NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Merck Serono

2. **Clarification questions and company responses**

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

4. **Evidence Review Group report** prepared by Aberdeen HTA Group

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

6. **Technical engagement response** from Merck Serono
   a. Response form
   b. Appendices

7. **Technical engagement responses from experts:**
   a. Alison Birtle – clinical expert, nominated by Fight Bladder Cancer
   b. Syed Hussain – clinical expert, nominated by Merck Serono
   c. Kevin Gorman – patient expert, nominated by Action Bladder Cancer UK

8. **Technical engagement response from consultees and commentators:**
   a. Action Bladder Cancer UK
   b. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

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

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

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Document B

Company evidence submission

October 2020

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ID3735_Avelumab_UC_Document_B_6Oct2020	1.0	Yes	6 October 2020

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Abbreviations

ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
admin	administration
AE	adverse event
AESI	adverse events of special interest
AIC	Akaike information criterion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aRCC	advanced renal cell carcinoma
AST	aspartate aminotransferase
AUC	area under the curve
BIC	Bayesian information criterion
BICR	blinded independent central review
BNF	British National Formulary
BOR	best overall response
BSA	body surface area
BSC	best supportive care
carbo	carboplatin
CDF	Cancer Drugs Fund
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
cis	cisplatin
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPS	combined positive score
CR	complete response
CS	company submission
DC	disease control
DLT	dose-limiting toxicity
DOR	duration of response
DRS-E	Disease Related Symptoms – Emotional
DRS-P	Disease Related Symptoms – Physical
DSU	Decision Support Unit
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic market information tool
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
EQ-VAS	EuroQol-visual analogue scale
EudraCT	European Clinical Trials Database
FAS	full analysis set
FBISI-18	Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index
FcR	FC receptor
FGFR	fibroblast growth factor receptor
G-CSF	granulocyte-colony stimulating factor
gem	gemcitabine
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage colony stimulating factor
GP	general practitioner
HR	hazard ratio

HRG	healthcare resource group
HRQoL	health-related quality of life
IA	interim analysis
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IERC	independent endpoint review committee
IgG1	immunoglobulin G1
IMDC	independent data monitoring committee
INV	investigator
IO	immune-oncology
irAE	immune-related adverse event
irBOR	immune-related best overall response
irPFS	immune-related progression-free survival
IRR	infusion-related reaction
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
LY	life-year
m	metre
MCC	Merkel cell carcinoma
mg	milligram
MHC	major histocompatibility complex
MIBC	muscle invasive bladder cancer
min	minute
ml	millilitre
MRI	magnetic resonance imaging
MVAC	methotrexate, vinblastine, adriamycin and cisplatin
N	number of patients evaluable
n	number of patients in the category
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NE	not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	natural killer cell
NMIBC	non-muscle invasive bladder cancer
NR	not reached
NSAID	non-steroidal anti-inflammatory drugs
OP	outpatient
OR	objective response
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
pac	paclitaxel
PartSA	partitioned-survival analysis
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFS-INV	progression-free survival (investigator assessed)
PK	pharmacokinetics
PPS	post-progression survival
PR	partial response

PRO	patient-reported outcome
PS	performance status
PSA	probabilistic sensitivity analysis
PSSRU	Personal and Social Services Research Unit
Q2W	every 2 weeks
QALY	quality-adjusted life-year
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SLR	systematic literature review
SmPC	summary of product characteristics
TA	technology appraisal
TEAE	treatment-emergent adverse event
TNM	Tumour, Node, Metastasis Classification system
TRAE	treatment-related adverse event
Treg	Regulatory T cell
TTD	time to treatment discontinuation
TTR	time to tumour response
Tx	treatment
UC	urothelial carcinoma
UK	United Kingdom
USA	United States of America
UTI	urinary tract infection
vs	versus

