacted]	[redacted]
DMFS (exploratory endpoint)		
Events, n (%)	48 (34.3)*	64 (45.1)*
Median, months (95% CI)	N.A. (26.0, N.E.)*	20.7 (10.8, N.E.)*
Hazard Ratio (95% CI)	0.60 (0.41, 0.88)*	
6 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	[redacted]	[redacted]
LRDFS (exploratory endpoint)		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Hazard Ratio (95% CI)	[redacted]	
6 months, % (95% CI)	[redacted]	[redacted]
12 months, % (95% CI)	[redacted]	[redacted]

[1]primary definition of DFS accounts for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer. Abbreviations: CI: confidence interval; DFS: disease-free survival; DMFS: distant metastasis-free survival; LRDFS: locoregional disease-free survival; N.A.: not reached; N.E.: not estimable; NUTRFS: non-urothelial tract recurrence-free survival.

Source: BMS 2022 (data on file)[29], *Galsky 2021[23]

At the updated DBL (11 months minimum FU), patients with tumour cell PD-L1 ≥ 1% treated with nivolumab (Table 7) had a clinically relevant improvement in DFS compared with placebo (HR 0.53 [95% CI: 0.38, 0.75]), with KM curves separating after 3 months, favouring nivolumab (Figure 19).[23]

The secondary definition of DFS accounted for disease assessments occurring on or after initiation of subsequent anticancer therapy, and the results [redacted] primary definition (HR [redacted]).[29]

At the updated DBL (11 months minimum FU), nivolumab treatment also resulted in a clinically meaningful improvement compared with placebo in NUTRFS (HR 0.54 [95% CI: 0.39, 0.77]) and DMFS (HR 0.60 [95% CI: 0.41, 0.88]).[23] KM curves separating after 3 months, favouring nivolumab (Figure 20. and Figure 21). Similarly, nivolumab was associated with clinically meaningful improvement in locoregional disease-free survival (LRDFS; HR [redacted]) and time to recurrence (HR [redacted]; Table 7).[29]

DFS, NUTRFS and DMFS rates were also markedly higher in the nivolumab arm than with placebo at 6 months (74.5% vs 55.7%, 75.3% vs 56.7%, and [redacted]% vs [redacted]%, respectively) and 12 months (67.6% vs 46.3%, 69.2% vs 47.1%, and [redacted]% vs [redacted]%, respectively).[23,30]

Nivolumab treatment resulted in [redacted] in, exploratory endpoint, progression-free survival on next line systemic therapy (PFS2) in all randomised patients with PD-L1 expression ≥ 1%: median was [redacted] for nivolumab and [redacted] months for placebo (HR [redacted]).[30] PFS2 rates were [redacted] in the nivolumab arm than in the placebo arm at 6 and 12 months ([redacted]% vs [redacted]% and [redacted]% and [redacted]%, respectively).[29]

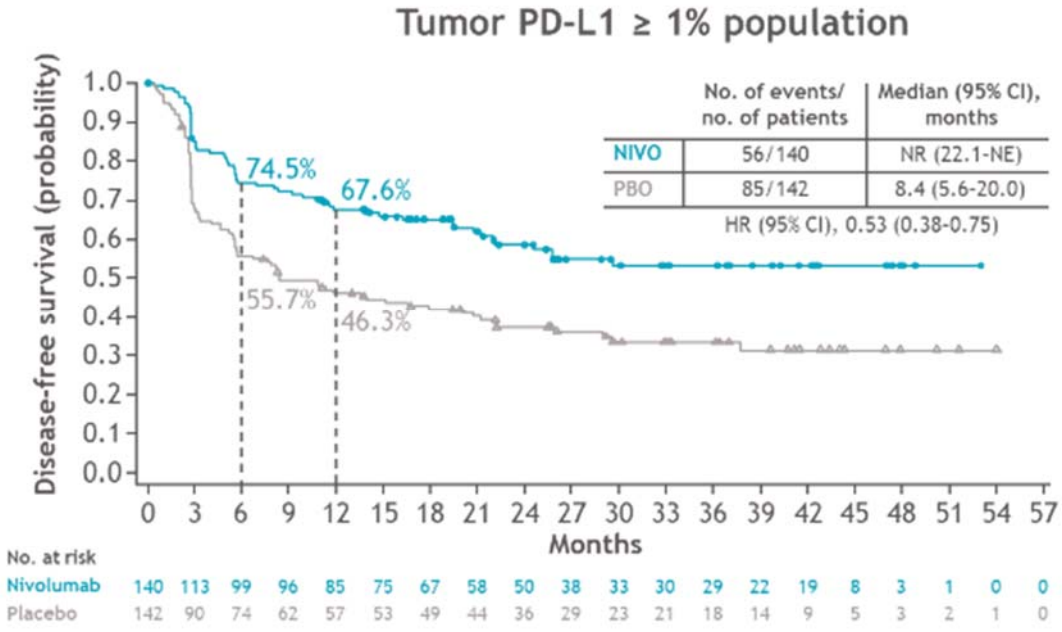


Figure 19. KM plot of DFS (primary definition) – CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Source: Galsky 2021[23]

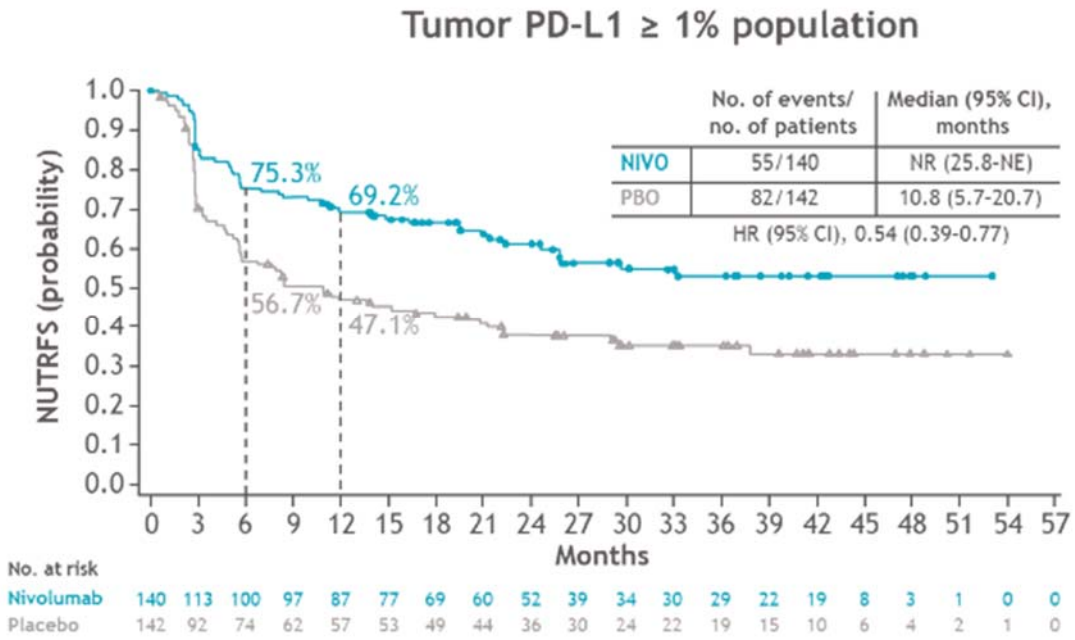


Figure 20. KM plot of NUTRFS – CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Source: Galsky 2021[23]

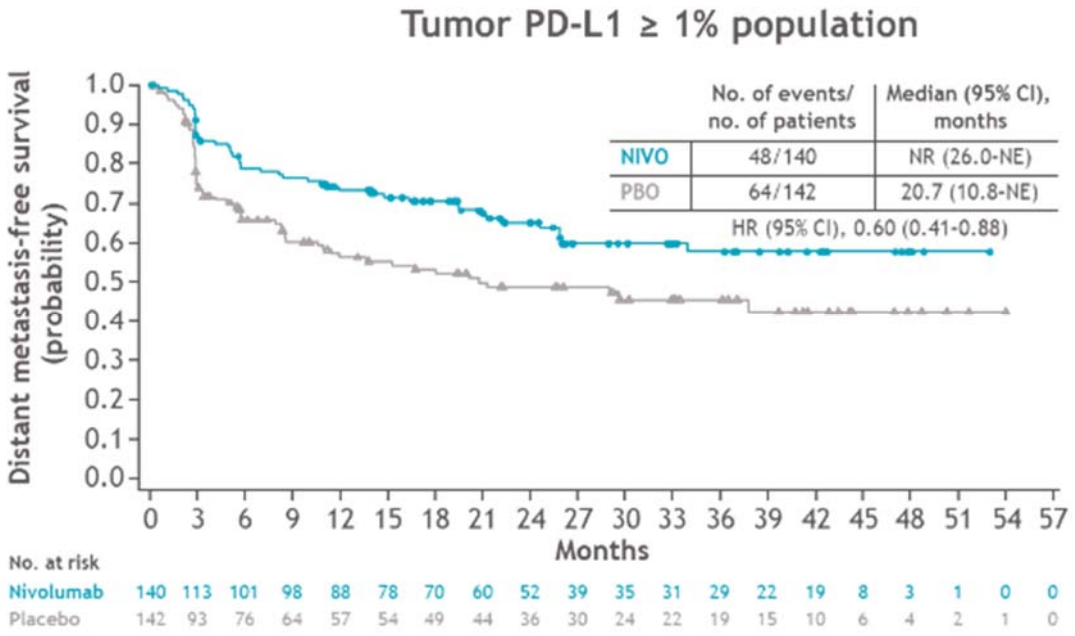


Figure 21. KM plot of DMFS –CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Source: Galsky 2021[23]

6.3 Subsequent anti-cancer therapy

Subsequent anti-cancer therapy was received by [redacted] of patients in the nivolumab arm and [redacted] of patients in the placebo arm (Table 8). The most common form of subsequent anti-cancer therapy was systemic therapy, [redacted] patients in the nivolumab arm and [redacted] patients in the placebo arm.[29]

Table 8. Subsequent anti-cancer therapy - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

	Nivolumab (N = 140)	Placebo (N = 142)
Patients with any subsequent therapy, n (%)	[redacted]	[redacted]
Subsequent therapy, n (%)		
Radiotherapy	[redacted]	[redacted]
Surgery	[redacted]	[redacted]
Systemic therapy	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Source: BMS 2022 (data on file)[29] Full details of therapies are available in BMS 2022 (data on file), Section 3.1.19[29]		

6.4 Deaths

Death from any cause at the updated DBL (11 months minimum FU) was reported in [redacted] of patients from the nivolumab arm and [redacted] patients in the placebo arm. The most frequent reason for death in both treatment arms was disease progression, [redacted] patients in the nivolumab arm and [redacted] patients in the placebo arm. Death related study drug toxicity was reported for two patients in the nivolumab arm and none in the placebo arm.[29] A summary of deaths up to the updated DBL (11 months minimum FU) can be found in Table 9.

Table 9. Summary of deaths - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

	Nivolumab (N = 140)	Placebo (N = 142)
Number of patients who died, n (%)	[redacted]	[redacted]
Primary reason for death, n (%)		
Disease	[redacted]	[redacted]
Drug toxicity	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
Source: BMS 2022 (data on file)[29]		

6.5 Subgroup analysis

Additional subgroup analyses are available from the updated DBL (11 months minimum FU). Results of the subgroup analysis for the CheckMate 274 patients with tumour cell PD-L1 ≥ 1% arms are summarised below.

6.5.1 Disease-free survival

At the updated DBL (11 months minimum FU), DFS hazard ratios favoured nivolumab for most subgroups, as shown in Figure 22 and Figure 23, including the use of prior neoadjuvant cisplatin therapy (Yes: HR [redacted]; No: HR [redacted]).[29] Nivolumab was superior to placebo suggesting a consistent clinical benefit for nivolumab-treated patients in all pre-defined subgroups, with the exception of patients with initial tumour originating in the renal pelvis. A number of subgroups had low patient numbers and thus the results should be interpreted with caution as the study was not stratified or powered for analyses in these subgroups.

Figure 22. Forest plot of subgroup analyses for DFS - CheckMate 274, PD-L1 ≥ 1% – updated DBL (11 months minimum FU) 1/2

Source: BMS 2022 (data on file)[29]

Figure 23. Forest plot of subgroup analyses for DFS - CheckMate 274, PD-L1 ≥ 1% – updated DBL (11 months minimum FU) 2/2

Source: BMS 2022 (data on file)[29]

6.5.2 Non-urothelial tract recurrence free survival

At the updated DBL (11 months minimum FU), for the secondary endpoint, NUTRFS, the unstratified hazard ratios favoured nivolumab over placebo for most subgroups, as shown in Figure 24 and Figure 25, including the use of prior neoadjuvant cisplatin therapy (Yes: [redacted]; No: [redacted]).[29] Nivolumab was superior to placebo suggesting a consistent clinical benefit for nivolumab-treated patients in all pre-defined subgroups, [redacted] Of note, the study was not powered to detect statistically significant differences in the treatment effect in these subgroups, thus results for all subgroups should be interpreted with caution.[28]

Figure 24. Forest plots of subgroup analyses for NUTRFS - CheckMate 274, PD-L1 ≥ 1% – updated DBL (11 months minimum FU) 1/2

Source: BMS 2022 (data on file)[29]

Figure 25. Forest plots of subgroup analyses for NUTRFS - CheckMate 274, PD-L1 ≥ 1% – updated DBL (11 months minimum FU) 2/2

Source: BMS 2022 (data on file)[29]

7 Appendix 2: Single AFT model fit (for transparency and completeness)

As illustrated in Section 3.2.2, a single AFT model is not appropriate to describe the event time distribution of DFS. However, for transparency and completeness, the visual fits (Figure 26 for nivolumab arm and Figure 27 for placebo arm) and goodness of fit statistics (Table 10) are presented below. For the single AFT assumptions, the standard parametric models chosen are lognormal, log logistic and generalised gamma. It is clear from the plots below that a single AFT model does not fit the data well and should not be used to inform economic modelling.

Figure 26. DFS for nivolumab, standard statistical models with a single AFT assumption overlaid upon KM (short-term fit) with joint modelling approach - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Figure 27. DFS for placebo, standard statistical models with a single AFT assumption overlaid upon KM (short-term fit) with joint modelling approach - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Table 10. Measure of goodness of fit for parametric models with joint modelling using the parametric distributions that hold a single AFT assumption for observed DFS, CheckMate 274, PD-L1 ≥ 1% population, updated DBL (11 months minimum FU)

	Assumption	Joint models	
		AIC	BIC
Gen gamma	Single AFT	[redacted]	[redacted]
Log normal	Single AFT	[redacted]	[redacted]
Log logistic	Single AFT	[redacted]	[redacted]
AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; PH: proportional hazards			

8 Appendix 3: Addressing select clarification questions

This appendix provides responses to specific questions from the clarification stage that the ERG were seeking updated responses to in relation to the PD-L1 ≥ 1% population.

A8. Priority: CS Table 16, page 53. The table shows time to recurrence data for all randomised patients.

a) Please clarify why no Kaplan-Meier (KM) plot of time to recurrence was provided alongside Table 16.

A time to recurrence KM plot has not been generated as the KM product-limit method is not designed to accommodate the competing risk. Therefore, given the presence of competitive risk, time to recurrence is presented in Figure 28. It is worth noting that the median time to recurrence was [redacted] for nivolumab versus [redacted] (95% CI: [redacted]) months for placebo at the updated DBL (11 months minimum FU), giving a meaningful benefit in median time to recurrence.[29]

[redacted]

Figure 28. Cumulative incidence of time to recurrence - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

b) Please clarify whether the time of death events could be inferred if the company has the KM for DFS events and the KM for recurrence.

The exact time of death events cannot not be inferred as there is no KM for recurrence as explained in a).

c) Please provide breakdown of disease-free survival (DFS) events for both arms by whether the event was a disease recurrence or death. If these rates are substantially different then please incorporate this within the economic model.

Across both arms in CheckMate 274, only [redacted] events (out of [redacted] total DFS events) were deaths, representing a very small proportion of DFS events. This represents only [redacted]% of events, and the number of death events was similar between arms, [redacted] and [redacted] events for nivolumab and placebo, respectively (Table 11). Additionally, whilst the total number of death events is known, the company remains blinded to OS data, and, as a result, do not have information on when these death events took place. Timing of these death events will only be ascertained when OS is fully unblinded. Due to the highly immature nature of the data for death pre-recurrence, the low number of death events, and the lack of information on the timing of these events, it is not considered appropriate to stratify these values in the economic model by treatment arm.

Table 11. Number of death events in both treatment arms - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

	Nivolumab (N=353)	Placebo (N=356)
Number of events (%)	[redacted]	[redacted]
Type of events (%)		
Disease at baseline	[redacted]	[redacted]
Recurrence	[redacted]	[redacted]
Death	[redacted]	[redacted]
Source: BMS 2022 (data on file)[29]		

A10. CS Figure 7, page 51. Please supply a version of the DFS KM function plots with 95% confidence intervals (CIs).

[redacted]

Figure 29. DFS KM curves - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Table 12. Number of cumulative censors at each 6 month interval in each arm - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Time (Months)	6	12	18	24	30	36	42	48	54
Nivolumab	[redacted]								
Placebo	[redacted]								

A11. Please provide the KM plot for time on treatment for patients on nivolumab.

[redacted]

Figure 30. Time on treatment KM curve for nivolumab - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

A15. CS Table 10, page 45. Please clarify whether those patients who continue in the study received any further treatment. In addition, please clarify why the numbers of patients who are categorised as continuing the study or discontinuing the study do not sum to the total number of treated patients.

Details of subsequent anti-cancer therapy received by patients in the study are reported in Table 8. Subsequent therapies included radiotherapy, surgery, systemic therapy and immunotherapy; full details of therapies are available in BMS 2022 (data on file), Section 3.1.19.[29]

The values for the patients categorised as continuing the study or discontinuing the study do not sum to the total number of treated patients because these values refer to patients who completed or discontinued treatment in the treatment period only, and therefore, exclude those receiving ongoing treatment in the treatment period. For example, [redacted] ([redacted]) nivolumab treated patients completed or discontinued treatment, and of these [redacted] patients, [redacted] continued the study and [redacted] discontinued the study.[29]

B10. CS Figure 29, page 112. Please comment on whether the mode may simply be an artefact of the delay until 3 months before first assessment and whether a monotonically decreasing hazard may be more realistic as this has implications for survival model selection.

The figure in reference (CS Figure 29, page 112) is in relation to the ITT population. The addendum refers to the new analysis with updated DBL (11 months FU) for the PD-L1 >1% population.

The hazard profiles, including the three month spike of the hazard are included when assessing which parametric curve should be used in the base case analysis (see Section 3.2.3).

B11. CS Section 3.3.2.1.4, page 118. Please provide more details of the logistic regression used to estimate the probability a recurrence is a death. For example, were any covariates included?

Note: additional covariates were not included and so this response remains the same.

The economic model consists of only three states, the transition rates between which are dependent only upon time. Therefore, additional covariates were not included in the model, as the distribution of these predictive covariates is not predicted per state within the economic model, i.e. the models are marginal. Various transforms of the time covariate, and linear combinations thereof, were explored as possible forms for the linear predictor of a logistic regression model.

B12. CS Section 3.3.2.1.5, pages 118-120. We note that in Figure 32 of the CS that (i) the base case distribution does not lie between the Bellmunt et al and De Santis et al curves between approximately 1.25 and 3 years, (ii) that the median survival in the base case is greater than in both KM curves and also that (iii) the long-term survival appears to be underpredicted in the base case suggesting that the derived curve is not appropriate. Please comment on whether it would be more appropriate to synthesise the parameters of survival models fitted to the two survival curves from the literature. If appropriate, please conduct an analysis with a better fitting distribution.