B.1. Decision problem, description of the technology and clinical care pathway

Executive summary

Urothelial carcinoma

- Urothelial carcinoma (UC) is the most common type of bladder cancer, accounting for over 90% of cases in the United Kingdom (UK)[1]
- In England, approximately 11,000 patients per year were diagnosed with UC between 2013 and 2017; 23.4% were adults with Stage III–IV tumours at diagnosis.[2] Bladder
- The estimated age-standardised mortality rates for bladder cancer in England and Wales are 14.0 per 100,000 population for men and 4.7 per 100,000 population for women (4,825 deaths in 2018)[3]
- Survival is especially poor in patients with locally advanced or metastatic bladder cancer, with five-year survival rates decreasing from approximately 80% at Stage I, to <5% at Stage IV,[4-7] and median survival of [redacted] months[2]
- The burden of UC symptoms, coupled with the poor prognosis results in a significant negative impact on physical, mental, and social quality of life (QoL), which deteriorates further in more advanced cases[8-10]
- First-line treatment options for advanced or metastatic UC are limited, with systemic platinum-based chemotherapy regimens being the current standard of care in the UK[11]
- Although up to 70% of patients respond to first-line platinum-based chemotherapy,[12-36] durable responses are uncommon and most patients will ultimately experience disease progression[37,38]
- Although maintenance therapies are already an effective approach in multiple cancers,[39-45] there are currently no approved maintenance treatment options in the first-line setting for patients with locally advanced or metastatic UC
- A clear unmet need exists for improved therapies, in order to extend survival and maintain health-related QoL for patients with locally advanced or metastatic UC

Avelumab

- Avelumab is a human immunoglobulin G1 monoclonal antibody directed against the programmed death-ligand 1 molecule expressed by tumour cells and a number of immune cells[46]
- As the first and only maintenance therapy to demonstrate efficacy in locally advanced or metastatic UC,[47,48] avelumab offers an important and efficient new targeted treatment option for patients whose disease has not progressed following first-line platinum-based chemotherapy

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication (locally advanced or metastatic urothelial carcinoma [UC]). A summary of the decision problem is provided in Table B.1.1.

Table B.1.1. The decision problem

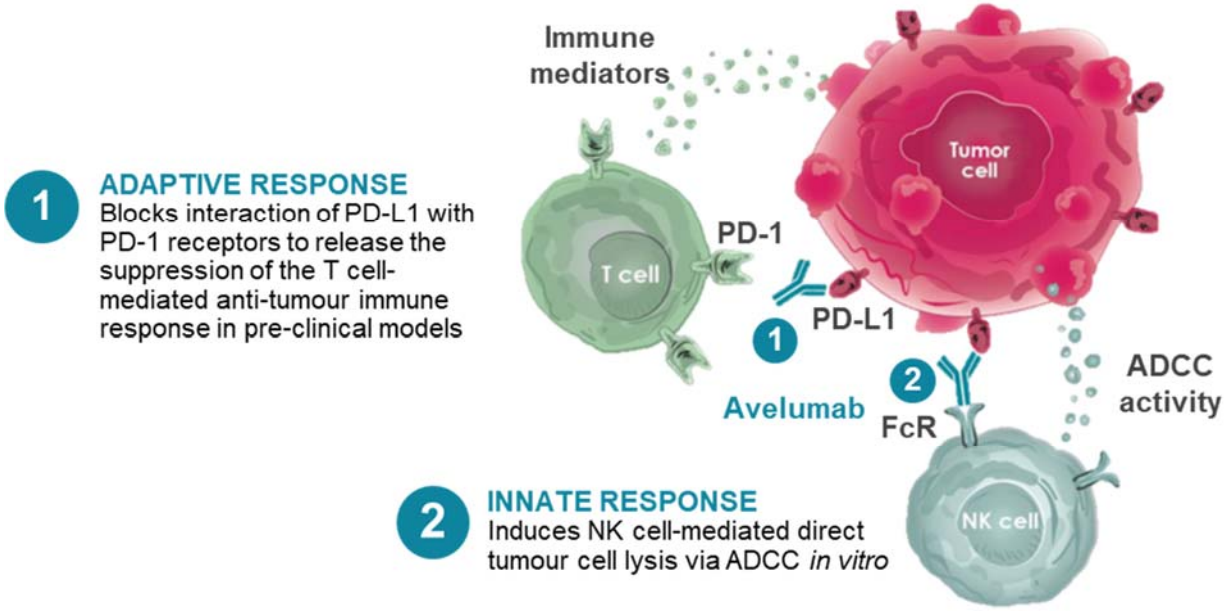
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy	As per scope	N/A
Intervention	Avelumab	As per scope	N/A
Comparator(s)	Established clinical management without avelumab (including but not limited to routine surveillance, symptom control and pain management [including palliative radiotherapy])	As per scope	N/A
Outcomes	• OS • PFS • Response rates • Time to relapse or progression • Adverse effects of treatment • HRQoL	As per scope	N/A