Note: the updated analysis within this addendum utilises the same post-recurrence survival approach as the original company submission; however we have updated the scenario analyses presented below to support the response.

While synthesising the parameters of the survival models from the literature would have been more appropriate, it would have added more complexity to the model, with potentially little difference in the outcomes. We have conducted sensitivity analyses using doubled post-recurrence and halved post-recurrence survival based on Bellmunt et al. and de Santis et al. curves (Section 1.3.3.6 in cost-effectiveness appendix). The changes were minimal (£9,976/QALY and £11,614/QALY, versus £11,105/QALY within the base case) and nivolumab remains cost effective.

Therefore, the model is not sensitive to this parameter, and conducting this analysis with a more complex curve-fitting would not strongly influence the results.

Table 13. Scenario analysis: impact of altered recurrence to death transition (doubled survival post-recurrence)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,976
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

Table 14. Scenario analysis: impact of altered recurrence to death transition (halved survival post-recurrence)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,614
ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years.							

B13. CS Section 3.3.2.1.6, page 121. Please provide further details of how expert opinion was used in survival model selection including any elicited survival proportions which were used as selection criteria. Also, in Appendix K, Section 3.1.7, page 33. Please clarify how the clinician predictions of DFS were obtained. The value of 26% suggests that some averaging may have been used. If possible, please provide the full range of elicited values.

Note: This question originally referred to survival based on the initial company submission. Since the initial submission an additional data cut became available (with 11 months minimum follow-up) and the survival analysis has been conducted from scratch to reflect the change in

licence for the PD-L1 ≥ 1% population. As such this question is less relevant to the current submission. However a response is provided below.

In terms of clinical expert opinion, the primary feedback is related to how recurrence should be included in the model over the long term. Clinical experts informed a value of 5 years for determining long-term disease-free status, after which point patients have negligible risk of recurrence, and survival aligning to the general population. As such, DFS extrapolations were only relevant up to this 60 month point.

The process for selecting the base case DFS curve (independent modelling using generalized gamma) is explored within this survival appendix. In addition, extensive scenario analyses have been conducted, regardless of clinical plausibility or appropriateness in terms of fit to the available trial data, where different independent curves, and curves based on the PH assumption are used. These different methods will approximate a range of survival outcomes for nivolumab and BSC. The base case ICER using the generalised gamma independent models for nivolumab and placebo was £11,105/QALY, with the remaining curves tested as scenario analyses providing ICERs which ranged from £10,481/QALY to £11,723/QALY (see Section 1.3.3.4 of the cost-effectiveness appendix).

B14. Appendix K, Figure 4, page 20. Please supply a version of the DFS Hazard functions showing Kernel-smoothed and B-spline plots, together with the life-table derived hazard, with both arms on one plot, with 3-month divisions on the time axis and keeping the full-time range of the observed data.

Figure 31. DFS, smoothed hazard function estimates for nivolumab and placebo arms - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

These smoothed hazard estimates can be found in the main body of the report (See Figure 4 and Figure 5).

B15. Appendix K, Figures 7 & 8, page 23. Please supply two separate larger, clearer versions of these figures excluding the exponential and Weibull models but including also the generalised-F distribution and the Exp/Weib and Lnorm/Weib mixture parametric model. As currently done, please provide separate figures for the observed period as well as the full extrapolation.

Note: This question originally referred to survival analysis based on the initial company submission. Since the initial submission an additional data cut became available (with 11 months minimum follow-up) and the survival analysis has been conducted from scratch to reflect the change in licence for the PD-L1 ≥ 1% population. As such this question is not relevant to the current submission. The new survival analysis, using the PD-L1 ≥ 1% population, indicated that the independent modelling of the two arms with generalised gamma distribution is the most appropriate model as discussed in Section 3.2.

B16. Appendix K, Section 3.1.4, page 24. Please clarify in detail how the models fitted in this section relate to the first equation in Section 2.2.8, page 14. It is not clear whether the mixture model is modelling only the excess risk or whether one component is modelling the excess and the other modelling the LT risk. Also, please clarify if the parameter rho represents the variable p.

Note: As above, this question is not relevant to the current submission.

B17. Appendix K, Section 3.1.4, page 24. The ERG notes that just because two models agree, it doesn't mean that they are right and the model that disagrees is wrong. Please clarify whether any external data were used to inform the model choice.

Sternberg et al. (2015)[33] was deemed the most appropriate source of external data for the ITT population; however, this is a different population to the PD-L1 ≥ 1% subgroup, for which there are no appropriate external data available for validation. Nevertheless, the modelling was robust, with a range of curves used in accordance with NICE TSD 14[1] and as noted in B13, the range of curves will approximate various survival outcomes for nivolumab and BSC. UK clinicians also validated the 5 year cure point, used to apply remission for patients who have not recurred by 5 years.

B18. Please clarify whether there is any clinical rationale for assuming that the cut-point for changing from the KM to a parametric curve differs for nivolumab ([redacted] months) and for placebo ([redacted] months)

Note: This question originally referred to survival analysis based on the initial company submission. Since the initial submission an additional data cut became available (with 11 months minimum follow-up) and the survival analysis has been conducted from scratch to reflect the change in licence for the PD-L1 ≥ 1% population. As such this question is not relevant to the current submission.

9 Appendix 4: Additional ERG requests

This appendix provides further detail, where relevant, with respect to specific requests to BMS from NICE with regards to email communication from 14 February 2022, “RE: Brief Call - ID2694 - Nivolumab Adj Bladder”.

Provide versions of all KM plots which include confidence intervals.

Figure 32. KM plot of DFS (primary definition) with CIs - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Provide breakdown of DFS events for both arms by whether the event was a disease recurrence or death.

Breakdown provided as part of Appendix 3 (A8c).

Include a KM plot for time on treatment for patients on nivolumab

Plot provided as part of Appendix 3 (A11).

Provide details of how expert opinion was used in survival model selection including any elicited survival proportions which were used as selection criteria

See Appendix 3 (B17).

Provide plots of the DFS Hazard functions showing unsmoothed hazards, Kernel smoothed and B-spline smoothed hazards, together with the life-table derived hazard, with both arms on one plot, with 3-month divisions on the time axis and keeping full-time range of the observed data. Please also supply the smoothed hazards together with predicted hazards from the fitted survival models on separate axes for each arm.

Figure 33. DFS for unsmoothed hazard function estimates - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Figure 34. DFS unsmoothed hazard function estimates for nivolumab - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Figure 35. DFS unsmoothed hazard function estimates for placebo - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

See Figure 13 and Figure 14 in the main body of the text for smoothed hazards with predicted hazards from the fitted parametric survival models.

When presenting comparison of survival model fits to KM functions provide versions for the observed period only (to aid visual inspection of goodness of fit) as well as for the long term extrapolation.

Figures are presented in the main text, see Figure 9 to Figure 12.

In addition to the long term extrapolations plots above, provide a version in which those for both arms are presented on a single plot. Do this for all fitted models and also for only those models which are reasonable plausible.

The generalised gamma and Gompertz parametric models provide a good fit to the DFS event time distribution for PD-L1 ≥ 1% population, as shown in Figure 36 and Figure 37. All other distributions (exponential, Weibull, log normal and log logistic) provide a poor fit both visually and from a goodness of fit perspective; however, for completeness and transparency all six parametric distributions independently fitted to nivolumab and placebo arms are presented in Figure 38 and Figure 39.

Figure 36. DFS, independent standard statistical models Gompertz and Generalised Gamma overlaid upon KM (short-term fit) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Figure 37. DFS, independent standard statistical models Gompertz and Generalised Gamma overlaid upon KM (long-term projections) - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Figure 38. DFS, independent standard statistical models upon KM (short-term fit) using all models - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

Figure 39. DFS, independent standard statistical models upon KM (long-term projection) using all models - CheckMate 274, PD-L1 ≥ 1% population - updated DBL (11 months minimum FU)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: Addendum

Nivolumab for treating resected high-risk invasive urothelial cancer

ID2694

Appendix: Cost-effectiveness results update

March 2022

Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
BSC	best supportive care
CPS	combined positive score
DFS	disease-free survival
EMA	European Medicines Agency
HRU	healthcare resource utilisation
ICER	incremental cost-effectiveness ratio
Inc.	incremental
ITT	intention to treat
LY	life-year
NIVO	nivolumab
OS	overall survival
PAS	patient access scheme
PD-L1	programmed death-ligand 1
PSA	probability sensitivity analysis
QALY	quality-adjusted life-year
ToT	time on treatment

1 Summary of cost-effectiveness results

Note: all incremental cost effectiveness ratios (ICERs) presented below apply the patient access scheme (PAS) for nivolumab of [redacted].

During the technical engagement stage of the NICE process changes were applied to the cost-effectiveness model, these are summarised in Table 1 along with the associated ICER. Post-technical engagement, and as noted in the covering letter, there has been a change in relation to the licensed indication population where the wording of the licence is reflective of patients with tumour cell PD-L1 ≥ expression level 1%, henceforth referred to as the PD-L1 ≥ 1% population. Hence, Table 1 also summarises the subsequent changes to the economic model to provide results which are reflective of the expected licenced indication (i.e. the PD-L1 ≥ 1% population), along with the corresponding ICER.

Table 1. Summary of changes to cost-effectiveness outcomes when updating model to reflect changes in the PD-L1 ≥ 1% population

Model change	Assumption	ICER (cost/QALY) after cumulative impact of model change
Changes in model applied at technical engagement (ITT population)		
-	Model based on ITT population – base case model as presented at technical engagement • Time on treatment: ITT population, KM data using updated DBL (11 month minimum follow-up) • DFS: ITT population, generalised F (11 month minimum follow-up) • PAS of [redacted]% • Ara and Brazier age-dependent utility values All other inputs unchanged from company submission	£27,030
Changes in model to reflect PD-L1 positive patients		
1	Model updated to reflect outcomes for PD-L1 ≥ 1% patients receiving nivolumab and BSC (changes to time on treatment and DFS) • Time on treatment: PD-L1 ≥ 1% population, KM data (11 month minimum follow-up) • DFS: PD-L1 ≥ 1% population, generalised gamma (11 month minimum follow-up)	£11,105
BSC: best supportive care; KM: Kaplan Meier; ITT: intention-to-treat; PD-L1: programmed death-ligand 1; QALY: quality-adjusted life-year		

1.1 Base-case and data updates

1.1.1 Context

Following technical engagement, the company model has been updated to reflect the European Medicines Agency (EMA) expected licensed indication population "*OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC*".

The key impact of the change to the PD-L1 ≥ 1% population is a change in DFS. For both the ITT and PD-L1 ≥ 1% populations of CheckMate 274 there is a separation of the curves at 3 months favouring nivolumab, however this separation, in favour of nivolumab over placebo, is greater in the PD-L1 ≥ 1% population and is maintained throughout the extrapolation period. Please see Appendix 1 for the respective Kaplan-Meier plots. The greater separation of the curves in the PD-L1 ≥ 1% population is reflected in the hazard ratios of the two populations, where the hazard ratio of 0.53 (95% CI 0.38, 0.75) for the PD-L1 ≥ 1% population is lower than that of the ITT population.[1]

We have seen from the original submission that DFS is the primary driver of the economic model. Therefore, given the relative efficacy demonstrated for nivolumab versus placebo in the PD-L1 ≥ 1% population, it is logical to anticipate a lower ICER for nivolumab versus BSC than in the original submission, and, due to the to the magnitude of separation of the Kaplan-Meier curves, an ICER that is robust and stable. This conclusion is borne out and reflected in the results of the cost-effectiveness modelling presented within this document, where nivolumab is highly cost effective, presenting a low base case ICER, which is robust when tested through extensive sensitivity and scenario analyses.

1.1.2 Updates to company base case

To capture the change to the licensed indication (i.e. to reflect the PD-L1 ≥ 1% population), the economic model has been updated to incorporate the following updates to clinical effectiveness using data from the updated DBL (11 months minimum FU), summarised in Table 2.

Table 2. Updates to time on treatment and DFS

	Time on treatment	Disease-free survival
Nivolumab	Applied directly using CheckMate 274 data for PD-L1 ≥ 1% nivolumab arm	Generalised gamma, modelling of CheckMate 274 data for PD-L1 ≥ 1% nivolumab arm
BSC	Applied directly using CheckMate 274 data for PD-L1 ≥ 1% placebo arm	Generalised gamma, modelling of CheckMate 274 data for PD-L1 ≥ 1% placebo arm
Note: rationale and decision process for selection of independent modelling of generalised gamma are further described within the survival appendix.		

As noted above, the primary driver of the economic model is DFS and we have seen from sensitivity analysis previously presented by the company, and ERG critique, that other variables have limited, to no impact on the economic model and conclusions. In terms of the selection of the appropriate DFS functions to use in the economic modelling, a more detailed description of the DFS estimates and methodology used can be found within the addendum survival analysis appendix.

The time on treatment update has been applied directly based on the Kaplan Meier data from the trial so that treatment costs are reflective of the PD-L1 ≥ 1% population and the corresponding DFS data.

The remainder of the model and model assumptions remain unchanged from the analysis presented at technical engagement. The term 'base case' from herein describes the updated company base case aligning to these changes to a PD-L1 ≥ 1% population.

1.2 Base case results

1.2.1 Base-case incremental cost-effectiveness analysis results

Updates applied to the company base case are described in Section 1.1.2. Total discounted costs associated with nivolumab (with PAS), accrued over the modelled time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with BSC were [redacted]. Incremental discounted costs therefore were predicted to be [redacted] under base case assumptions. Total discounted quality-adjusted life-years (QALYs) experienced by patients receiving nivolumab were [redacted] compared to [redacted] QALYs experienced by patients receiving BSC. Incremental discounted QALYs were therefore predicted to be [redacted] QALYs. The resulting ICER estimate was £11,105 per QALY gained.

The results of the base-case analysis are summarised in Table 3 and Table 4.

Table 3. Deterministic analysis results (with PAS)

Outcome	Nivolumab	BSC (Routine surveillance)	Incremental
Costs (discounted)	[redacted]	[redacted]	[redacted]
Life Years (undiscounted)	[redacted]	[redacted]	[redacted]
QALYs (discounted)	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£11,105
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

Table 4. Base-case results, disaggregated

	Component	Nivolumab	BSC (Routine surveillance)	Incremental
Disaggregated costs (discounted)	Disease-free	[redacted]	[redacted]	[redacted]
	Disease-free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Treatment	[redacted]	[redacted]	[redacted]
	AEs	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)	Disease-free	[redacted]	[redacted]	[redacted]
	Disease-free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]
	AEs	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Clinical outcomes (years, undiscounted)	Median DFS	[redacted]	[redacted]	[redacted]
	Mean DFS	[redacted]	[redacted]	[redacted]
	Median OS	[redacted]	[redacted]	[redacted]
	Mean OS	[redacted]	[redacted]	[redacted]
Time in health state (years, undiscounted)	Disease-free	[redacted]	[redacted]	[redacted]
	Disease-free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]

AE: adverse event; BSC: best supportive care; DFS: disease-free survival; OS: overall survival; QALY: quality-adjusted life-year

1.3 Sensitivity analyses

Uncertainty around the input data has been assessed using probabilistic analyses (PSA), while alternative assumptions have been examined in scenario analyses. The impact of parameters on the model outcomes was assessed using deterministic sensitivity analyses by varying the data inputs by a set amount.

1.3.1 Probabilistic sensitivity analysis

In the PSA, for all inputs a non-parametric bootstrapping approach was taken, sampling values from distributions around the means of input parameters in the model. Sampling utilises information of the mean and standard error of parameters to derive an estimated value using an appropriate distribution (costs: gamma; age; utilities, probabilities and proportions: beta, survival; multivariate normal). These analyses were used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters.

Several inputs were derived from sources where it has not been possible to ascertain standard errors. To assess uncertainty surrounding these inputs, the standard error has been assumed to be 20% of the mean value for the purposes of the PSA.

In order to enable the model results to converge to a sufficient degree of accuracy, 1,000 simulations of the model were required.

1.3.1.1 PSA results

The ICER scatter plot for the base case analysis, arising from 1,000 simulations of the model with all parameters sampled is presented in Figure 1, while the cost-effectiveness acceptability curve is presented in Figure 2. The stochastic and deterministic mean estimates are presented in Figure 1 via the red (deterministic) and black (stochastic) points on the graph. Both estimates are very similar suggesting that the PSA has converged correctly. The cost effectiveness acceptability curve (shown in Figure 2) shows nivolumab to be cost effective 50% of the time with a willingness to pay threshold of [redacted]. In addition, based on the analysis presented in Figure 2, the probability that nivolumab is cost-effective versus BSC is estimated to be [redacted]% at a willingness-to-pay threshold of £30,000 per QALY.

Figure 1. ICER scatter plot: Nivolumab versus BSC

QALY: quality-adjusted life-year

Note: the large red dot represents the deterministic cost effectiveness estimate, while the large black dot shows the mean of the stochastic estimates from the PSA

Figure 2. Cost-effectiveness acceptability curve: Nivolumab versus BSC

BSC: best supportive care; NIVO: nivolumab; QALY: quality-adjusted life-year

The base case probabilistic results are presented in Table 5 below.

Table 5. Base case results (probabilistic): Nivolumab versus BSC

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,300
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.2 Deterministic sensitivity analysis

A range of one-way (deterministic) sensitivity analyses have been conducted, on various parameters (Table 6).

Table 6. Parameters varied within the deterministic sensitivity analysis

Parameter Name	Applicable Arm	Base Case	Variation		
		Value	Type	Lower Value	Upper Value
Time Horizon	Both	40	Absolute	30	50
Costs Discounting	Both	3.50%	Absolute	0.00%	6.00%
Benefits Discounting	Both	3.50%	Absolute	0.00%	6.00%
Life Tables	Both	-	Percent	0.8	1.2
Age-Dependent Utility Decrements	Both	-	Percent	0.8	1.2
Age	Both	[redacted]	Percent	0.8	1.2
Proportion Male	Both	[redacted]	Absolute	0	1
Recurrence to Death Transition	Both	-	Percent	0.8	1.2
Treatment Costs	Treatment	-	Percent	0.8	1.2
Treatment Costs	Control	-	Percent	0.8	1.2
Adverse Event Probabilities	Treatment	-	Percent	0.8	1.2
Adverse Event Probabilities	Control	-	Percent	0.8	1.2
Health State Costs	Both	-	Percent	0.8	1.2
Death Cost	Both	£7,970.55	Percent	0.8	1.2
Disease-free HRU reduction	Both	-	Percent	0.8	1.2
Adverse Event Costs	Both	-	Percent	0.8	1.2
Health State Utilities	Both	-	Percent	0.8	1.2

Adverse Event Utility Decrements	Both	-	Percent	0.8	1.2
Note: where (± 20%) is specified, the mean value is multiplied by 0.8 or 1.2 so to assess the impact of a 20% change in a value.					

Results of the deterministic sensitivity analysis are presented in Figure 3. The figure demonstrates the impact of specific parameters on ICER estimates. The factors with the greatest impact on the ICER were baseline age of patients, discounting, and treatment costs.

For all of the parameters varied in the one-way (deterministic) sensitivity analysis, the ICER for nivolumab versus BSC stayed below the £30,000 per QALY willingness-to-pay threshold. The scenario with the highest impact on the estimated ICER was age, which had an estimated ICER range of £[redacted] per QALY to £[redacted] per QALY, the upper bound of which was well below the £30,000 per QALY threshold.

[redacted]

Figure 3. Deterministic sensitivity analysis for nivolumab versus BSC: impact on ICER

HRU: healthcare resource utilisation

1.3.3 Scenario analysis

1.3.3.1 Atezolizumab as subsequent treatment

1.3.3.1.1 Post-recurrence survival

Atezolizumab has recently been approved by NICE for untreated PD-L1 positive (PD-L1 ≥ 5% combined positive score [CPS], corresponding to PD-L1 expression in tumour cells and immune cells) advanced urothelial cancer when cisplatin is unsuitable.[2] Therefore, atezolizumab is a relevant subsequent treatment for a proportion of patients in the BSC arm (which was informed by placebo data from CheckMate 274).

Clinicians advised the company that there are no clear guidelines around immunotherapy rechallenge in this setting.[3] It is unclear whether patients treated with an immunotherapy in the adjuvant setting would be retreated with an immunotherapy in subsequent lines. Atezolizumab is only approved for the first line treatment of locally advanced or metastatic urothelial cancer, and patients must not have received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies.[2,4] As nivolumab is an anti-PD-1 immunotherapy, patients who have received nivolumab as an adjuvant therapy may be considered previously treated. As such, it is assumed atezolizumab will only be applied as a subsequent treatment in the BSC arm.

As described within the original company submission, post-recurrence treatment within the economic model informs post-recurrence survival, and health state cost. A weighted average median overall survival (OS) is calculated based on the split between subsequent treatments and their individual median OS values. This weighted average (consolidated) median OS is used to estimate a static annual transition probability for recurrence to death. Where atezolizumab is incorporated as a subsequent treatment, the median OS of 18.6 months is used within this weighted average calculation, based on data reported from the IMvigor 130 trial.[2]

Within this scenario, a total of [redacted] of patients were estimated to receive atezolizumab as a subsequent treatment in the BSC arm, aligning to the proportion of PD-L1 ≥ 1% patients who were also PD-L1 ≥ 5% within CheckMate 274.[5] This is in keeping with the request made by the ERG, that 100% of the BSC cohort with PD-L1 ≥ 5% should receive atezolizumab as a subsequent treatment and therefore the analysis may be considered conservative. It should be noted that the IMvigor 130 trial measured PD-L1 status using CPS, whereas CheckMate 274 used PD-L1 expression in tumour cells (not immune cells), and there may not be alignment between these two measures. Nevertheless, [redacted] provides an upper estimate of the proportion of patients who could receive atezolizumab. The remaining [redacted] of patients were assumed to be split equally between cisplatin and carboplatin regimens.

Using this split of subsequent treatments, and associated median OS values, the corresponding annual probability of death post-recurrence was 0.2996, with a consolidated (weighted average) median OS of 16.85 months (Table 7).

Table 7. Probability of death post-recurrence, atezolizumab scenario [BSC arm only]

Treatment	Median OS (months)	% on regimen	Consolidated median OS (months)	Annual probability of death
Cisplatin regimens[6]	12.7	[redacted]	16.85	0.2996
Carboplatin regimens[7]	9.3	[redacted]		
Atezolizumab[2]	18.6	[redacted]		
Note: in the base case a 50:50 split is assumed between cisplatin and carboplatin regimens (i.e. cisplatin eligible and ineligible populations) OS: overall survival				

By contrast, in the base case where no patients for either the nivolumab or the BSC arm received atezolizumab as a subsequent therapy the annual probability of death was 0.4204, assuming a 50:50 split of patients going onto subsequent carboplatin or cisplatin regimens.

Figure 4 below plots the post-recurrence survival for base case analysis (i.e. 0% atezolizumab as a subsequent therapy in both the nivolumab and BSC arms) and in the scenario analysis (i.e. where [redacted] of patients receive atezolizumab as a subsequent therapy in the BSC arm only). The decrease in the annual probability of death with the introduction of atezolizumab post-

recurrence (i.e. a reduction in the probability of death to 0.2966) means post-recurrence survival is increased in the BSC arm within the scenario (Figure 4).

Figure 4. Post-recurrence survival with 0% and [redacted] of patients receiving atezolizumab as a subsequent treatment based on transition probabilities described (0% reflects base case approach for both arms, whereas [redacted] reflects this scenario and only impacts the BSC arm).

1.3.3.1.2 Post-recurrence treatment costs

As described above, it is unlikely that patients receiving an immunotherapy would be subsequently rechallenged with another immunotherapy (that is, patients receiving atezolizumab would likely only undergo one round of immunotherapy). This assumption was used within TA739,[2] where 0% of patients receiving atezolizumab went on to receive atezolizumab again as a subsequent therapy. Therefore, as a conservative assumption, atezolizumab acquisition and administration costs were calculated over the mean duration of atezolizumab treatment only (Table 8).

By contrast, cisplatin and carboplatin regimens can be given repeatedly. For patients receiving cisplatin and carboplatin as a subsequent treatment, treatment costs were applied for the remainder of patient life (as per the company base case).

Ultimately, a weekly cyclical cost post-recurrence in the BSC arm of £1,320.75 was calculated per patient for atezolizumab treatment (Table 8). Given [redacted] of patients in the BSC arm received atezolizumab, [redacted] received cisplatin regimens, and [redacted] received carboplatin regimens, an average weekly cost per patient of [redacted] was calculated per patient in the BSC arm (Table 9).

Table 8. Atezolizumab post-recurrence acquisition and administration treatment costs

	Value [List price]*	Source
Total acquisition cost atezolizumab	£71,114	TA739 (based on mean treatment duration of 12.9 months)[2]
Acquisition cost single dose atezolizumab	£3,807.69	TA739[2] [List price]
Total number of atezolizumab doses	18.68	Calculated, total acquisition cost divided by cost per dose
Administration cost single dose atezolizumab	£159	Intravenous infusion, NHS reference costs [as per original submission]
Total administration cost atezolizumab	£2,969.55	Calculated, total doses multiplied by single administration cost
Total acquisition and administration costs atezolizumab	£74,083.55	Calculated total administration plus total acquisition costs
Weekly cost (over time on treatment)	**£1,320.75**	Calculated, over 12.9 months (mean ToT from TA739)[2]
*Note: at list price, in practice a confidential PAS may be applied to this cost PAS: patient access scheme; ToT: time on treatment		

Table 9. Post-recurrence treatment costs in the BSC arm, scenario including atezolizumab at list price

	Year 1	Year 2+
Weekly HRU cost	**£106.68**	**£93.27**
Total Weekly cost cisplatin regimens	£176.58	£176.58
% Patients receiving cisplatin regimens*	[redacted]	[redacted]
Weekly cost cisplatin regimens	**£20.31**	**£20.31**
Total Weekly cost carboplatin regimens	£180.66	£180.66
% Patients receiving carboplatin regimens*	[redacted]	[redacted]
Weekly cost carboplatin regimens	**£20.78**	**£20.78**
Total Weekly cost atezolizumab regimens	£1,302.75	£1,302.75
% Patients receiving atezolizumab regimens*	[redacted]	[redacted]
Weekly cost atezolizumab regimens	**£1,016.98**	**£1,016.98**
TOTAL WEEKLY COST	[redacted]	[redacted]
Rate of survival•	0.356	0.644
WEEKLY COST APPLIED IN MODEL	[redacted]	
*2L+, all therapies: [redacted] cisplatin, [redacted] atezolizumab, [redacted] carboplatin •based on median OS for cisplatin of 12.7 months (Bellmunt et al.),[6] median OS for carboplatin of 9.3 months (De Santis et al.),[7] median OS for atezolizumab 18.6 months (TA739)[2] OS: overall survival		

Since, as previously described, atezolizumab is not a relevant subsequent treatment in the nivolumab arm (i.e. nivolumab patients are assumed to be ineligible for atezolizumab), subsequent treatment costs are applied as per the original company submission. Namely, assuming a 50:50 split between cisplatin and carboplatin regimens as subsequent treatments, with an annual probability of death post-recurrence of 0.4204. The treatment distributions and resulting post-recurrence treatment cost in the nivolumab arm are as per the original company submission (Table 10).

Table 10. Post-recurrence treatment costs for the nivolumab arm, scenario including atezolizumab at list price

	Year 1	Year 2+
Weekly HRU cost	**£106.68**	**£93.27**
Total Weekly cost cisplatin regimens	£176.58	£176.58
% Patients receiving cisplatin regimens*	50%	50%
Weekly cost cisplatin regimens	**£88.29**	**£88.29**
Total Weekly cost carboplatin regimens	£180.66	£180.66
% Patients receiving carboplatin regimens*	50%	50%
Weekly cost carboplatin regimens	**£90.33**	**£90.33**
TOTAL WEEKLY COST	£285.30	£271.89
Rate of survival•	0.545	0.454
WEEKLY COST APPLIED IN MODEL	**£279.21**	

*2L+, all therapies: 50% cisplatin, 50% carboplatin

•based on median OS for cisplatin of 12.7 months (Bellmunt et al.),[6] median OS for carboplatin of 9.3 months (De Santis et al.),[7]: overall annual probability of death post-recurrence of 0.4204

HRU: healthcare resource utilisation; OS: overall survival

1.3.3.1.3 Impact on cost-effectiveness results

Incorporating atezolizumab into the subsequent treatments of the BSC arm of the economic model results in a [redacted] increase in BSC total costs from [redacted] in the base case to [redacted] per patient, and an increase in BSC total QALYs from [redacted] in the base case to [redacted] (Table 11). This results in a decrease in the ICER from £11,105 per QALY in the base case to a situation where nivolumab dominates BSC. It should be noted that this is using the atezolizumab list price.

Table 11. Scenario results: atezolizumab as relevant subsequent treatment for a proportion of patients in the BSC arm, list price atezolizumab; nivolumab subsequent treatment as per original company submission.

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab dominates
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.2 Impact of different long-term disease-free timepoints

The base case analysis assumed that patients still in the disease-free state after 5 years would enter a long-term disease-free state to which only all-cause mortality would be applied. An exploratory scenario analysis was undertaken to evaluate sensitivity to the point at which this happened in the model.

Increasing the timepoint at which patients switch to the long-term disease-free state to 10 years resulted in a small increase to incremental costs ([redacted] vs [redacted] in the base case) and a small increase to incremental QALYs compared to the base case ([redacted] vs [redacted] in the base case). This led to a corresponding decrease in the ICER from £11,105/QALY in the base case to £10,841/QALY.

Table 12. Scenario analysis: impact of 10-year timepoint for long-term disease-free consideration

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,841
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

Decreasing the timepoint at which patients switch to the long-term disease-free state to 3 years resulted in a small decrease to incremental costs ([redacted] vs [redacted] in the base case) and a small decrease to incremental QALYs compared to the base case ([redacted] vs [redacted] in the base case). This led to a corresponding increase in the ICER from £11,105/QALY in the base case to £11,229/QALY (see Table 13).

Table 13. Scenario analysis: impact of 3-year timepoint for long-term disease-free consideration

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,229
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.3 Impact of altered baseline age

The base case analysis uses the baseline age from the ITT population in CheckMate 274. Within the technical engagement response form, the company concluded that although other sources may exist to inform the age of the patient population, the age from CheckMate 274 remains the most appropriate for the decision problem. The company explored an alternative baseline age scenario, using a median of [redacted] for the patients' age based on a weighted average between patients that received neoadjuvant chemotherapy and those who did not. Within this weighted average, the split between patients receiving and not receiving neoadjuvant chemotherapy was based on CheckMate 274 data and median age values were based John et al. estimates.[8] The impact of using this alternative baseline age has also been explored within the updated base case for PD-L1 ≥ 1% patients, and the results are presented below (Table 14).

Increasing the baseline age of patients resulted in a small increase to incremental costs ([redacted] vs [redacted] in the base case) and a decrease in incremental QALYs compared to the base case ([redacted] vs [redacted] in the base case). This led to a corresponding increase in the ICER from £11,105/QALY in the base case to £12,455/QALY.

Table 14. Scenario analysis: impact of alternative age

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,455
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.4 Impact of alternative survival curves using independent modelling

As described within the survival appendix, DFS for nivolumab and placebo is modelled independently, with the generalized gamma identified as the appropriate curve to use in the base case analysis (see Section 3.2 of survival appendix). Scenarios have been undertaken with each of the six independent distributions. It is noted that the exponential, Weibull, log-

logistic, and log-normal curves are a particularly poor fit to the trial data, as illustrated in the survival appendix Section 3.2.3.1, and are included for completeness but should not be considered for decision making in this appraisal.

The results show that nivolumab remains cost effective in all scenarios, even when including scenarios containing poor fits, indicating the ICER is not sensitive to parametric curve selection, with the ICER ranging from £10,944/QALY to £11,723/QALY (see Table 15).

Table 15. Estimated ICERs from independently modelled arms across the standard 6 parametric distributions

Technologies or Parametric distribution	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Generalised Gamma (Base case)							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,105
Gompertz							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,723
Weibull (provided for illustration only)							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,147
Exponential (provided for illustration only)							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,525
Log-logistic (provided for illustration only)							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,958
Log-normal (provided for illustration only)							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,944
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.5 Impact of alternative survival curves using PH modelling

A scenario analysis is presented using PH modelling and the Gompertz function. Exponential and Weibull models were not considered in the cost-effectiveness modelling as they as they were considered especially poor fits to the trial data, for more detail see Section 3.2.3.2 of Survival report. Results are shown in Table 16 for the proportional hazards Gompertz model, showing a small decrease in the ICER to £10,481 compared to £11,105 in base case, suggesting the ICER is not sensitive to the choice of survival analysis method.

Table 16. Estimated ICERs using proportional hazard modelling approach

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Gompertz							
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	=
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,481
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.6 Altered recurrence to death transition

As explained in the original resubmission (See section B.3.3.2.1.5), due to limited available data, the transition from recurrence to death is informed by recurrence data from Bellmunt et al. and De Santis et al. [6,7]. These studies report post-recurrence survival in patients post-cystectomy after treatment with cisplatin (12.7 months median OS), and carboplatin (9.3 months median OS), respectively. In the model, the midpoint of these values is taken, based on an assumption that 50% of patients receive cisplatin, and the other 50% receive carboplatin. A conservative assumption was made to estimate a single static transition probability (equal to 0.4204 a year) for recurrence to death using a rate based on the median OS. The sensitivity of the model to this probability was established through scenario analyses where median survival was doubled (Table 17) and halved (Table 18). The impact on the ICER was small, with the former decreasing the ICER by £[redacted] and the latter increasing the ICER by £[redacted], indicating that the ICER is not sensitive to this parameter despite substantial changes in post re-occurrence survival in this scenario (doubling and halving).

Table 17. Impact of altered recurrence to death (doubled survival post-recurrence)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	=
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,976
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

Table 18. Impact of altered recurrence to death (halved survival post-recurrence)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,614
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.7 Altered death upon recurrence probability

An alternative scenario suggested by the ERG during technical engagement critiqued the company's use of a probability of death upon recurrence pooled across both arms and determined through linear regression, due to the immaturity of this evidence and low number of death events. The ERG preferred approach uses treatment-specific raw numbers of events to predict death upon recurrence. This alternative approach was evaluated in a scenario (noting that both the base case and scenario used data from the ITT population). Amending this probability of death upon recurrence resulted in a small decrease to incremental costs (£[redacted] vs £[redacted] in the base case) and incremental QALYs compared to the base case ([redacted] vs [redacted] in the base case). This led to a corresponding decrease in the ICER from £11,105 per QALY in the base case to £11,053 per QALY (Table 19). The small magnitude of the difference indicates the economic model is not sensitive to this parameter.

Table 19. Impact of altered probability of death upon recurrence

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,053
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.8 Stratification by recurrence type

The base case of the economic model does not assess the type of recurrence, i.e. local/distant and urothelial/non-urothelial recurrences are all grouped together within the 'recurrence' health state, assuming all recurrences are subject to pharmacological (chemotherapy) treatment only. A scenario analysis was undertaken to separate local urothelial recurrence (which may be treated using surgical resection) from other recurrences (non-urothelial or distant recurrence), which are treated pharmacologically. This scenario impacts both mortality and health state costs for local recurrence. Distant recurrence was assumed to have the same cost and mortality as the combined 'total recurrence' state in the base case. The results (Table 20) show that nivolumab remains cost effective, with a moderate increase in the ICER by £254 (to £11,359 per QALY).

Table 20. Estimated ICER when including stratification by distant recurrence

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,359
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.3.3.9 Impact of increased cisplatin-based chemotherapy post-recurrence

The base case analysis assumed that post-recurrence, half of patients receive cisplatin-based chemotherapy regimens, and half receive carboplatin-based chemotherapy regimens. A scenario analysis was undertaken to evaluate sensitivity to this simplifying assumption, by increasing the proportion of patients on cisplatin-based chemotherapy regimens post-recurrence to a total of 65%. This had implications on both post-recurrence survival and post-recurrence health state costs.

Increasing the proportion of patients on cisplatin-based regimes post-recurrence resulted in a small decrease to incremental costs and QALYs compared to the base case ([redacted] vs [redacted] in the base case, and [redacted] vs [redacted] in the base case). This led to a corresponding decrease in the ICER from £11,105 per QALY in the base case to £11,080 per QALY (Table 21).

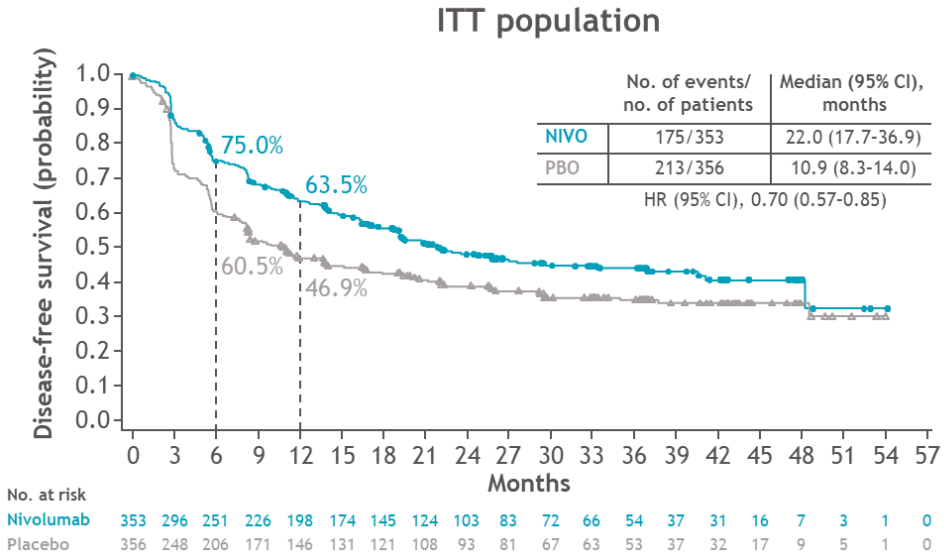
Table 21. Impact of increased Cisplatin-based chemotherapy post-recurrence

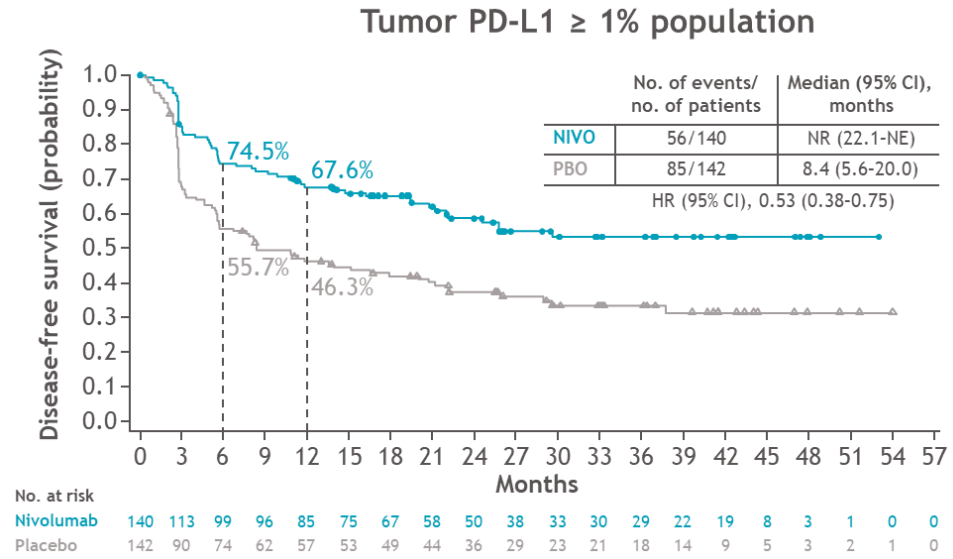
Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,080
ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs: quality-adjusted life years.							