Abbreviations: HRQoL = health-related quality of life; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression free survival; UC = urothelial carcinoma

B.1.2 Description of the technology being appraised

Avelumab (Bavencio®) is a human immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to the programmed death-ligand 1 (PD-L1) cell-surface molecule and blocks the interaction between PD-L1 and its receptors, programmed death 1 (PD-1) and CD80 molecule. PD-L1 is expressed by tumour cells and a number of immune cells; avelumab blocks PD-L1 interaction with PD-1 on tumour-infiltrating T cells, releasing T cells from PD-1-mediated inhibition and potentiating tumour killing. In addition, avelumab has been shown to induce natural killer cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity *in vitro* (Figure B.1.1).[46]

Figure B.1.1. Avelumab mechanism of action



Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; FcR = FC receptor; NK = natural killer; PD-1 = programmed death-1; PD-L1 = programmed death-ligand-1
Source: Boyerinas et al, 2015;[49] Dolan et al, 2014;[50] Dahan et al, 2015;[51] Hamilton et al, 2017;[52] Kohrt et al, 2012[53]

A summary of the technology being appraised, avelumab, is provided in Table B.1.2 and the summary of product characteristics is included in Appendix C.

Table B.1.2. Technology being appraised

UK approved name and brand name	Avelumab (Bavencio®)
Mechanism of action	Avelumab is a human IgG1 monoclonal antibody directed against the PD-L1 molecule expressed by tumour cells and a number of immune cells. Avelumab blocks PD-L1 interaction with PD-1 on tumour-infiltrating T cells, releasing T cells from PD-1-mediated inhibition and potentiating tumour killing. In addition, avelumab has been shown to induce natural killer cell-mediated direct tumour cell lysis via ADCC *in vitro*.[46]
Marketing authorisation/CE mark status	Worldwide, avelumab is currently authorised in 52 countries across multiple indications: for the treatment of MCC, locally advanced or metastatic UC (second-line only in Canada, Israel and the USA), and aRCC (in combination with axitinib).[54] The EMA has approved avelumab as monotherapy for the treatment of adult patients with metastatic MCC, and in combination with axitinib for the first-line treatment of adult patients with aRCC.[46] A variation to the marketing authorisation for a new indication of maintenance therapy in UC was submitted to the EMA on 26 May 2020. Avelumab was granted positive EAMS scientific opinion by the MHRA on 1st September 2020, for the treatment of patients with locally advanced or metastatic UC.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated indication Avelumab is indicated as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy.
Method of administration and dosage	The recommended dose of avelumab as monotherapy is 800 mg administered intravenously over 60 minutes Q2W. Administration of avelumab should continue according to the recommended schedule until disease progression or unacceptable toxicity. Patients must be premedicated with an antihistamine and with paracetamol prior to the first four infusions of avelumab. If the fourth infusion is completed without an infusion related reaction, premedication for subsequent doses should be administered at the discretion of the physician.[46]
Additional tests or investigations	N/A
List price and average cost of a course of treatment	£768.00 per 200 mg vial, equating to a price of £3,072 for an 800 mg dose.
Patient access scheme (if applicable)	Simple PAS discount of [redacted] applied to the list price of avelumab

Abbreviations: ADCC = antibody dependent cell mediated cytotoxicity; aRCC = advanced renal cell carcinoma; EAMS = Early Access to Medicines Scheme; EMA = European Medicines Agency; IgG1 = immunoglobulin G1; MCC = Merkel cell carcinoma; mg = milligram; MHRA = Medicines and Healthcare products Regulatory Agency; N/A = not applicable; NK = natural killer; PAS = patient access scheme; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; Q2W = every 2 weeks; UC = urothelial carcinoma; USA = United States of America

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Bladder cancer consists of UC and non-urothelial cancers, of which UC is the most common type, accounting for over 90% of cases. Other forms of bladder cancer include squamous cell carcinomas (1.6%), adenocarcinomas (1.7%), and small-cell carcinomas (0.2%).[1]