1.4 References

1. Galsky MD, Witjes JA, Gschwend JE, et al. Disease-free survival with longer follow-up from the Phase 3 CheckMate 274 trial of adjuvant nivolumab in patients who underwent surgery for high-risk muscle-invasive urothelial carcinoma. 2021. Available at: https://suo-abstracts.secure-platform.com/a/gallery/rounds/12/details/1592 [Accessed 9 December 2021].
2. National Institute for Health and Care Excellence. Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable. Technology appraisal guidance [TA739] Committee papers. 2021. Available at: https://www.nice.org.uk/guidance/ta739/evidence [Accessed 21 December 2021].
3. Bristol Myers Squibb. Clinician insights [Personal Communication] 2022.
4. NHS England. National Cancer Drugs Fund List: ver1.206, 03-Mar-22 2022. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.206.pdf [Accessed 17 March 2022].
5. Bristol Myers Squibb. Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2020.
6. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-13.
7. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30(2):191-9.
8. John JB, Varughese MA, Cooper N, et al. Treatment Allocation and Survival in Patients Diagnosed with Nonmetastatic Muscle-invasive Bladder Cancer: An Analysis of a National Patient Cohort in England. European urology focus. 2020.

1.5 Appendix 1





CheckMate 274: Disease-free survival Kaplan-Meier plots (updated database lock, 11 months minimum follow up) for the ITT population (top) and PD-L1 ≥ 1% population (bottom)

Source: Galsky 2021[1]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for treating resected high-risk invasive urothelial cancer

ID2694

Appendix 2: Indirect treatment comparison report

CheckMate 274 trial subgroups and treatment comparators

In addition to surveillance, for which direct head-to-head data are available from CheckMate 274 (placebo controlled), a secondary comparison in patients who are eligible to receive cisplatin-based chemotherapy was requested by NICE for nivolumab vs. adjuvant chemotherapy in patients with a PD-L1 tumour expression >=1%.

The CheckMate 274 (N=709) trial assessed patients who were ineligible for (due to prior neoadjuvant cisplatin-based therapy or clinically defined ineligibility criteria) or actively refusing cisplatin-based adjuvant chemotherapy. Whilst the proportion of patients who refused chemotherapy (N=[redacted]; n=[redacted] who received nivolumab; n=[redacted] who received placebo) may be clinically equivalent to those who may actually receive cisplatin-based adjuvant therapy in a clinical setting, these patients would not have received cisplatin-based chemotherapy in the clinical setting due to their active refusal. For patients with a PD-L1 tumour expression >=1% in this population, n=[redacted] received nivolumab, while n=[redacted] received placebo.

Based on prior treatment and status of cisplatin-eligibility, the CheckMate 274 study population can be divided into three different patient subpopulations, as detailed in Table 1.

A. Patients who received neo-adjuvant cisplatin chemotherapy before undergoing radical resection (defined in this document as group A)
B. Patients who did not receive neo-adjuvant therapy and were not eligible for adjuvant cisplatin chemotherapy (group B)
C. Patients who did not receive neo-adjuvant therapy and were eligible, but actively refused, adjuvant cisplatin chemotherapy (group C)

Table 1: Breakdown of the CheckMate 274 study population and relevant treatment comparators

Patient group			CM-274 population	Relevant comparator
Neoadjuvant CT		A	X	Surveillance
No neoadjuvant CT	Cis-ineligible	B	X	Surveillance
	Cis-eligible, refused CT	C	X	Surveillance*
	Cis eligible, received CT	-	∅	Adj. chemotherapy

CT, cisplatin-based chemotherapy; X = included; ∅ = not included
*Though patients who refuse adjuvant CT would be eligible, their refusal would remove chemotherapy from being a relevant comparator. However, if ignoring their active refusal, adjuvant CT may be considered a treatment option on an exploratory basis.

Patients in groups A and B could not receive cisplatin in the adjuvant setting because they had received cisplatin already or were cisplatin-ineligible. Therefore, only patient group C, on a clinical eligibility basis, may be considered to be relevant for an ITC with cisplatin-based

adjuvant therapy. It is worth noting that CheckMate 274 was not stratified by eligibility for cisplatin and the study was not powered for any efficacy analyses within only this subgroup (group C).

Identification of relevant studies

A SLR was performed to identify relevant studies for potential inclusion in the ITC for comparison with group C. The SLR methods used to identify trials for potential inclusion in the ITC are described in Section B.2.1. Based on the studies identified in the SLR, an evidence network of interlinked RCTs was identified, allowing for the conduct of an ITC.

As previously described, only group C in the CheckMate 274 trial was clinically eligible for cisplatin-based adjuvant therapy and therefore was exclusively selected for the ITC. Study selection for the ITC was based on real-world evidence (BMS data on file), the NCCN clinical guideline[1] and clinical experts' opinion (virtual ad-board August 2020; virtual ad-board February 2021; BMS data on file). Studies with patients who only have upper tract disease (UTUC) were excluded from the ITC as treatment effect is expected to differ for UTUC compared to bladder urothelial carcinoma trials since there are differences in biology and surgical approaches, where neoadjuvant therapy is uncommon in UTUC and recovery time from surgery is generally shorter (virtual ad-board August 2020).[2] As this approach was taken in the base case, comparator trials were selected excluding patients only having upper tract disease. For the CheckMate 274 trial in this sensitivity analysis, patients were selected based on PD-L1 tumour expression instead of UTUC exclusion. Patients without a PD-L1 tumour expression >=1% were excluded, It was noted per UK clinical expert opinion that MVAC (methotrexate, vinblastine, doxorubicin and cisplatin or methotrexate, vinblastine, pirubicin and cisplatin) is rarely used in UK clinical practice anymore, based on a randomised trial that compared GC versus MVAC and showed similar effect of the two regimens but less haematological side effects for GC (sepsis, neutropenia).[3] Since MVAC was shown to be more toxic in this study, UK practice has gone for the more tolerable regimen of GC (virtual ad-board February 2021). Therefore, MVAC was considered irrelevant and excluded from the ITC to remain relevant to UK clinical practice within this decision problem. Gemcitabine plus cisplatin (GC) was the comparator of interest as this is the main option used in UK clinical practice as an adjuvant therapy.

In total, 4 RCTs provided the evidence base used in the ITC (Table 2), forming the network of evidence for DFS. Excluded studies are summarised in Table 3.

Table 2: The list of studies included in the ITC for group C

#	Study	Intervention	Comparator	Treatment of interest
1	*CheckMate 274 trial*	*Nivolumab, Placebo*	*Placebo*	*Nivolumab monotherapy*
2	Cognetti 2012[4]	Gemcitabine + Cisplatin (GC)	Treatment (GC) on relapse	GC
3	Sternberg 2015[5]	Cisplatin based chemotherapy (Methotrexate + Vinblastine + Doxorubicin + Cisplatin [MVAC], High dose-MVAC, or Gemcitabine + Cisplatin)	Deferred chemotherapy	GC
4	Zhegalik 2020[6]	Gemcitabine + Cisplatin	Treatment on relapse	GC

Both Cognetti[4] and Zhegalik[6] studies investigated GC only, whereas Sternberg[5] included MVAC, high dose-MVAC and GC as shown in the study flowchart in Figure 1. Of those in the immediate chemotherapy arm who received treatment, 84% received GC, 15% received HD-MVAC and 1% MVAC. Due to the majority of patients in Sternberg 2015[5] received GC and to increase the statistical power of the ITC analysis, it was decided to pool Sternberg 2015[5] with the two GC studies, recognizing that this is a limitation of the available evidence identified from the SLR.

Figure 1: Sternberg study flowchart[5]

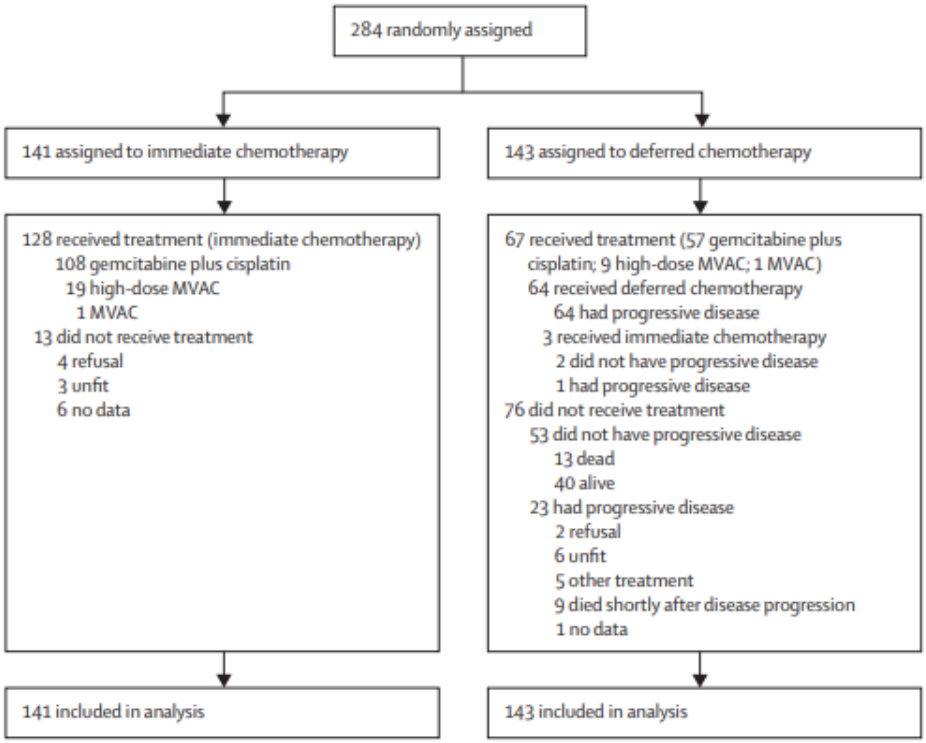


Table 3: The list of studies excluded from the ITC for group C

#	Study	Treatment	Treatment of interest for UK decision problem (GC)?	UTUC only?	Reason for exclusion
5	Bono 1997[7]	Cisplatin + Methotrexate	No	No	Treatment
6	Birtle 2020[8]	Gemcitabine–platinum combination	Yes	Yes	UTUC
7	Chihara 2009[9]	Cyclophosphamide + Doxorubicin + Cisplatin	No	Yes	Treatment, UTUC
8	Freiha 1996[10]	Cisplatin + Methotrexate + Vinblastine	No	No	Treatment
9	Lehman 2005[11]	"Cisplatin + Methotrexate, Methotrexate + Vinblastine + Epirubicin + Cisplatin"	No	No	Treatment
10	Lehmann 2006[12]	Methotrexate + Vinblastine + Doxorubicin + Cisplatin or Methotrexate + Vinblastine + Epirubicin + Cisplatin	No	No	Treatment
11	Luo 2019[13]	Gemcitabine+Cisplatin	Yes	Yes	UTUC
12	Otto 2001[14]	Methotrexate + Vinblastine + Epirubicin + Cisplatin	No	No	Treatment
13	Paz-Ares 2010[15]	Paclitaxel + Cisplatin + Gemcitabine	No	No	Treatment
14	Skinner 1991[16]	Cisplatin based (mostly CAP: Cyclophosphamide + Doxorubicin + Cisplatin)	No	No	Treatment
15	Stadler 2011[17]	Methotrexate + Vinblastine + Doxorubicin + Cisplatin	No	No	Treatment

Heterogeneity assessment

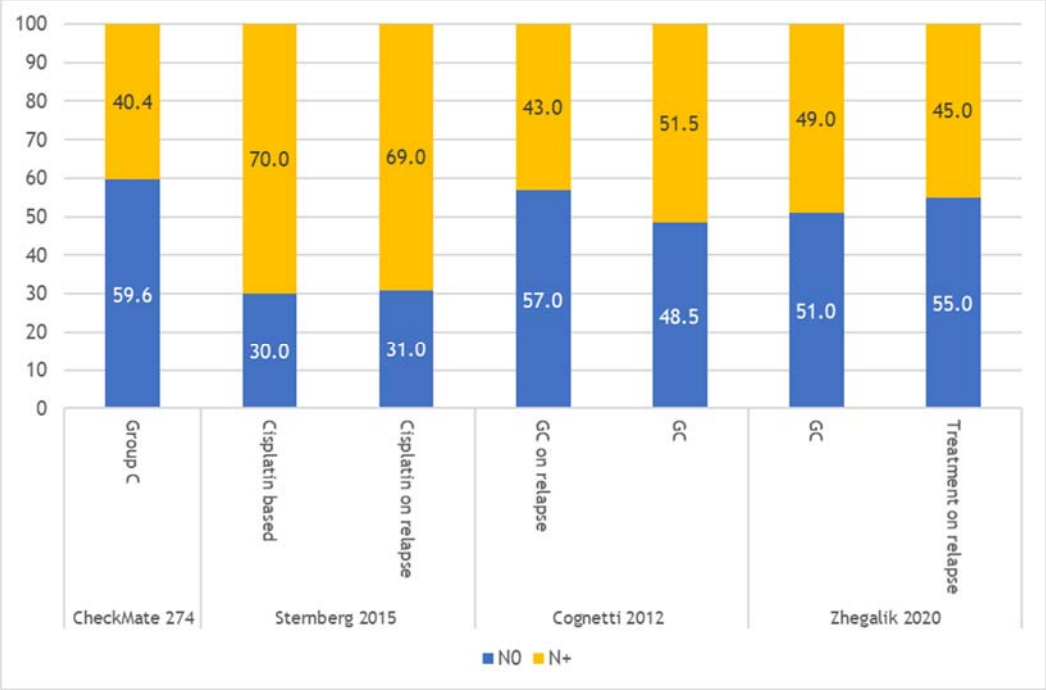
A heterogeneity assessment (HA) was undertaken to evaluate whether the assumption of homogeneity and similarity of the trials included in the network of evidence holds true to yield meaningful comparative evidence. The similarity of studies was assessed by comparing the studies according to the PICOS (population, intervention, comparator, outcome, study design) framework, focusing on variables that could impact relative treatment effects. Note that the heterogeneity assessment included all group C CheckMate 214 patients rather than the PD-L1 tumour expression 1>=% patients only.

Population

Tumour location was reported in all included trials. No major heterogeneity was observed for the tumour location except for the CheckMate 274 group C, which included [redacted] of patients with UTUC.

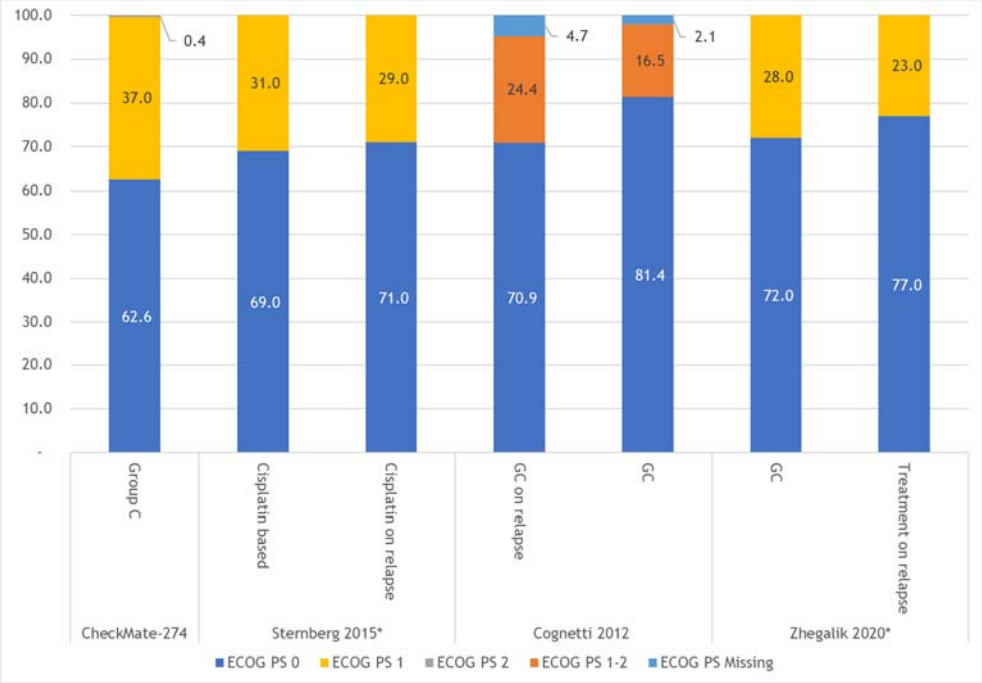
Tumour stage and the number of nodes at baseline according to the TNM classification were reported in all included studies. However, different cut-off points were used for classification due to changes in clinical documentation over time when these studies were conducted. In order to leverage the studies for analysis, re-categorisation was applied across the studies into two pooled categories: N+ category (categories N+, N1, N1-2, N2, N>=2, N2+, N2-5, N3, N5, N>5 pooled) and N0 category (N0/x with <10 nodes removed and N0 with ≥10 nodes removed pooled). Figure 2 shows variability across the included studies with regards to tumour stage.

Figure 2: Population characteristic: Tumour stage based on the number of nodes in % (after re-categorisation)



In terms of ECOG performance status, CheckMate 274 and Cognetti 2012[4] enrolled a slightly larger proportion of more severe patients compared to the other studies. Based on the reported data, it is unclear whether between study differences exist. Only Cognetti 2012[4] includes patients with ECOG PS 2, which may indicate a slightly more severe patient population in terms of ECOG and TNM versus other studies, which excluded ECOG PS 2 patients.

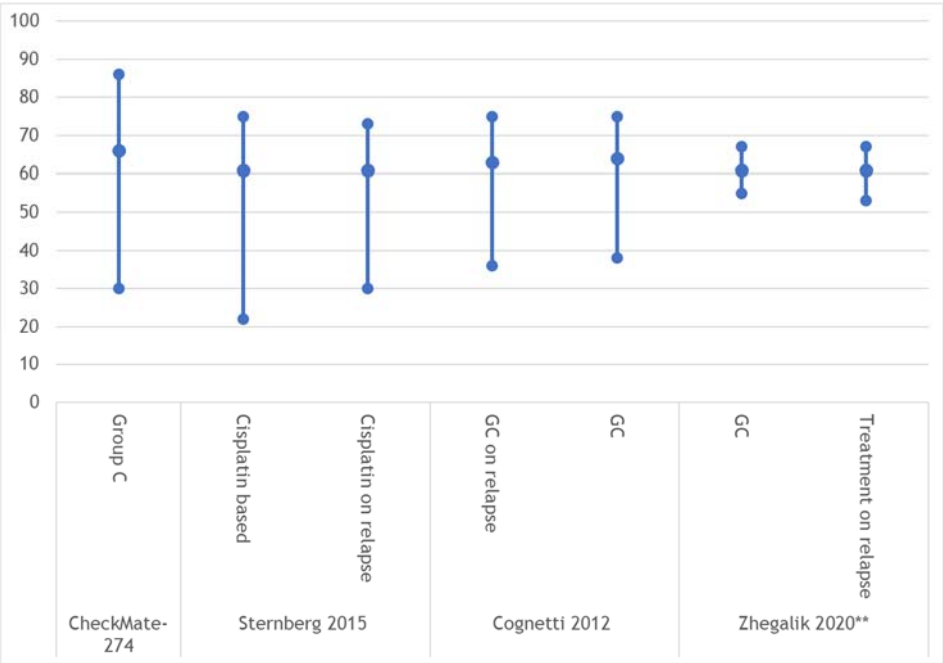
Figure 3: Population characteristic: The ECOG performance status at baseline in %



The percentage of male patients ranged from 78.7% to 92.8% and no major heterogeneity was observed for the sex ratio reported across the studies. The median age of patients was comparable across the studies. Patients in the included trials did not receive prior neo-adjuvant chemotherapy; patients in group C of CheckMate 274 were also not exposed to neo-adjuvant chemotherapy. Studies were thus comparable with regards to prior treatment.

Figure 4: Population characteristic: Median age (min, max) in years

*No minimum and maximum available; **Interquartile range



PD-L1 positive (>=1%)

In group C of CheckMate-274, there were [redacted] patients with a positive PD-L1>=1% status. Of these, [redacted] were treated with nivolumab, while [redacted] received placebo. In the current analysis, these patients were selected for inclusion in the NMA rather than the total group C population. Other studies did not report in the PD-L1+ status.

Intervention and comparators

Variability was identified amongst the control arms of the included RCTs. Studies reported placebo, observation, or different chemotherapy treatments at relapse as control arms; there was no single control arm. The feasibility assessment indicated that assumptions about the common comparator are therefore needed to establish an interlinked network of randomized trials.

Outcomes

Efficacy outcomes and definitions of events differed across the studies. Sternberg 2015[5] and Zhegalik 2020[6] reported PFS, whilst CheckMate 274 and Cognetti 2012[4] reported DFS. The baseline was the randomization in all studies. The endpoints varied and included first local, locoregional or distant progression, death from any cause or UC cancer death. Patients in the Zhegalik 2020[6] study without an event were censored at their last visit.

Table 4: DFS definition across included studies

#	Article	DFS/ Progression-free survival (PFS)	Definition
1	CheckMate 274 trial	DFS	Time from randomization until death from any cause or is local recurrence, distant recurrence or death, whichever occurs first
2	Cognetti 2012[4]	DFS	Time from randomization to the earliest occurrence of recurrence or death from any cause
3	Sternberg 2015[5]	PFS	Time from randomization to first local, locoregional, or distant progression, or death from any cause. Patients without an event were censored at their last visit.
4	Zhegalik 2020[6]	PFS	Time from randomization to local or systemic relapse or bladder cancer death

Study design

Heterogeneity in the design of the included studies was assessed in terms of enrolment period, region, definition of efficacy population, blinding and follow-up time.

Differences in the enrolment period were present, however, the evidence did not allow to conclude whether this is a relative effect modifier. Patients for CheckMate 274 were enrolled between 2016 and 2019 while patients in Zhegalik 2020[6] were enrolled from 2008 to 2013.

Both Sternberg 2015[5] and Cognetti 2012[4] closed patient recruitment early due to poor accrual and enrolled patients between 2002-2008 and 2001-2007, respectively.

From the studies included in the ITC, single-centre studies were conducted in Belarus (Zhegalik 2020[6]) and Italy (Cognetti 2012[4]). One study took place in 12 European countries and Canada (Sternberg 2015[5]) and the Checkmate 274 was a multi-regional trial conducted in 30 countries.

The definition of efficacy population across different studies is displayed in Table 5. All included studies reported the Intention-To-Treat (ITT) size that ranged from 100 to 709 patients, but the population analysed differed across the trials. Conducting an ITT analysis preserves randomization and it was reported in two studies. For Cognetti 2012[4], no clear description of ITT or PP was provided. Cognetti 2012[4] conducted the analyses on the patient set after excluding 11 patients that were lost after randomization, resulting in a total number of 86 (control arm) and 97 (chemotherapy arm) patients included in the final analysis. Notably, excluding patients after randomization will influence efficacy results. However, due to the low sample size identified across all the studies, all effects should be regarded with caution.

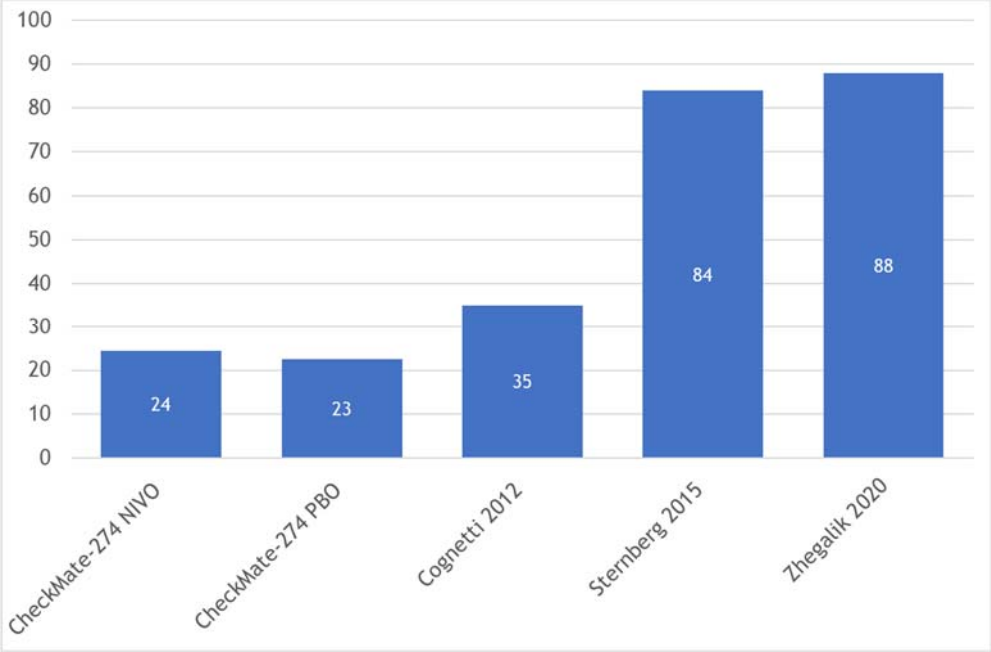
Table 5: Definition of efficacy and safety population

#	Study	Design	ITT	Population analyzed
1	CheckMate 274 trial	Randomised, double-blinded, multicentre, multi-regional (30 countries)	709	Group C: n=[redacted]
2	Cognetti 2012[4]	Randomised, open-label, multicenter	194	183[†]
3	Sternberg 2015[5]	Randomised, open-label, multi-regional, multi-centre	284	ITT
4	Zhegalik 2020[6]	Randomised, open-label, single-center	100	ITT

[†]Cognetti 2012[4]: "194 patients were entered on to the trial, 92 in the control arm and 102 in the chemotherapy arm. Eleven patients, six in arm A and five in arm B, were lost after randomization and were not considered assessable for final analysis."

Of the included studies, only one (CheckMate 274) was double-blinded. Blinding was not reported in the other studies; therefore, these studies were assumed to be open label given the control arm (e.g., no placebo or treatment at recurrence). The lack of reporting concerning the clinical design of the trials limits further assessment of heterogeneity. All four studies reported the median follow-up time that ranged from 23 to 88 months (Figure 5).

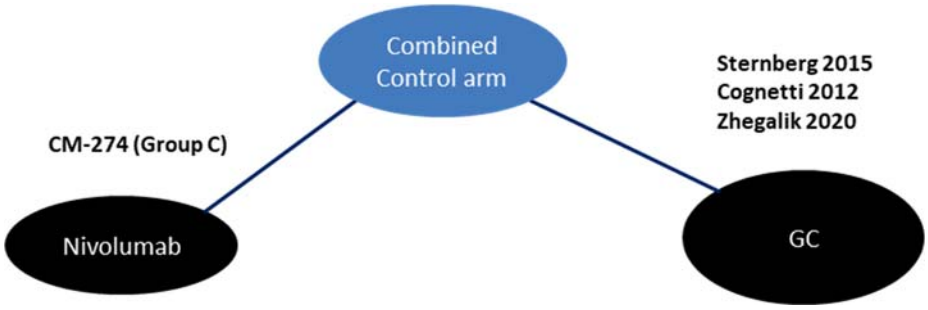
Figure 5: Median study follow-up time (months)



Methods

The final evidence network utilised for the ITC of DFS is presented in Figure 6. As previously explained, the majority of patients (84% in the immediate chemotherapy arm) in Sternberg 2015[5] received GC and therefore the study was pooled with the other two GC studies of Cognetti 2012[4] and Zhegalik 2020[6] to increase the statistical power of the ITC.

Figure 6: Evidence network for ITC



Combined control arm includes placebo, deferred chemotherapy and treatment (GC) on relapse

The ITC was conducted based on log-HRs and corresponding standard errors (SE). Hazard ratios and CIs were transformed to log hazards using the methods by Higgins et al.[18] The HR for DFS of group C (selecting PD-L1>=1% positive patients) in CheckMate 274 was estimated by fitting a Cox regression on the patient-level data. Further, the logHR was adjusted for the stratification factors.

Further data transformation employed a generalized linear model to analyse treatment differences, the approach proposed by The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 2.[19] It uses an identity link and treats log HR as a normally distributed continuous variable. See program 7 in

Dias et al.[19] for the details of the statistical model and programming codes. The following part describes the transformation of the observed data in Table 4 to an appropriate format for conducting an ITC.

Hazard ratios take a value on the range zero to positive infinity $(0, \infty)$ and are not normally distributed, which violates the assumption of program 7, Dias et al. [20]. To mitigate this violation the natural logarithm transformation was applied to the HRs.

To calculate the standard error, the natural logarithm was first applied to the CI of the HRs, and then a formula to transform CI to standard error was applied (see Higgins et al.[18] for further details): $se = (CI_{right} - CI_{left})/3.92$. This formula assumes that the transformed variable is normally distributed.

An overview of the input data for the ITC and the transformations per study for DFS are presented in Table 6.

Table 6. Efficacy data of all relevant studies included for the base case ITC of DFS and OS

#	Study	Treatment of interest	Comparator	DFS HR (95%CI)
1	CheckMate 274 trial	Nivolumab	Placebo	[redacted]
2	Cognetti 2012[4]	GC	Treatment (GC) on relapse	1.08 (0.73-1.59)
3	Sternberg 2015[5]	GC/HD-MVAC	Deferred chemotherapy	0.54 (0.40-0.74)
4	Zhegalik 2020[6]	GC	Treatment on relapse	0.77 (0.46-1.27)

In the Monte Carlo simulation, three simulation chains were used with 100,000 iterations, 50,000 burn-in and 1 thinning in the Monte Carlo simulations. The Gelman-Rubin statistics, the size of the Monte Carlo error, auto-correlation function, trace plots and Kernel density plots were examined to assess the convergence.

Proportional hazards assumption

Most ITCs for survival outcomes use a linear model fitted on log-HRs. An assumption for this model is the proportional hazards (PH) assumption, where the HR between any two treatments is assumed to be constant over time. Therefore, the PH assumption was tested for the CheckMate 274 group C population (with PD-L1 tumour expression >=1%), using the steps specified in Table 7.

Table 7. Methods to test PH assumption

Analysis steps	Method
Fit Cox regression model	*survival* package R
Plot log(cumulative hazard) vs log(time)	Visual inspection crossing treatment groups
Plot Schoenfeld residuals vs time	Visual inspection of slopes
Analysis of Schoenfeld hazard residuals (non-zero slope)	Grambsch and Therneau test (p-value < 0.05)

AIC

The Grambsch and Therneau test indicated no violation of the PH assumption (p-value test statistic: 0.1101 in group C [with PD-L1 tumour expression >=1%]). However, the log cumulative hazard plots show crossing of the two curves in the tails, indicating a violated PH assumption (Figure 7).

Figure 7: Cumulative hazard plot for DFS from group C (with PD-L1 tumour expression >=1%) in CheckMate 274

Figure 8: Log-cumulative hazard plot for DFS from group C (with PD-L1 tumour expression >=1%) in CheckMate 274

Figure 9. Schoenfeld residuals plot (DFS from group C [with PD-L1 tumour expression >=1%] in CheckMate 274)

As previously mentioned, there are a number of limitations in the evidence base for the included studies, with added heterogeneity in a number of important variables are previously summarised. In addition, the sample size of this comparison is very limited, adding further uncertainty to any form of ITC. Due to these limitations, a time-varying hazard approach, which would be preferred per NICE TSD 2[19] considering the potential PH assumption violation detailed above, was deemed unreliable due to the high uncertainty such an approach would introduce to a limited, heterogeneous evidence base. Therefore, recognising these limitations, and that of the PH assumption being violated, single HRs were derived. BMS wish to emphasize that any such comparison with group C and only PD-L1 tumour expression >=1% patients is uncertain and lacks robustness therefore, any results of such comparison should be interpreted with a high degree of caution and should only be considered on an exploratory basis.

Results

As the random effects model did not converge due to the small amount of data available for the analysis, only the fixed effect models are presented here.

The HR of nivolumab versus placebo from group C (with PD-L1 tumour expression >=1%) was [redacted]. It should be noted that CheckMate 274 was neither stratified nor powered for this subgroup and further, UTUC patients were removed leading to even further segmenting of the trial data, and therefore these results should be interpreted with caution.

The HR of nivolumab from group C (with PD-L1 tumour expression >=1%) versus adjuvant chemotherapy from the two GC studies and Sternberg pooled was [redacted].

Discussion

As previously highlighted, there are significant limitations with any ITC comparing CheckMate 274 with adjuvant chemotherapy. A number of key differences exist between included studies and the limitations impact the ability to reliably inform HTA decision making for this treatment comparison. CheckMate 274 demonstrated an efficacy benefit for nivolumab monotherapy versus placebo in the full efficacy population; the study was neither stratified nor powered for subgroup analyses based on cisplatin eligibility (group C). In addition, considering patients actively refused cisplatin-based chemotherapy, they would not have received chemotherapy in clinical practice and instead would undergo observation. Therefore, any results of a comparison of nivolumab monotherapy with adjuvant chemotherapy are exploratory in nature and should be interpreted with a high degree of caution.

In the current analysis, only group C patients with a PD-L1 tumour expression >=1% were included This decreased the pooled group C sample size from [redacted] to [redacted] patients across the nivolumab (n=[redacted]) and placebo (n=[redacted]) arms, significantly reducing the ability to draw any conclusions from the results versus GC.

In addition to the limitations highlighted above for the chemotherapy evidence base for inclusion in this ITC, the latest guidelines from the European Association of Urology (EAU) on muscle invasive and metastatic bladder cancer explicitly state that *“adjuvant chemotherapy*

after radical cystectomy for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate."[21]

The EAU guidelines further state: *"There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy*[22,4,23-27]*. An individual patient data meta-analysis*[23] *of survival data from six RCTs of adjuvant chemotherapy*[28, 10,29-31] *included 491 patients (unpublished data from Otto et al., were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases).*[22] *In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and Adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [485], and one trial used cisplatin monotherapy.*[30] *The data were not convincing to give an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies*[32,15,17] *resulting in the inclusion of 945 patients from nine trials.*[24] *None of the trials had fully accrued and individual patient data were not used in the analysis.*[24]*"*[21]

Therefore, in conclusion, an ITC for nivolumab versus cisplatin-based adjuvant therapy is subject to major uncertainty, lacks robustness, is exploratory in nature and is insufficient to be used to inform HTA decision making.

References

1. National Comprehensive Cancer Network. NCCN Guidelines - Bladder Cancer, Version 2.2021. 2021. Available at: [Accessed 16/04/2021].
2. Bristol Myers Squibb. Advisory board: Nivolumab for post-resection adjuvant treatment of high-risk muscle invasive urothelial cancer. 2021.
3. von der Maase H, Hansen SW, Roberts JT, 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(17):3068-77.
4. Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol. 2012;23(3):695-700.
5. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. The Lancet Oncology. 2015;16(1):76-86.
6. Zhegalik AG, Polyakov SL, Rolevich AI, et al. Long-term results of a single-center prospective randomized trial assessing efficacy of a shortened course of adjuvant chemotherapy after radical cystectomy in patients with locally advanced bladder cancer. Cent European J Urol. 2020;73(1):26-32.
7. Bono A, Lovisolo, J., & Vio, P. Short-term prophylaxis with pefloxacin in transurethral surgery. Acta Urologica Italica. 1997;11.
8. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet. 2020;395(10232):1268-77.
9. Chihara Y, Fujimoto K, Miyake M, et al. Adjuvant chemotherapy with cisplatin/cyclophosphamide/doxorubicin for patients with urothelial carcinoma of the upper urinary tract. Journal of Nara Medical Association. 2009;60.
10. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol. 1996;155(2):495-9; discussion 9-500.
11. Lehmann J, Retz M, Wiemers C, et al. Adjuvant Cisplatin Plus Methotrexate Versus Methotrexate, Vinblastine, Epirubicin, and Cisplatin in Locally Advanced Bladder Cancer: Results of a Randomized, Multicenter, Phase III Trial (AUO-AB 05/95). Journal of Clinical Oncology. 2005;23(22):4963-74.
12. Lehmann J, Franzaring L, Thüroff J, et al. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int. 2006;97(1):42-7.
13. Luo Y, Feng B, Wei D, et al. Prospective controlled observation ofeffect of adjuvant chemotherapy onsurvival and prognosis ofhigh-risk upper tract urothelial carcinoma patients underwent radical nephroureterectomy. Zhonghua yi xue za zhi. 2019;99:3158-63.
14. Otto T, Börgemann, C., & Krege, S. . Adjuvant chemotherapy in locally advanced bladder cancer [pT3/pT4a,pN1-2,M0] - A phase III study. 2001;39.
15. Paz-Ares LG, Solsona E, Esteban E, et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: Results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. Journal of Clinical Oncology. 2010;28(18_suppl):LBA4518-LBA.