UC originates in the urothelium or transitional epithelium, which is the innermost layer of the bladder,[55,56] and is caused by genetic alterations in urothelial cells.[57] Tobacco smoking is the major risk factor for bladder cancer, accounting for approximately 50% of cases (up to 65% and 30% of cases in males and females, respectively). The incidence of bladder cancer is directly related to the duration of smoking and the number of cigarettes smoked per day. Occupational exposure to chemicals is the second most important risk factor, and exposure to ionising radiation has also been associated with increased risk of bladder cancer.[58,59]

B.1.3.1.1 Staging

Bladder cancers are classified according to the level of primary tumour invasion, regional lymph node metastasis, and distant metastasis in accordance with the Tumour, Node, Metastasis Classification system (TNM), and grouped by stage (see Table B.1.3).[58,59] Non-muscle-invasive bladder cancer (NMIBC; Stage 0–I) is minimally invasive, and classified into one of three stages of tumour invasion (Ta, Tis, and T1). Muscle-invasive bladder cancer (MIBC; Stage II–III) is classified into higher stages of tumour invasion (T2 to T4a), ranging from superficial muscle invasion to more advanced invasion of the prostate, seminal vesicles, uterus or vagina.[58,59] Locally advanced or metastatic (Stage IV) bladder cancer includes disease that has invaded the pelvic or abdominal wall (T4b), has spread to one or more lymph nodes (N1–N3), or has metastasised to distant sites (M1).[58-60]

Table B.1.3. Staging of bladder cancer according to TNM classification

	Stage	TNM classification*		
NMIBC	Stage 0	Ta or Tis	N0	M0
	Stage I	T1	N0	M0
MIBC	Stage II	T2a–T2b	N0	M0
	Stage III	T3a–T3b, T4a	N0	M0
Locally advanced or metastatic bladder cancer	Stage IV	T4b Any T Any T	N0 N1–N3 Any N	M0 M0 M1

Abbreviations: MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle invasive bladder cancer; TNM = tumour, node, metastasis

*M0 = no distant metastasis; M1 = non-regional lymph node or other distant metastases; Ta = non-invasive papillary carcinoma; N0 = no regional lymph node metastasis; N1 = metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral); N2 = metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral); N3 = metastasis in common iliac lymph node(s); Tis = carcinoma in situ: 'flat tumour'; T1 = tumour invades subepithelial connective tissue; T2a = tumour invades superficial muscle (inner half); T2b = tumour invades deep muscle (outer half); T3a = tumour invades perivesical tissue (microscopically); T3b = tumour invades perivesical tissue (macroscopically [extravesical mass]); T4a = tumour invades prostate stroma, seminal vesicles, uterus or vagina; T4b = tumour invades pelvic wall or abdominal wall

Source: Bellmunt et al., 2014;[60] European Association of Urology, 2018;[58,59] Smolensky et al., 2016[61]

B.1.3.2 Epidemiology

In the United Kingdom (UK), the age-standardised bladder cancer incidence rate is 16.6 cases per 100,000 population, making it the eleventh most common cancer overall (3% of all new cancer cases between 2015 and 2017).[62] Bladder cancer is more common in men than in women (eighth and sixteenth most common cancer, respectively), and incidence is strongly related to age, with 56% of cases between 2015 and 2017 in people aged 75 and over.[62] The majority of bladder cancer cases are UC – 91.7% of cases in a UK study of 66,873 patients.[1]

In England, the National Cancer Registration and Analysis Service reported 8,686 cases of bladder cancer (International Classification of Disease, 10th Revision [ICD-10] C67) in 2017, of which 1,464 (16.9%) were Stage IV.[63] A non-interventional study that collected data from Public Health England's national cancer registry reported [redacted] (ICD-10 C65–68) between 2013 and 2017 [redacted]. Of these, there were [redacted] ([redacted]) adult patients with Stage IV UC,[2] equating to an annual incidence of approximately [redacted] cases per year. In addition, approximately 10–15% and 50% of patients diagnosed at Stage I and Stages II–III, respectively are estimated to progress to Stage IV disease.[64,65]

B.1.3.3 Symptomatology and clinical presentation

Patients with UC often present with painless macroscopic haematuria (visible blood in the urine).[66] This may be accompanied by dysuria (pain or discomfort during urination) and urinary storage symptoms[66]. Less commonly, the presenting symptom is a urinary tract infection.[67]

Patients with early disease may have no apparent symptoms, and the symptoms of UC can be inconsistent. As such, diagnosis may not occur until the disease is locally advanced or metastatic.[66] Patients with advanced disease may present with upper tract obstruction or pain, and may experience symptoms due to the spread or metastasis of the disease, which can include flank pain from retroperitoneal muscle-invasive disease, obstruction of the ureter from bladder or regional invasion, or bone pain.[66,67]

B.1.3.4 Burden to patients, carers and society

B.1.3.4.1 Mortality burden

In England and Wales, there were 4,825 bladder cancer deaths in 2018, accounting for 3.2% of all cancer deaths. The estimated age-standardised mortality rates in 2018 were 14.0 per 100,000 population for men and 4.7 per 100,000 population for women.[3] Bladder cancer mortality is strongly related to age, and age-specific mortality rates rise steeply (more so in males) from approximately age 55–59 years.[68]

Survival is especially poor in patients with locally advanced or metastatic bladder cancer (Table B.1.4). Among patients diagnosed between 2013 and 2017 in England, the one-year survival rate decreased from 95.3% for those diagnosed at Stage I, to 35.7% at Stage IV. Similarly, five-year survival rates decreased from 79.4% for Stage I, to 41.2% for Stage III, however Stage IV data are not available for England.[5] In Northern Ireland, 4.7% of patients diagnosed at Stage IV between 2005 and 2012 survived beyond five years,[4] and similar five-year survival rates have been reported in the US (4.6%)[6] and Australia (4.6%).[7] The median survival for adult patients in England diagnosed with Stage III–IV UC between 2013 and 2017 was [redacted] months (95% confidence interval [CI]: [redacted], [redacted]).[2]

Table B.1.4. Bladder cancer survival rates (patients diagnosed between 2013 and 2017 in England)

	OS rate, %			
	Stage I	**Stage II**	**Stage III**	**Stage IV**
One-year	95.3	74.2	68.8	35.7
Five-year	79.4	45.7	41.2	Not available

Abbreviations: OS = overall survival
Source: Office for National Statistics, 2019[5]

B.1.3.4.2 Humanistic burden

In addition to high levels of mortality, bladder cancer is associated with a significant humanistic burden.[8-10] In a 2012 analysis, bladder cancer was associated with 69,591 disability-adjusted life years in the UK.[69] The burden of bladder cancer symptoms and poor prognosis associated with bladder cancer results in a significant negative impact on physical, mental and social quality of life (QoL), which deteriorates further in more advanced cases.[10] Significant health-related quality of life (HRQoL) decrements have been demonstrated across domains and summary scores, including physical functioning/role, general health, social functioning, and vitality.[10]

Current treatment options for locally advanced or metastatic UC are frequently associated with high levels of adverse events (AEs) and reduced HRQoL.[70] Although the nature and toxicity of treatments vary, there is evidence that treatment can impact urinary,[71] bowel,[72] and sexual function,[73,74] which can lead to anxiety and depression.[72] A study conducted in England on long-term HRQoL in individuals 1–5 years post diagnosis of bladder cancer identified that reduced HRQoL is common following bladder cancer treatment.[70]

B.1.3.4.3 Economic burden

Bladder cancer is associated with a significant economic burden; driven by high recurrence rates and treatment costs.[75] In a study of annual costs associated with bladder cancer across the European Union, the estimate of total healthcare expenditure, productivity losses and informal care costs in the UK in 2012 was €543 million (£438 million), representing 5% of total cancer-related healthcare costs and 3% of all cancer costs. Total healthcare costs comprised inpatient (53.4%), outpatient (25.0%), medication (18.8%), accident and emergency (1.5%), and primary care (1.3%) costs.[69]