16. Skinner DG, Daniels JR, Russell CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol. 1991;145(3):459-64; discussion 64-7.
17. Stadler WM, Lerner SP, Groshen S, et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. J Clin Oncol. 2011;29(25):3443-9.
18. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, . www.training.cochrane.org/handbook2021.
19. Dias S, Welton NJ, Sutton AJ, et al. NICE Decision Support Unit Technical Support Documents. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London: National Institute for Health and Care Excellence (NICE)
20. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011.
21. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2021. ISBN 978-94-92671-13-4. Available at: [Accessed
22. Sylvester R, Sternberg C. The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: what we do not know and why. Ann Oncol. 2000;11(7):851-6.
23. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol. 2005;48(2):189-99; discussion 99-201.
24. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol. 2014;66(1):42-54.
25. Ellis MJ, Babiera G, Unzeitig GW, et al. ACOSOG Z1031: A randomized phase II trial comparing exemestane, letrozole, and anastrozole in postmenopausal women with clinical stage II/III estrogen receptor-positive breast cancer. Journal of Clinical Oncology. 2010;28(18_suppl):LBA513-LBA.
26. Fraser SE, Perkel DH. Competitive and positional cues in the patterning of nerve connections. J Neurobiol. 1990;21(1):51-72.
27. Thonar EJ, Glant T. Serum keratan sulfate--a marker of predisposition to polyarticular osteoarthritis. Clin Biochem. 1992;25(3):175-80.
28. Ramani VA, Maddineni SB, Grey BR, et al. Differential complication rates following radical cystectomy in the irradiated and nonirradiated pelvis. Eur Urol. 2010;57(6):1058-63.
29. Stöckle M, Meyenburg W, Wellek S, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J Urol. 1995;153(1):47-52.
30. Studer UE, Bacchi M, Biedermann C, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol. 1994;152(1):81-4.
31. Skinner DG, Daniels JR, Russell CA, et al. Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. Semin Urol. 1990;8(4):279-84.
32. Sosis M. Anesthesia for laser surgery. Int Anesthesiol Clin. 1990;28(2):119-31.

Confidential until published

Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal/ Addendum: ERG comments on company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Geoff Holmes, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	28th January 2022

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/39/77.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

1 Introduction

In January 2022, the company submitted its technical engagement (TE) response for the appraisal of nivolumab for treatment of resected high-risk invasive urothelial cancer.[1] The company's response was structured around the nine key issues raised within the Evidence Review Group (ERG) report. The company's TE response includes a written technical engagement response document, including appendices, together with updated version of the executable model.

This document provides a commentary on the company's TE response and should be read in conjunction with the ERG report.[2] Section 2 provides a summary of the company's changes in the updated model and provides information relating to the new analyses of time-to-event data from CheckMate 274 based on a data cut-off 1st February 2021 which is later than in the original company submission (CS)[3]. Section 3 provides a detailed description of the company's TE response and the ERG's critique of these points. Section 4 presents the results of the company's updated base case and scenario analyses and additional analyses undertaken by the ERG. Overall conclusions are presented in Section 5.

All results presented in this document include the Patient Access Scheme (PAS) discount for nivolumab. Since the initial submission, the company has changed the discount within the PAS, which has increased from [redacted] to [redacted].

In order to aid reading this report, the key limitations in the company's updated base case are summarised in advance of the more detailed critique, along with the approaches undertaken by the ERG to provide incremental cost-effectiveness ratios (ICERs), expressed in terms of cost per quality-adjusted life year (QALY) gained, that attempt to address these limitations.

1.1 Key limitations within the company's updated base case

The company's updated base case assumes that based on goodness-of-fit statistics a generalised F distribution is the best model to estimate disease-free survival (DFS) and that at after 5 years residing in the disease-free state that a patient is cured. A distinction should be made between those patients who are deemed cured of their urothelial carcinoma (UC) episode, but who have a greater risk of death due to the clinical burden relating to the UC, and patients who have the same utility and risk of death as an age- and sex-matched population; this latter group have been denoted by the ERG as 'fully cured'.

The company's assumption that patients are fully cured at 5 years is at odds with the extrapolation of its chosen generalized F distribution which indicates that at 5 years the hazard of death is considerably higher in patients with resected high-risk UC than for an age- and sex-matched population. This incompatibility is further supported by data from a study, with similar patients, with longer follow-up[4]

and clinical opinion suggesting that relapse after 5 years is possible. In order to address this inconsistency, the ERG has explored three alternative assumptions.

1) Using the generalized F distribution preferred by the company, but assuming an increased risk of death, for an additional 5-year period in the disease-free state associated with the clinical burden of people with a history of resected high-risk UC and other evidence sources. After 10 years in the disease-free state the patient is assumed to be fully cured.
2) Using the Gompertz distribution to model DFS, noting that at 5 years the risk of death predicted by the Gompertz models is similar to that of an age- and sex-matched population and assuming that patients are fully cured at this time point. Note that in this exploratory analysis the model has been amended such that the risk of DFS cannot fall below mortality risk of an age- and sex-matched population.
3) Increasing the time in the disease-free state before which a patient is considered cured to 10 years and assuming that the patient is also fully cured at this timepoint and using the generalized F distribution preferred by the company. This exploratory analysis removes the impact of assumptions related to increased hazards of death.

All three of the ERG's exploratory analyses have limitations. The first and third apply arbitrary time points at which the increased risk of death or a DFS event is assumed to cease. The second has the same limitation as the company's base case in that the evidence does not support the assumed full cure at 5 years, but unlike the company's base case, it avoids an excess hazard of mortality which is instantly reduced at 5 years. The ERG notes that neither the company's base case nor any of its exploratory analyses are ideal in modelling longer-term risk of death or DFS but believes that consideration of the four methods will be informative to the NICE Appraisal Committee.

The company's base case has two further key limitations which the ERG could not address and produce a formal ICER. The first is that no ICER has been provided when a patient could be appropriately treated with cisplatin-based adjuvant chemotherapy, the second is that ICERs have not been presented based on different PD-L1 status of the resected tumour, with observed data from CheckMate 274 indicating that adjuvant nivolumab treatment may be relatively more efficacious in patients where the PD-L1 expression of the tumour was ≥1%. Because of these unaddressed limitations, the ERG highlights that the ICERs presented are indicative only.

1.2 Summary of differences in the company's updated base case and the ERG alternative scenarios

As a reference point, Table 1 summarises key characteristics of the company's updated base case and the three alternative scenarios run by the ERG.

Table 1: Summary of key characteristics of the company's updated base case, and three alternative scenarios run by the ERG.

Scenario	Distribution used to model DFS	Time point at which a cure of UC is assumed (years)	Time point when a patient is considered fully cured†	Is a utility decrement applied for disease-free patients compared with age- and sex-matched general population values?	Method for calculating the proportion of DFS events that are deaths
Company's updated base case	Generalised F	5	5	No	Pooled from a logistic regression
ERG Alternative Scenario 1	Generalised F	5	10	Yes	Treatment-specific
ERG Alternative Scenario 2	Gompertz	5	5	Yes	Treatment-specific
ERG Alternative Scenario 3	Generalised F	10	10	Yes	Treatment-specific

†At which point the risk of death and utility are assumed to be equal to the age- and sex-matched general population values
DFS – disease-free survival; ERG – Evidence Review Group; UC – urothelial cancer.

2 Summary of the company's response to technical engagement

The CS was submitted in August 2021; subsequently, further data relating to the pivotal study, CheckMate 274, have become available. The company's TE response presents additional clinical effectiveness evidence from an updated database lock (DBL) (data cut-off 1st February 2021), compared with a DBL of 27th August 2020, thus providing approximately an additional five months of follow-up and a minimum follow-up period of eleven months.

The company's original base case deterministic incremental cost-effectiveness ratio (ICER) in the CS, expressed in terms of cost per quality-adjusted life year (QALY) gained, was £32,932 when compared to best supportive care (BSC). The company's post-TE base case, which includes changes to the distributions used (either in functional form or parameter inputs) to estimate DFS, and death on recurrence based on the updated DBL, together with an updated PAS, is £27,030. Probabilistic results were not provided. Scenario analyses were presented by the company although not all are presented in this document for brevity.

Table 2 summarises the company's original base case model, the ERG's preferred analysis at the time of the ERG report and the company's updated base case model as presented in the TE response. A more detailed discussion of each issue including an ERG critique and, where appropriate, changes to the ERG base case is provided in Section 3, although a summary of the more mature data from CheckMate 274 is provided in Section 2.1.

Table 2: Summary of company's original base case (CS), ERG preferred analysis (ERG report) and company's updated base-case (TE response)

Aspect of model	Company's original base case	ERG preferred analysis	Company's updated base case model	Did the assumption change between the original and updated base case?
Amendments relating to key issues presented in ERG Report				
Issue 1: Exclusion of cisplatin-based adjuvant chemotherapy as a comparator	Cisplatin-based adjuvant chemotherapy was excluded from the decision problem	Cisplatin-based adjuvant chemotherapy to be included in the decision problem or recommendations only to apply to those in whom cisplatin-based treatment is not an option	Cisplatin-based adjuvant chemotherapy remains excluded from the decision problem	No
Issue 2: The use of semi-parametric models to fit to DFS Kaplan-Meier (KM) estimates	Use of the KM estimates and then Weibull distributions for both nivolumab and BSC	Use of the Gompertz distribution for both nivolumab and BSC	Use of the generalized F distribution for both nivolumab and BSC	Yes
Issue 3: Use of utility data from Janssen *et al*.[5]	Data sourced from Janssen *et al.*[5]	Data to be sourced from Ara and Brazier[6]	Data sourced from Ara and Brazier[6]	Yes
Issue 4: The average age of patients in the UK is likely to be older than those recruited to CheckMate 274	Company base case uses the mean age from CheckMate 274 ([redacted] years)	Not known, but clinical advice suggests that in English practice the mean patient age would be greater than that seen in CheckMate 274	Uses the mean age from CheckMate 274 ([redacted] years). An additional scenario analysis using a higher age ([redacted] years) is provided.	No
Issue 5: Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo	Assuming the same proportion ([redacted]) of DFS events are deaths in the nivolumab and the BSC arms.	Using treatment-specific values for each arm.	Assuming the same proportion ([redacted]) of DFS events are deaths in the nivolumab and the BSC arms. An additional scenario analysis was presented using arm-specific proportions.	No
Issue 6: Patients in the DFS health state have the same utility values as an age- and sex-matched population	That patients in the DFS state had the same utility values as an age- and sex-matched population	That a utility decrement be applied to the age- and sex-matched general population utility to consider the impacts of having had a resected UC	That patients in the DFS state have the same utility values as an age- and sex-matched population. An additional scenario analysis was	No

Aspect of model	Company's original base case	ERG preferred analysis	Company's updated base case model	Did the assumption change between the original and updated base case?
			presented using a utility decrement of 0.02.	
Issue 7: Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population	That patients in the DFS state had the same life expectancy as an age- and sex-matched population	That it is plausible that the life expectancy for people with DFS and resected UC is lower than that of the general population.	That patients in the DFS state have the same life expectancy as an age- and sex-matched population. An additional scenario analysis was presented using a standardised mortality ratio (SMR) of 1.1	No
Issue 8: Uncertainty surrounding the assumed cure point	Cure point assumed at 5 years	Exploration of longer cure points due to clinical advice stating that recurrence can occur after five years and due to published data also indicating this.	Cure point assumed at 5 years	No
Issue 9: The lack of ICERs related to subgroup analysis in the company's submission	The company did not provide ICERs conditional on PD-L1 status of the tumour	Analyses to be presented based on whether the PD-L1 status of the tumour was ≥ 1% or not. The ERG notes that the NICE scope stated that these would be considered if evidence allows and that CheckMate 274 was stratified on this factor	The company does not provide ICERs conditional on PD-L1 status of the tumour	No
Other amendments detailed in the company's Technical Engagement response				
Additional issue 1: Change in the PAS	Simple discount of [redacted]	Not applicable	Simple discount of [redacted]	Yes

2.1 Additional data from CheckMate 274

The company's TE response reports new disease-free survival (DFS) data from CheckMate 274, an ongoing Phase III, randomised (1:1 ratio), international multi-centre, double blind, placebo-controlled study. The updated DBL provided DFS data with eleven months minimum follow-up. In its updated survival analyses, the company followed the ERG's preferred approach of fitting only the fully parametric survival models to the data instead of considering the semi-parametric models which they previously preferred. Seven fully parametric models were considered which included the generalized F distribution in addition to the six standard parametric models previously considered in the original submission. Independent models were fitted to the two arms. The company presented Kaplan-Meier (KM) functions for the nivolumab and placebo arms alongside plots of the predicted survival functions from the fitted models. These are reproduced here as Figure 1 for the nivolumab arm and Figure 2 for the placebo arm.

Figure 1. Investigator-assessed DFS for nivolumab: Standard statistical models overlaid upon Kaplan-Meier functions. (redacted)

Figure 2. Investigator-assessed DFS for placebo: Standard statistical models overlaid upon Kaplan-Meier functions. (redacted)

The company also presented Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics for the fitted survival models which are reproduced in Table 3 and Table 4. The evidence for how well specific models fit the observed data summarised by the company is reproduced in Figure 3 based on Burnham and Anderson[7] and Raftery.[8] The AIC and BIC values for models fitted to the nivolumab DFS data are provided in Table 3, with the corresponding values for placebo DFS data shown in Table 4.

AIC difference	Evidence for a specific model
≤ 2	Substantial support
2 < Δ < 4	
4 ≤ Δ ≤ 7	Considerably less support
7 < Δ ≤ 10	
Δ > 10	Essentially no support

BIC difference	Evidence of difference to alternative model
0-2	Weak
2-6	Positive
6-10	Strong
>10	Very strong

Figure 3. Evidence of support for a model compared to the model with the lowest AIC / BIC value.

Table 3. Nivolumab DFS: AIC and BIC values for parametric models based on the updated DBL (11 months minimum FU)

Extrapolation model	DFS			
	AIC		BIC	
	Value	Difference to base case	Value	Difference to base case
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalized F (base case)	[redacted]		[redacted]	

Table 4. Placebo DFS: AIC and BIC values for parametric models based on the updated DBL (11 months minimum FU)

Extrapolation model	DFS			
	AIC		BIC	
	Value	Difference to base case	Value	Difference to base case
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized F (base case)	[redacted]		[redacted]	

The company correctly notes that, according to the AIC and BIC statistics, the generalized F model is the model with best fit to the observed data for both arms. The BIC values support this conclusion for the placebo arm but is less definitive for the nivolumab arm with both the log-normal and Gompertz models having a BIC value which is only 2-6 higher than the generalized F.

The company chose the generalized F distribution to represent DFS for both treatment groups in its updated economic analysis. Further evidence presented by the company is discussed in the ERG critique in Section 3.2.

3 ERG critique of the company's TE response

This ERG addendum is also structured around the nine key issues in the initial ERG report which are detailed in Sections 3.1 to 3.9; a small apparent error in the company's model was identified by the ERG, and this is described in Section 3.10. Sections 3.1 to 3.9 summarise the issues as reported by the ERG, new data presented by the company (if any), the view put forward by the company, and any new ICERs generated when using the company's preferred assumptions. Each section also includes the ERG's opinion on the new data/assumptions; the impact of these assumptions on the ICER is presented in Section 4 alongside the company's preferred ICER and an indicative ICER preferred by the ERG. The ICER is labelled indicative as potentially key factors in the decision problem could not be explicitly modelled.

3.1 Key Issue 1: Exclusion of cisplatin-based adjuvant chemotherapy as a comparator

In the CS, and reiterated in the TE response, the company states that '*Cisplatin is not a relevant comparator of interest for nivolumab in this indication*.' It notes that '*Patients who were eligible and willing to receive adjuvant cisplatin based adjuvant chemotherapy were not eligible per study inclusion criteria.*', that '*cisplatin-eligible patients may not have been willing to be randomized to a placebo arm.*', and that therefore there '*is no evidence available from CheckMate 274 for patients who would have actually received chemotherapy in a non-clinical trial*'. The company provides further evidence from John *et al*.[9], Witjes *et al*.[10], and from clinical advice to the company all supporting that the proportion of patients likely to receive cisplatin-based adjuvant chemotherapy is low, and that European Association of Urology (EAU) guidelines do not report an '*unequivocal recommendation for the use of adjuvant chemotherapy.*'. Critically, the ERG notes that none of these sources suggests that the percentage is zero with the company stating that '*only a minority of patients actually receive adjuvant cisplatin-chemotherapy.*'

The company reiterates the limitations in the ITC conducted, which was updated for the TE response. The key limitations cited by the company were the considerable heterogeneity of studies, limitations in the evidence base and small sample sizes. EAU guidelines were quoted which stated that '*All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases).*[10]' The results from the company's ITC had wide credible intervals which crossed unity. The company reports that '*using the latest data from the updated DBL (11-month minimum FU), the updated hazard ratio (HR) of nivolumab versus placebo from group C (excluding UTUC patients from both arms) was* [redacted] *and the updated HR of nivolumab from group C (UTUC patients removed) versus adjuvant chemotherapy from the two gemcitabine studies and Sternberg pooled was* [redacted].' The ERG

acknowledges the limitations of the ITC but notes that the onus is on the company to show that the evidence strongly indicates nivolumab is more clinically effective than cisplatin-based treatment given the marked difference in acquisition prices.

The ERG maintains its view that cisplatin-based adjuvant chemotherapy is likely to be an appropriate treatment option for a (small) proportion of patients as per the clinical advice received by the ERG. For these patients, the company declined to present an ICER to support any assumption that nivolumab would be a cost-effective use of resources. However, the ERG maintains its opinion that '*based on the current available evidence, the ERG deems that it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY*.' The ERG also still believes that '*the ICERs presented in the company submission are applicable only to the comparison of adjuvant nivolumab and BSC*'.

3.2 Key Issue 2: The use of semi-parametric models to fit to DFS Kaplan-Meier (KM) estimates

Having reviewed the evidence presented in the company's TE response in light of the CS and data provided in the clarification response, the ERG is satisfied that the generalized F is a reasonable choice of distribution to model the DFS in both treatment arms. However, this is subject to a number of limitations, described in the rest of this section, which means the choice of this distribution over the Gompertz is not as clear-cut as the company concluded.

As in our previous report, the ERG notes the company's statements in the CS that the Gompertz distribution *"does not accurately capture the pattern of the KM data from the trial, in particular the protocol-induced features, such as the 'stepwise' nature of the data, particularly in the first year"*. In addition, the company highlighted *"the complex hazard profiles underlying DFS – chiefly the steepness of the increase at 3 months – [which] were predominantly a protocol-induced feature due to the timing of tumour assessments"*. The generalized F distribution has 4 parameters whilst the Gompertz has 2 parameters. This gives extra flexibility which allows a much better fit to the protocol-induced features. The ERG's view is that fitting to the protocol-induced features remains potentially undesirable if these patterns would not be observed in clinical practice. For this reason, the significantly better fit of the generalized F distribution, judged on the basis of AIC and BIC values could be misleading if the true underlying hazard was monotonically decreasing rather than having an increasing hazard which peaks at the time of first tumour assessment and then declining thereafter.

In the TE response, the company presented only the Royston-Parmar spline version of smoothed hazard which accentuates the initial steep rise and height of the modal peak in the hazard (which as noted by the company is largely protocol-driven) and which provided the best match to the hazard predicted by the generalized F distribution. The ERG notes that different valid smoothing processes give differing

results depending on how they weight the observations, especially those at the boundaries of the observed time range. In response to a request from the ERG and for consistency with the presentation in the clarification response, the company subsequently provided B-spline smoothed and kernel smoothed versions of the hazards (Figure 4). The B-spline version of smoothed hazard was monotonically decreasing, which may be more clinically plausible and which matched very closely to the hazard predicted by the Gompertz model. The company made the valid point, however, that it is implausible for the hazard in the placebo arm to fall below that estimated from life-tables which is predicted from 42 months by the Gompertz model fitted to the updated data.

One key feature to consider relating to the company's preferred generalized F distributions is that the hazard of a DFS event at 5 years is higher (considerably so for the placebo arm) than the hazard of death estimated from life-tables which is not compatible with the company's assumption that the patient is fully cured at 5 years.