B.1.3.5 Clinical pathway of care

B.1.3.5.1 Diagnostic pathway

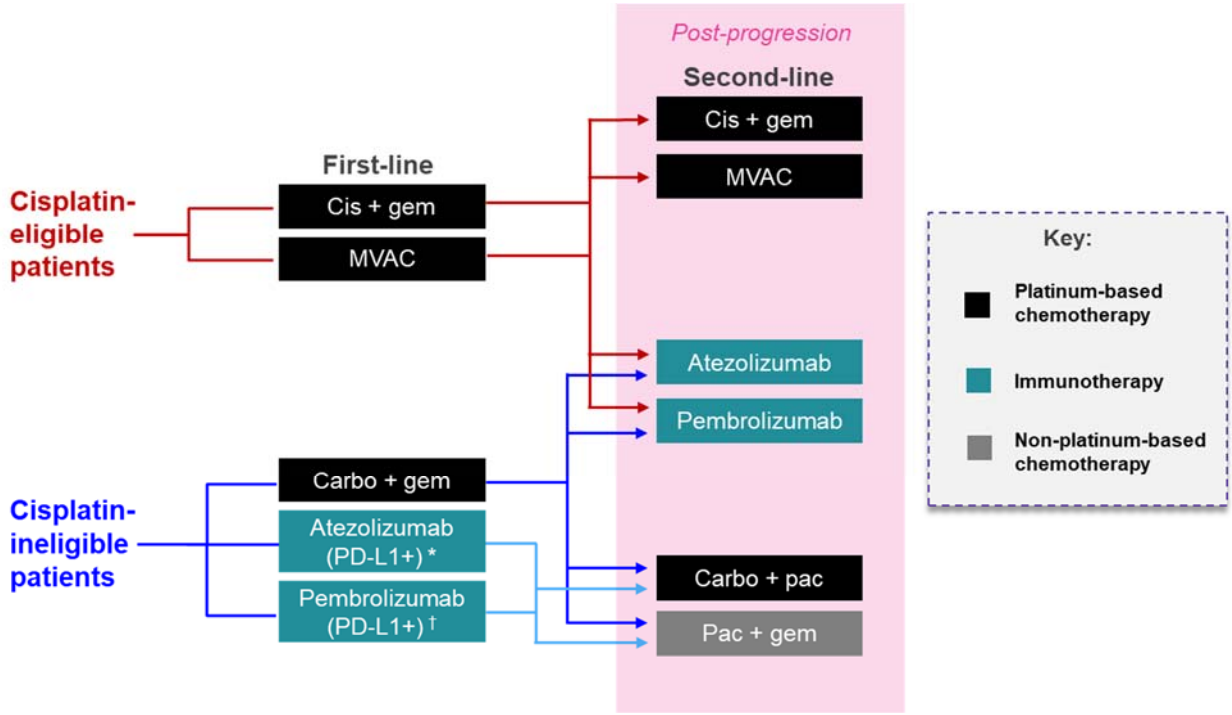
At present, there is no screening programme in place for detecting bladder cancer in the UK, and cases are usually identified on the basis of painless macroscopic haematuria.[11] Upon presentation, patients are referred for urine cytology, cystoscopy, and upper tract imaging to identify the presence of a lesion.[67] Transurethral resection of bladder tumour is performed to resect all visible tumour and to sample bladder muscle to identify possible invasion.[11] National Institute for Health and Care Excellence (NICE) guidelines recommend either computerised tomography or magnetic resonance staging if MIBC is suspected at cystoscopy.[11]

B.1.3.5.2 Treatment pathway

The goal of treatment for patients with locally advanced or metastatic UC is to prevent disease progression, maintain HRQoL, provide relief from cancer symptoms, and extend life. However, treatment options are limited, with systemic platinum-based chemotherapy regimens being the current standard of care in the UK.[11] While the role of immunotherapy was first established in NMIBC in the 1970s, no systemic immunotherapy was licensed for advanced disease until the approval of the PD-1/PD-L1 inhibitors atezolizumab, pembrolizumab and nivolumab.[67,76-78] While the development of these targeted immuno-oncology (IO) agents represents a significant milestone after a void of new treatment options for over 30 years, their use is limited either to treatment of cisplatin-ineligible patients with tumours that express PD-L1, or second-line treatment after failure of platinum-based chemotherapy.[76-78]