Figure 4 Investigator-assessed DFS for nivolumab (left) and placebo (right) (CheckMate 274, updated DBL with 11 months minimum follow up): Smoothed observed hazard function estimates for the trial data together with predictions from the Gompertz and generalized F distribution models.

In its TE response, the company also presented a smoothed hazard for progression or death derived from Sternberg *et al.*[4] (progression free survival was assumed to be generalisable to DFS) as evidence against the Gompertz distribution in the placebo arm. The company noted that *"there are limitations in evaluating the smoothed hazards from published literature*" and clarified subsequently that this hazard was reconstructed via a number of stages. These are standard steps for creating pseudo IPD but these inevitably increase uncertainty. The smoothed hazard presented by the company is shown in Figure 5.

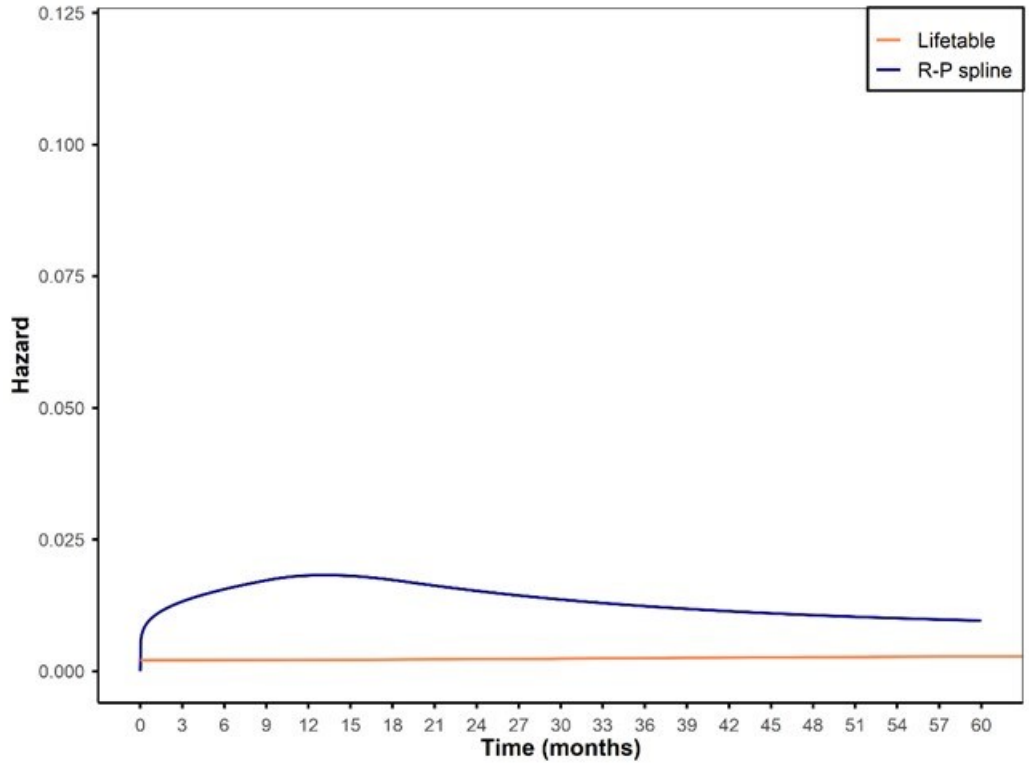


Figure 5: Smoothed hazard estimates of PFS from the Sternberg *et al.* deferred arm against life-table hazard (reproduced from Figure 4 of the company's TE response)

The ERG notes that the estimates of a PFS event derived from Sternberg *et al*. shows a substantially higher hazard than the hazard of death from life-tables at 5 years. As with the distributions fitted to data from CheckMate 274 this is incompatible with the assumption that a patient is fully cured at 5 years.

In its TE response, the company compared the 5- and 10-year survival predictions from the Gompertz and generalized F distributions to those presented in Sternberg *et al*. (Table 5), stating that "*the generalized F functional form aligns closely with (…) the data from Sternberg et al*" and implying that the Gompertz functional form does not. The ERG notes that whilst the 10-year survival proportions are not particularly relevant due to the 5-year cure assumption made by the company, the Gompertz model prediction nevertheless lies well within the 95% confidence interval (CI) of estimated 10-year survival. At 5 years, the Gompertz model prediction is closer to the estimate in Sternberg *et al*. than is the generalized F model, though both are well within the 95% CI.

Table 5 Reported and predicted survival probabilities for the placebo arm. The 95% confidence interval (CI) at 5 years is reported in Sternberg *et al.*, the 95% CI at 10 years was derived by the company from the KM data presented in Sternberg *et al.*

Source	5 years (%)	95% CI (%)	10 years (%)	95% CI (%)
Sternberg[4]	31.8	24.2-39.6	25.7	19.5-35.0
Generalized F	[redacted]		[redacted]	
Gompertz	[redacted]		[redacted]	

The company further presented a range of plausible 5-year survival probabilities, estimated by clinicians who were informed by the KM data from the updated DBL from CheckMate274. The ERG note that the upper limit of this range is 31.8% which is exactly the point estimate from Sternberg *et al*. without taking into account the uncertainty represented by the 95% CI. The ERG does not believe this presents reliable evidence against the Gompertz distribution.

For the nivolumab arm, the generalized F and Gompertz distributions achieve approximately equal survival proportions at 5 years, as shown in Figure 6, and it is the survival difference between arms at this point which is a driving factor of the ICER. Where two models are equivalent it is good practice to adopt the simpler of those models. However, for consistency it is reasonable to choose the same survival distributions for both arms.

For the placebo arm, the ERG accepts the company's contention that it is implausible for the hazard to fall below the background life table hazard as predicted by the Gompertz model. However, it can be seen from Figure 4 that the hazard predicted by the generalized F model is inflated relative to the smoothed observed hazard and is likely therefore to underestimate survival at 5 years in the placebo arm.

Figure 6 Comparison of KM functions from the updated database lock (11 months minimum follow-up) and fitted survival models using the generalized F and Gompertz distributions.

In conclusion, the ERG is satisfied that the generalized F distribution is a reasonable choice for both arms but that the use of this distribution is incompatible with an assumption that patients are fully cured at 5 years. A Gompertz distribution is also plausible and would be compatible with this assumption.

3.3 Key Issue 3: Use of utility data from Janssen et al

In its CS, the company used utility estimates from Janssen *et al*.[5] The ERG preferred an alternative source, Ara and Brazier[6], which used more recent data, and importantly did not assume that utility remained constant after 75 years of age. In its TE response, the company has amended the model to use data from Ara and Brazier.[6] The ERG considers this issue to be resolved.

3.4 Key Issue 4: The average age of patients in the UK is likely to be older than those recruited to CheckMate 274

In the CS, the company modelled a cohort of patients with the mean age as observed in CheckMate 274 ([redacted] years). Clinical advice provided to the ERG suggested that patients seen in clinical practice in England would likely be older than in the RCT. The ERG explored the sensitivity of the ICER to an arbitrary increased age of 70 years, but did not have an accurate estimate of the true mean age for patients in the decision problem.

In its TE response, the company has stated that '*UK clinicians agree there is no major discordance between the mean age for MIUC patients in the CheckMate 274 trial versus UK clinical practice*.' This advice differs to that provided to the ERG who believe that the age of patients in English practice will be higher than in CheckMate 274. The company provides a discussion of alternative data sources commenting on the limitation of these publications in accurately estimating the mean age for patients with muscle-invasive urothelial cancer (MIUC) at high risk of recurrence following radical resection of invasive urothelial carcinoma, with a common reason being the heterogeneity of patients included in the studies. The company provides an alternative scenario which uses data from John *et al*.[9] to estimate a weighted median age of patients. Using the proportions of patients receiving neoadjuvant chemotherapy, or not, the weighted median age was estimated to be [redacted] years, compared with 67 years in CheckMate 274.

The ERG has considered the comments in the company's TE response, keeping in mind the experts' opinions providing clinical advice to the ERG. In the ERG base case, the age of the population has been maintained as the mean age of those in CheckMate 274, but an additional sensitivity analysis has been conducted using a mean age of 67 years.

3.5 Key Issue 5: Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo

The company approach in the CS was to pool data from the nivolumab and BSC arms to calculate the probability that a DFS event was a death and to use the same proportion for both treatment arms. The pooled value was calculated from a logistic regression using covariates (full details were not provided). The company maintained this approach although the proportion of DFS events that were deaths has been recalculated using the updated DBL. The longer follow-up has amended the proportion of deaths from [redacted] in the CS to [redacted]. The company commented that the numbers of deaths in both arms were similar, but immature ([redacted] deaths in the nivolumab arm and [redacted] in the placebo arm).

The ERG had commented that the '*observed proportion of deaths among DFS events were different between the trial arms:* [redacted] *versus* [redacted] *for nivolumab and placebo respectively*' and that the treatment-specific probabilities should be used. In its TE response, the company undertook an analysis using [redacted] for patients treated with nivolumab and [redacted] for patients treated with BSC. This slightly increased the ICER observed (from £27,030 to £27,186). Whilst this modest increase in the ICER is noted, the ERG prefers the use of treatment-specific proportions as the results from the logistic regression predicts a lower proportion than both of the treatment-specific values potentially showing an unwanted impact of adjusting for covariates.

3.6 Key Issue 6: Patients in the DFS health state have the same utility values as an age- and sex-matched population

The company assumed that the utility for people in the DFS state was equal to that of an age- and sex-matched population as the utility values calculated from CheckMate 274 exceeded those of the general population. However, the advice from ERG's clinical experts indicated that history of having a resected UC would, on average, have detrimental effect on the patient's health-related quality of life compared with an average person of the same age and sex without resected UC assuming a similar distribution of comorbidities amongst patients with resected high-risk UC and those without.

The company has maintained the approach used in the CS stating in its TE response that the 0.02 decrement in utility explored by the ERG was arbitrary. The ERG acknowledges the arbitrary nature of the value, but believes this is a more plausible estimate than assuming no decrement which is not aligned with the clinical advice provided to the ERG. Analyses provided by the company indicate that assuming a 0.02 decrement increases the company's base case from £27,030 to £27,754.

The ERG has maintained the 0.02 utility decrement for patients in the DFS state until the time at which it was assumed that there would be no excess risk of mortality for patients treated with nivolumab

compared with an age- and sex-matched population (See Issue 7). This period was assumed to be for a maximum of 10 years in the disease-free state when using the generalised F distribution, for a maximum of 5 years in the disease-free state when using a Gompertz distribution and for a maximum of 10 years in the disease-free state when the cure point was assumed to be 10 years.

3.7 Key Issue 7: Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population

The company assumed that the life expectancy for people in the DFS state for at least five years was equal to that of an age- and sex-matched population. The TE response states that '*Clinical experts confirmed that 99% of recurrence would happen before the 5 year timepoint and it is reasonable to consider that patients will follow the general population mortality trend if they have not recurred after 5 years post-surgery.*' The company also states that such patients would be discharged with no further monitoring.

However, data reported by the company in its TE response, and replicated in Figure 5, indicate that the hazard of death remains much higher in those in the deferred arm of Sternberg *et al*. at 5 years. The company states that this has "*a population similar though not exactly aligned to the CheckMate 274 trial*." These data when considered with the increased hazard of death predicted from the generalized F distribution at 5 years compared with life-table data (Figure 4) indicate that there is likely to be a considerable excess of risk of death for people with high-risk resected UC beyond 5 years. The ERG appreciates that DFS is a composite endpoint that includes both recurrence and death, but deems it logical that if the company assumes that the patient is cured of UC then the event must be a death. In order to estimate a standardised mortality rate (SMR) that would describe the increased risk of death compared with an age- and sex-matched population the ERG used values presented in the company's model. The average of the hazard of a DFS event in the week before 60 months in the nivolumab and the placebo arm was extracted and divided by the extracted hazard of all-cause mortality for the same period. This resulted in an estimated SMR of [redacted]. This was applied in the ERG's base case for a period of 5 years, for years 6 to 10, at which point the chance of a DFS event was small (see Figure 7 in the discussion of Issue 9). After 10 years residing in the DFS state, it was assumed that patients were fully cured and the hazard of death reverted to that of an age- and sex-matched population.

Data provided by the company in the technical engagement process stated that the hazard at 60 months was: [redacted] from the generalised F for the nivolumab arm, [redacted] from the generalised F for the placebo arm, and was 0.00279 for an age- and sex-matched general population. Using the average for the two generalized F distributions [redacted] SMR of [redacted] at 5 years was estimated. The ERG does not know why there is a difference between the two estimates of SMR but notes that these hazards provided by the

company differ from those within the model. The ERG has used the SMR of 2.01 in an exploratory analysis.

For the additional scenario analysis using a Gompertz distribution to estimate DFS for both nivolumab and BSC it was assumed that the risk of death was equal to that of an age- and sex-matched population after residing in DFS for five years.

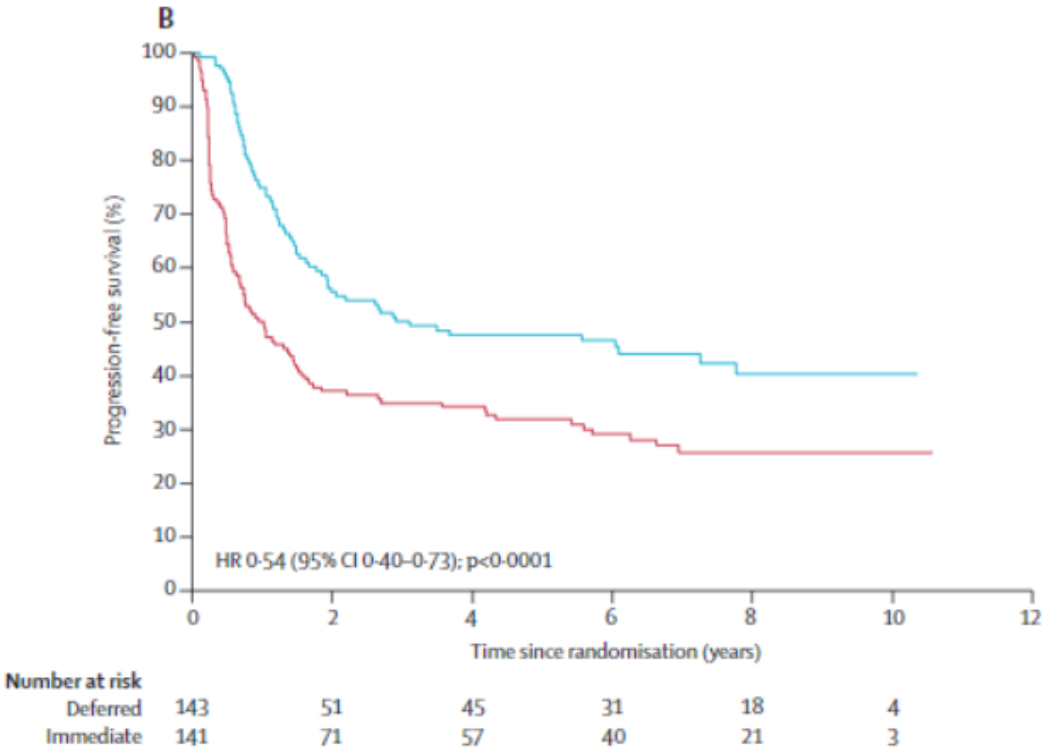
3.8 Key Issue 8: Uncertainty surrounding the assumed cure point

The company assumed that after 5 years residing in the DFS state, patients will not have a recurrence. Clinical advice to the ERG suggests that whilst the recurrence rate diminishes as the time since resected UC increases, it is not zero after 5 years, hence the ERG explored a longer time period over which patients are assumed to be at risk of recurrence.

In its TE response, the company state that within CheckMate 274 '*for DFS, hazards approach those of the general population by 5 years…… and indicate that patients who might be expected to experience recurrence would have done so prior to 5 years.*' The ERG believes that the company intended to state that based on clinical advice it received, 99% of patients *that recur* do so before 5 years. The company also highlights that these patients do not receive routine follow-up after 5 years based on rarity of recurrence.[11] The company further cites the study by Sternberg *et al*.[4] which is stated to provide '*further validation for a cure point at approximately 5 years*' as there were few events after approximately 4 years. A 10-year cure point was excluded by the company on the basis that the studies that supported this longer time point excluded patients that received neoadjuvant chemotherapy.[12, 13]

The ERG notes that the data from Sternberg *et al*. (shown in Figure 7) indicate that events do happen beyond 5 years, as also indicated by clinical advice provided to both the company and the ERG. Whilst some of the DFS events may be deaths, the numbers estimated the plot would not be compatible with those expected using life-table data.

Figure 7: KM plot of DFS events from Sternberg *et al.* (reproduced from Figure 7 of the company's TE response)



Due to the apparent incompatibility between a 5-year full cure point and the increased hazard of death compared with an age- and sex-matched population, the ERG has run an exploratory analysis assuming that the cure point is 10 years.

3.9 Key Issue 9: The lack of ICERs related to subgroup analysis in the company's submission

The short description of this issue has been amended based on comments made by the company in its TE response. The ERG clarifies that the issue was meant to relate to the lack of ICERs presented for clinical subgroups, not that the company did not provide clinical data on these subgroups. Following the updated DBL the company has provided updated HRs, conditional on PD-L1 status (≥ 1% or <1%) for DFS (primary definition, which accounts for subsequent anticancer therapy and new non-UC primary cancer). The HR is 0.53 (95% CI: 0.38 – 0.75) for the PD-L1 ≥ 1% group and [redacted] for the PD-L1 <1% group. On page 45 of the company's TE response, the HRs for DFS (the definition was not specified by the company) were reported to be 0.55 (95% CI: 0.39 – 0.77) for the PD-L1 ≥ 1% group and [redacted] for the PD-L1 ≥ 1% group.

The company states that '*the PD-L1 <1% subgroup is not powered to detect differences in outcomes in the CheckMate 274 trial. Moreover, the wide CIs, crossing 1, observed in the efficacy results of the PD-L1 <1% subgroup indicate a less precise estimate and results should be interpreted with caution.*' Additionally, the company has stated that PD-L1 expression "*has not been confirmed to be prognostic*". The company "*considered it inappropriate to conduct economic analyses based on the PD-L1 subgroups, as any such analyses are likely to produce biased and unreliable results, which will not be useful to inform economic model and therefore decision making*",

The ERG believes that the company should have provided (exploratory) ICERs for the two PD-L1 status subgroups noting that: (i) the NICE scope[14] stated that if evidence allows, subgroup analyses should be conducted according to PD-L1 expression of the resected tumour, and (ii) that PD-L1 status was a stratification factor within CheckMate 274, both of which indicate that the ICERs between the groups may differ. The ERG additionally comments that the ICERs can still differ between subgroups when a factor is not prognostic should an intervention have a differential efficacy between subgroups as the HRs from the updated DBL suggest.

Based on the current information, the ERG believes that formal cost-effectiveness analyses using the PD-L1 subgroup specific data would decrease the ICER for tumours with a PD-L1 value ≥1% but would increase the ICER for tumours with a PD-L1 value <1%. This information could be particularly important if the Appraisal Committee was to decide that the ICER for the complete population was close to the cost-effectiveness threshold considered appropriate by the committee. Overall conclusions made for the entire population could potentially result in cost-effective treatments for patients where the tumour expressed a PD-L1 value ≥1% being withheld, or result in cost-ineffective treatments being recommended for patients where the expressed a PD-L1 value <1%.