The current treatment pathway for patients with locally advanced or metastatic UC and a summary of NICE guidelines are presented in Figure B.1.2 and Table B.1.5, respectively. In treatment-naïve patients with confirmed locally advanced or metastatic UC, NICE guidelines recommend a cisplatin-based chemotherapy regimen.[11] Patients who are ineligible for cisplatin-based therapy because of poor performance status, inadequate renal function or other comorbidities may receive carboplatin-based regimens or, if their tumours express PD-L1, atezolizumab or pembrolizumab (both via the Cancer Drugs Fund [CDF]).[11,79,80] Cisplatin-ineligible patients with low PD-L1 tumour expression are not eligible for first-line immunotherapy, and are limited to first-line carboplatin-based regimens.[11,77,78]

Figure B.1.2. Treatment pathway for locally advanced or metastatic UC in England



Abbreviations: carbo = carboplatin; cis = cisplatin; gem = gemcitabine; MVAC = methotrexate, vinblastine, adriamycin and cisplatin; pac = paclitaxel; PD-L1 = programmed death-ligand 1; UC = urothelial carcinoma
*PD-L1 expression ≥5%; †PD-L1 with a combined positive score ≥10
Source: Merck Sharp & Dohme Ltd, 2019;[77] NICE, 2015;[11] NICE, 2018;[79] NICE, 2018;[80] NICE, 2018;[81] Roche Registration GmbH, 2020[78]

Table B.1.5. Summary of NICE guidance for first- and second-line treatment of locally advanced or metastatic UC

Line of treatment	Treatment	NICE guidance
First-line	Cisplatin-based chemotherapy	Offer a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] MVAC in combination with G-CSF) to people with locally advanced or metastatic urothelial bladder cancer who are otherwise physically fit (have an ECOG PS of 0 or 1) and have adequate renal function (typically defined as a GFR of ≥60 ml/min/1.73m^2)[11]
	Carboplatin + gemcitabine	Offer carboplatin + gemcitabine to people with locally advanced or metastatic urothelial bladder cancer with an ECOG PS of 0–2 if a cisplatin-based chemotherapy regimen is unsuitable, for example, because of poor ECOG performance status, inadequate renal function (typically defined as GFR of <60 ml/min/1.73m^2) or comorbidity[11]
	Pembrolizumab	Pembrolizumab is recommended for use within the CDF as an option for untreated locally advanced or metastatic UC in adults when cisplatin-containing chemotherapy is unsuitable, only if: • Their tumours express PD-L1 with a CPS ≥10 • Pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses; and, • The conditions of the managed access agreement for pembrolizumab are followed[80]

	Atezolizumab	Atezolizumab is recommended for use within the CDF as an option for untreated locally advanced or metastatic UC in adults when cisplatin-containing chemotherapy is unsuitable, only if: • Their tumours express PD-L1 at a level of ≥5%; and, • The conditions of the managed access agreement for atezolizumab are followed[79]
Second-line	Gemcitabine + cisplatin	For people with incurable locally advanced or metastatic urothelial bladder cancer whose condition has progressed after first-line chemotherapy if: • Their renal function is adequate (typically defined as a GFR of ≥60 ml/min/1.73m^2) and • They are otherwise physically fit (have an ECOG PS of 0–1)[11]
	Accelerated (high-dose) MVAC + G-CSF	For people with incurable locally advanced or metastatic urothelial bladder cancer whose condition has progressed after first-line chemotherapy if: • Their renal function is adequate (typically defined as a GFR of ≥60 ml/min/1.73^{m2}) and • They are otherwise physically fit (have an ECOG PS of 0– 1)[11]
	Carboplatin + paclitaxel	For people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it[11]
	Gemcitabine + paclitaxel	For people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it[11]
	Vinflunine	Not recommended, within its marketing authorisation, for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy[82]
	Atezolizumab	Treating locally advanced or metastatic UC in adults who have had platinum-containing chemotherapy, only if: • Atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, and • The company provides atezolizumab with the discount agreed in the patient access scheme[81]
	Nivolumab	Not recommended, within its marketing authorisation, for treating locally advanced unresectable or metastatic UC in adults who have had platinum-containing therapy[83]
	Pembrolizumab	Pembrolizumab is recommended for use within the CDF as an option for treating locally advanced or metastatic UC in adults who have had platinum-containing chemotherapy, only if: • Pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression; and • The conditions in the managed access agreement for pembrolizumab[84]

Abbreviations: CDF = Cancer Drugs Fund; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte-colony stimulating factor; GFR = glomerular filtration rate; m = metre; min = minute; ml = millilitre; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death-ligand 1; PS = performance status; UC = urothelial carcinoma