3.10 Model correction

Within the company's model the probability of having a DFS event (either a recurrence or cancer-related death) was calculated as the probability of leaving the disease-free state [p(leaving DF)] multiplied by (1- probability of all-cause mortality (pACM)). The ERG notes that by doing that p(leaving DFS) is treated as a cohort size instead of a probability. The ERG amended the model such that:

$$p(\text{having a DFS event}) = p(\text{leaving DFS}) - pACM$$

4 Additional analyses undertaken by the company and the ERG

4.1 Results of the analyses presented by the company

This section presents the central estimates of costs effectiveness using the deterministic version of the updated version of the company's model submitted as part of its TE response; probabilistic results were not provided, although the ERG notes that the original model in the CS appeared to be relatively linear with a deterministic ICER of £32,813 and a probabilistic ICER of £32,932. As mentioned in Section 2, for brevity the scenario analyses within the company's TE response are not presented here.

Table 6 presents the central estimate of cost-effectiveness generated using the company's updated model for the comparison of nivolumab versus BSC.

Table 6: Company's updated base case deterministic results

Options	LYGs	QALYs	Cost	Inc. LYGs	Inc QALYs	Inc Costs	ICER
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,030**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

4.2 Description of additional exploratory analyses undertaken by the ERG

In all exploratory and additional sensitivity analyses, the ERG has used the company's updated version of the model. The exploratory analyses are linked to the key issues identified in the ERG report. As stated, the ERG provides three alternative scenario analyses for the Appraisal Committee to consider, noting that all of these have limitations.

ERG exploratory analysis 1: Exclusion of cisplatin-based adjuvant chemotherapy as a comparator

The ERG could not formally assess the ICER when cisplatin-based adjuvant chemotherapy was a comparator, although believes it is highly likely that cisplatin-based regimens would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 per QALY.

ERG exploratory analysis 2: Use of alternative DFS survival functions

For alternative scenario analyses 1 and 3, the ERG used the generalized-F distribution chosen by the company. In alternative scenario analysis (ASA) 1, an increased risk of death was applied, whereas in ASA 3 the cure point was extended to 10 years. In ASA 2, the ERG explores the use of a Gompertz distribution, but uses the age- and sex-matched risk of death after 5 years in DFS. In all models,

distributions are amended such that the risk of a DFS event is never lower than the age- and sex-matched population value.

ERG exploratory analysis 3: Use of utility data from Janssen *et al*.

The company has changed its assumption to that preferred by the ERG and thus no further amendments are required.

ERG exploratory analysis 4: The average age of patients in the UK is likely to be older than those recruited to CheckMate 274

The company has provided additional analyses which provided some support to the assumption in the company's base case. The ERG has run an additional exploratory analysis using a mean age of 67 years to assess the impact on the ICER of increasing the patient age.

ERG exploratory analysis 5: Assumption of an equal proportion of DFS events being deaths for nivolumab and placebo

The ERG maintained its preference for treatment-specific proportions of DFS events that are deaths. This has been used in each of the alternative scenario analyses.

ERG exploratory analysis 6: Patients in the DFS health state have the same utility values as an age- and sex-matched population

Based on clinical advice, the ERG maintains an exploratory decrement of 0.02 in the first 5 years residing in the disease-free state for each of the alternative scenario analyses. As detailed in Section 3.7, this was further applied until a patient was considered fully cured. The additional times associated with utility decrements were five years in ASA1 and ASA3 and zero years in ASA2.

ERG exploratory analysis 7: Patients in the long-term DFS health state have the same life expectancy as an age- and sex-matched population

The ERG applies a SMR of [redacted] to the age- and sex-matched general population for the period of 5 to 10 years residing in the disease-free state in ASA1. For ASA2 and ASA3 the age- and sex-matched general population was used after 5 years residing in the disease-free state.

ERG exploratory analysis 8: Uncertainty surrounding the assumed cure point

For ASA1 and ASA2 the cure point of 5 years was used as preferred by the company. For ASA3 the cure point was extended to 10 years.

ERG exploratory analysis 9: The lack of ICERs related to subgroup analysis in the company's submission

The ERG could not formally assess the ICERs for different subgroups, in particular according to the PD-L1 expression of the resected tumour. However, the opinion of the ERG is that the ICER would decrease for tumours with a PD-L1 value ≥1%, but would increase for tumours with a PD-L1 value <1%.

The ERG's indicative ICER combines ERG exploratory analysis 6 and 7. This is not a preferred ICER as some potentially important factors could not be explicitly modelled (see Issue 1 and Issue 9). Additional scenario exploring potential plausible scenarios are provided to supplement the ERG's indicative ICER.

4.3 Description of additional scenario analyses undertaken by the ERG

ERG additional exploratory analysis 1: Increasing the mean age of patients
In this analysis, the ERG increases the mean age to 67 years.

ERG additional exploratory analysis 2: Assuming an alternative value for the SMR in ASA1
In this analysis, the ERG decreases the SMR applied in ASA1 to 2.01 as implied by the data provided by the company, rather than the value of [redacted] calculated by the ERG from data within the company's updated model.

4.4 Results of exploratory analyses undertaken by the ERG

Table 7 presents the deterministic results of the ERG's alternative scenario analyses; probabilistic results are similar. The largest change in the ICER occurs in ASA2 where Gompertz distributions were used for modelling DFS resulting in an increase of nearly £20,000. ASA3, which applies an SMR of [redacted] between years 6 and 10 of the disease-free state and assumes a utility decrement of 0.02 for the first 10 years of a patient being disease-free increased the ICER by more than £5000. ASA3, which assumes a cure point of 10 years and a utility decrement of 0.02 for the first 10 years of a patient being disease-free increased the ICER by approximately £1300.

Table 7: Deterministic results of the ERG's additional scenario analyses

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,030**
Company's updated base case (error corrected)							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,096**
ERG ASA1 indicative ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,125**
ERG ASA2 indicative ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,958**
ERG ASA3 indicative ICER†							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,386**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
† Indicative as some potentially important factors could not be explicitly incorporated in the ERG's base case (see Issues 1 and 9)

The impact of exploratory analysis 1, where the mean age of the patients was increased to 67 years made a modest change to the ICER, increasing it to £33,939 for ASA1, £48,606 for ASA2, and £29,499 for ASA3.

The impact of exploratory analysis 2, where an SMR of 2.01 was used in ASA1 decreased the ICER to £29,480.

5 Overall conclusions

The model submitted by the company was implemented to a good standard, although the ERG preferred alternative assumptions to those used by the company. The ERG believes that the generalized F extrapolations were better fits than semi-parametric extrapolations used by the company in the CS. However, the ERG does not believe that these distributions were compatible with the company's assumption that patients were fully cured after 5 years of being in DFS. The ERG also questions the use of generalized F distribution if the true hazard of DFS was in fact monotonically decreasing with the increase in the hazard observed at 3 months being an artifact of the time of first tumour assessment; in this instance the generalized F distribution would not represent the true hazards despite the better goodness-of-fit to the observed data.

The ERG provides alternative scenarios that may be informative to the Appraisal Committee. The first (ASA1) explicitly considers that the hazard of death is not the same as the age- and sex-matched general population after 5 years of being disease-free. The second, ASA2, uses Gompertz distributions rather than the generalized F distribution, whilst the third (ASA3) extends the time point of being fully cured to 10 years. All three analyses apply a utility decrement of 0.02 until a patient is considered fully cured.

All three analyses increase the ICER compared to the company's base case, although the increase in ASA3 is small (£1300). ASA1 increases the ICER by £6000 to an estimate which is greater than £30,000. ASA2 has the largest impact, increasing the ICER to over £45,000. All three analyses have limitations. ASA1 assumes arbitrarily that patients are fully cured at 10 years, as does ASA3, although they differ as an SMR is applied in ASA1, whereas the cure point is explicitly set to a longer duration in ASA3. ASA2 has the same limitation as the company's base case in that external data does not support a cure point at 5 years, although it has the advantage over the company's base case that the distributions chosen for both arms have a hazard of a DFS event at 60 months similar to the hazard of death estimated for general population at that time. Increasing the age of patients increased the ICERs modestly. Using a lower SMR in ASA1 decreased the ICER.

The ERG highlights that for two reasons the ICERs produced are indicative only: (i) the company provides no formal analysis of the cost-effectiveness of nivolumab compared with cisplatin-based regimens and (ii) the company has not provided ICERs for PD-L1 subgroups. Regarding the first point, the ERG believes that the cisplatin-based chemotherapy would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000. Regarding the second point, because the midpoint estimate for the HR for tumours with a PD-L1 expression of <1% is markedly higher than that for tumours with a PD-L1 expression of ≥1%, it is plausible that the ICER for the group

of patients with tumours with a PD-L1 expression of <1% could be greater than £30,000 whilst the ICER for the group of patients with tumours with a PD-L1 expression of ≥1% was below this threshold.

6 References

1. Bristol Myers Squibb. Nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]. Technical Engagement response; 2021.
2. Metry A, Holmes G, Leaviss J, Martyn-St James M, Clowes M, Aning J*, et al.* Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal. : School of Health and Related Research (ScHARR); 2021.
3. Bristol-Myers Squibb. Company evidence submission for nivolumab for treating resected high-risk invasive urothelial cancer [ID2694]; 2021.
4. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M*, et al.* Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol* 2015;16:76-86.
5. Janssen B SA. Population Norms for the EQ-5D. In: Szende A JBCJ, editor. *Self-Reported Population Health: An International Perspective based on EQ-5D*Dordrecht: Springer Netherlands; 2014:19-30.
6. Ara R, Brazier J. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010;13:509-18.
7. Burnham KP, Anderson DR. Model selection and multi-model inference [electronic resource] : a practical information-theoretic approach. 2nd edn: New York ; London: Springer; 2002.
8. Raftery A. Bayesian Model Selection in Social Research. *Sociological Methodology,* 1995;25:111-63.
9. John JB VM, Cooper N, Wong K, Hounsome L, Treece S, McGrath JS, Harden S. Treatment Allocation and Survival in Patients Diagnosed with Nonmetastatic Muscle-invasive Bladder Cancer: An Analysis of a National Patient Cohort in England. *Eur Urol Focus* 2021 Mar;7:359-65.
10. Witjes JA, Bruins HM, Cathomas R, Compérat E, Cowan NC, Gakis G*, et al.* EAU Guidelines in Muscle-invasive and Metastatic Bladder Cancer: European Association of Urology (EAU); 2021.
11. Health NIf, and Care Excellence. Bladder cancer: diagnosis and management [NG2]. UK: NICE; 2015.
12. Hautmann RE, de Petriconi RC, Pfeiffer C, Volkmer BG. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. *Eur Urol* 2012;61:1039-47.
13. Soria F, Moschini M, Wirth GJ, Gust KM, Klatte T, Briganti A*, et al.* Characterization of Late Recurrence After Radical Cystectomy in a Large Multicenter Cohort of Bladder Cancer Patients. *Urology* 2017;106:119-24.
14. National Institute for Health and Care Excellence. Final scope for the appraisal of nivolumab for treating resected high-risk invasive urothelial cancer. 2021.

Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal. ERG analysis of the additional indirect treatment comparison performed by the company

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Kate Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	13/05/2022

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/39/77.

Following receipt of the ERG's report after the change in the license for nivolumab for treatment of resected high-risk invasive urothelial cancer, the company updated the indirect treatment comparison (ITC) between nivolumab and adjuvant chemotherapy to focus only on the 'PD-L1 ≥1% population'. In CheckMate 274, the pivotal study, 97 patients were in the PD-L1 ≥1% population, of which 51 were treated with nivolumab and 46 received placebo.

The methodology used by the company was the same as in the initial company submission and the ERG's critique of this, contained in Section 3.4 of the ERG report, still stands.

In addition, the ERG notes the following additional methodological issues with this sensitivity analysis.

- Inconsistency in dealing with UTUC patients: UTUC patients were included from the CheckMate 274 study, but some comparator studies were excluded because of UTUC (see Table 3 of Appendix 2 of the company's response).
- Apparent error in the heterogeneity assessment conducted: it appears that the wrong patient group was used from the CheckMate 274 study in this analysis in that all 'group C' CheckMate 274 patients were considered, rather than the PD-L1≥1% population only.
- Inconsistency in the relative treatment effect used in ITC: the log hazard ratio (HR) derived from the CheckMate 274 study was adjusted for the stratification factors, which provides a conditional log HR. The log HRs from the comparator studies are marginal log HRs (i.e., log HRs without adjusting for covariates). The conditional log HR and marginal log HR are not the same and it is inappropriate to obtain the ITC estimate using a mixture of both conditional and marginal effect.

The results of the company's ITC produced a point estimate favouring adjuvant chemotherapy [redacted] although the confidence interval was wide and crossed unity.

The company contends that there were significant limitations within the ITC due to key differences within the included studies which included the time period in which patients were enrolled to the studies. The company notes that CheckMate 274 was neither stratified on eligibility for cisplatin treatment nor powered to detect a difference in patients who were eligible for cisplatin-based adjuvant treatment. The company also notes that the patients within CheckMate274 who are eligible for cisplatin treatment had actively refused this treatment.

The company concludes that '*an ITC for nivolumab versus cisplatin-based adjuvant therapy is subject to major uncertainty, lacks robustness, is exploratory in nature and is insufficient to be used to inform HTA decision making.*' As such, the company did not provide an ICER for this comparison.

The ERG agrees that the results produced by the company's ITC will be uncertain, however, notes that there is no strong evidence to support the conclusion that nivolumab is more efficacious that adjuvant chemotherapy in patients eligible for cisplatin-based adjuvant treatment, indeed the point estimate suggests that cisplatin-based treatment may be more efficacious than nivolumab in the group eligible to receive it. Additionally, clinical advice provided to the ERG stated that as cisplatin-based regimens are only given for six cycles, the administration burden on patients is limited compared with the longer duration of nivolumab treatment.

Based on the currently available evidence, the ERG maintains its view that it is likely that cisplatin-based chemotherapy would either dominate nivolumab or that the cost per QALY gained for nivolumab would be greater than £30,000 based on the ITC conducted by the company.

Nivolumab for treatment of resected high-risk invasive urothelial cancer [ID2694]. A Single Technology Appraisal/ Addendum: ERG updated results following error correction for recurrence to death transition probability

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	23/05/2022

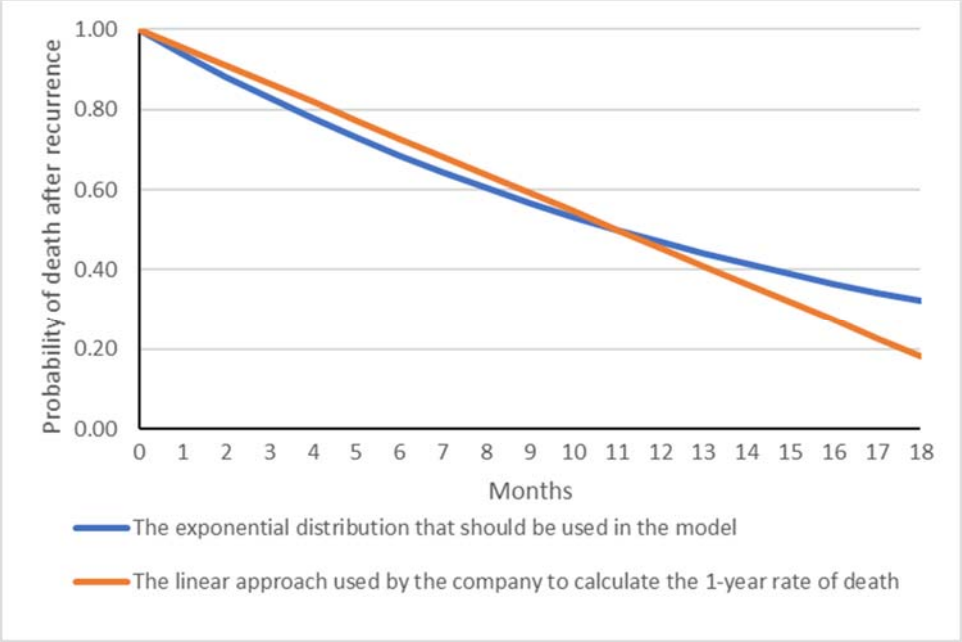
Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/39/77.

During the build-up to the Appraisal Committee, the lead team highlighted to the Evidence Review Group (ERG) that there appeared to be an error in the calculations performed by the company in the annual probability rate of death post-recurrence. This was checked, and the ERG agreed that there was an error in the method used by the company.

The company had calculated the annual rate of death after recurrence as 0.5/(median OS in months/12), after which the rate was converted to a probability. The ERG believes that the correct method was to calculate the rate of the exponential distribution based on the formula (lambda = LN(2) / median OS). The 1-year probability can then be directly calculated from this distribution. The amended approach resulted in an annual probability of death of 0.5305 (compared with 0.4204 in the company's model) when cisplatin and carboplatin regimens only are used, and 0.3896 (0.2996 in the company's model) when atezolizumab is added as an option as detailed in the company's updated submission.

Figure 1 shows the difference between the company's approach and the approach that the ERG believes is correct for the company's base case (without atezolizumab inclusion).

Figure 1: The different approaches used to calculate the annual probability of death post-recurrence for the company's base case (assuming 50:50 cisplatin to carboplatin regimens)



The ERG reports the updated results in this addendum having corrected the error.

It is noted that the calculations for key issue 11, where the ERG updated the costs of subsequent treatments when atezolizumab is included, was based on the mean survival post-recurrence. The increase in annual probability of death led to a decrease in post-recurrence mean survival from 24.7

months to 17.8 months. The recalculated weekly cost for patients on atezolizumab is £956.10, which amounts to an average weekly cost of £875.32 for all patients on subsequent treatments.

In this document, results are reported when atezolizumab is not used (Table 1), used only in the best supportive care (BSC) arm (Table 2), or used in both arms (Table 3). A confidential appendix provides the ICERs when the PAS for atezolizumab is incorporated.

Table 1 and Table 2 replicate Table 7 and Table 8 of the ERG report, whereas Table 3 replicates Table 1 of the separate addendum sent on NICE's request.

Table 1: Deterministic results of the ERG's additional scenario analyses

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,409**
Company's updated base case (error corrected as per key issue 10)							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,361**
ERG ASA 1 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,758**
ERG ASA 2 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£12,114**
ERG ASA 3 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,259**

Table 2: Deterministic results of the ERG's additional scenario analyses when atezolizumab is used as a subsequent treatment in BSC arm (list price)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's scenario results							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
Company's updated base case (errors corrected as per key issues 10 and 11)							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
ERG ASA 1 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
ERG ASA 2 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**
ERG ASA 3 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Nivolumab dominates**

Table 3: Deterministic results of the ERG's additional scenario analyses when atezolizumab is used as a subsequent treatment in both arms (using list price for atezolizumab)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's scenario results							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£1,615**
Company's updated base case (errors corrected as per key issues 10 and 11)							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£4,082**
ERG ASA 1 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£5,711**
ERG ASA 2 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£5,393**
ERG ASA 3 ICER							
BSC	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£4,306**

Conclusion

Using for the correct annual probability of death from the exponential curve increases the ICERs ~£300 per QALY gained for the scenarios where atezolizumab is not included in the post-recurrence subsequent treatment mix, however all ICERs remain below £14,000. Nivolumab remains dominant when atezolizumab is included only for the BSC arm, whereas similar ICERs were attained for the ERG ASAs when atezolizumab was considered as a subsequent therapy in both arms where the ICERs remain under £6,000.