In a survey of [redacted] UK oncologists, of the estimated [redacted] patients treated for advanced UC within the last year, [redacted] received first-line treatment with gemcitabine + cisplatin, [redacted] received gemcitabine + carboplatin, and [redacted] and [redacted] received pembrolizumab and atezolizumab, respectively.[85,86]

Options for patients who relapse after first-line therapies are limited. For those whose disease progresses following treatment with platinum-based chemotherapy, the only recommended

second-line treatment options are further platinum-based chemotherapy, gemcitabine + paclitaxel, atezolizumab and pembrolizumab (via the CDF).[11,81,84] For cisplatin-ineligible patients who received first-line immunotherapy, second-line treatment options are limited to paclitaxel in combination with carboplatin or gemcitabine.[11]

B.1.3.6 Unmet need

Currently, there is considerable variation across the National Health Service (NHS) in the diagnosis and management of bladder cancer, and there is evidence that the patient experience for people with bladder cancer is worse than that for those with other cancers.[11]

In England, cisplatin-based regimens are the standard of care in previously untreated patients with locally advanced or metastatic UC who are fit enough to tolerate cisplatin.[11] The majority of patients with locally advanced or metastatic UC respond to first-line platinum-based chemotherapy, with reported objective response rates of 24–70%, and complete and partial response rates of up to 29% and 55%, respectively.[12-36] However, durable responses following first-line chemotherapy are uncommon; complicated treatment regimens and severe side effects limit long-term use of these agents and most patients will ultimately experience disease progression.[37,38] In addition, platinum-based chemotherapy can cause substantial side effects, including nephrotoxicity, neuropathy, bone marrow suppression (thrombocytopenia, leukopenia) and gastrointestinal toxicities,[14,21,87,88] limiting repeated use to those patients able to tolerate multiple rounds of chemotherapy.

A summary of outcomes from studies of first- and second-line therapies for locally advanced or metastatic UC (based on the highest level of available evidence) is presented in Table B.1.6. Phase 3 randomised controlled trials have reported median progression-free survival (PFS) and overall survival (OS) of 7.4–9.9 months and 12.5–18.0 months, respectively, for first-line cisplatin-based regimens,[14,18,20-22,32,37] and 5.8 months and 9.3 months, respectively, for first-line carboplatin + gemcitabine.[87] Similarly, in a meta-analysis of seven Phase 2 and 3 studies of cisplatin-based chemotherapy in metastatic UC, the median PFS was 8.2 months and the median OS was 13.5 months.[89] Outcomes in single-arm studies of atezolizumab and pembrolizumab have been similar to those observed with first-line chemotherapy (median PFS and OS of 4.1–4.9 months and 12.3–18.5 months, respectively).[90-92] Furthermore, recent Phase 3 data have failed to demonstrate superiority of atezolizumab or pembrolizumab over first-line chemotherapy in extending OS.[93,94] Outcomes for patients whose disease progresses after first-line chemotherapy are also ultimately poor,[38,95] with median PFS and OS for second-line therapies in clinical trials of 2.1–5.3 months and 7.9–10.9 months, respectively.[96-99]

Table B.1.6. Survival outcomes for first-and second-line therapies for locally advanced or metastatic UC

Line of treatment	Treatment	Median OS, months	Median PFS, months
First-line	Cisplatin + gemcitabine[14,18,37]	12.7–18.0	7.4–7.8
	MVAC[20-22,32,37]	12.5–15.4	7.4–9.9
	Carboplatin + gemcitabine[87]	9.3	5.8
	Atezolizumab*[90]	12.3	4.1
	Pembrolizumab*[91,92]	18.5	4.9
Second-line	MVAC[98]	10.9	5.3
	Carboplatin + paclitaxel[99]	7.9	3.7
	Atezolizumab†[96,97]	7.9	2.1
	Pembrolizumab†[100]	10.1	2.1

Abbreviations: OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival
*Cisplatin-ineligible patients with PD-L1-positive tumours (in accordance with the licensed indications of atezolizumab and pembrolizumab)[77,78]; †Patients who have progressed following platinum-based chemotherapy, regardless of PD-L1 expression status (in accordance with the licensed indication of atezolizumab and pembrolizumab)[78]

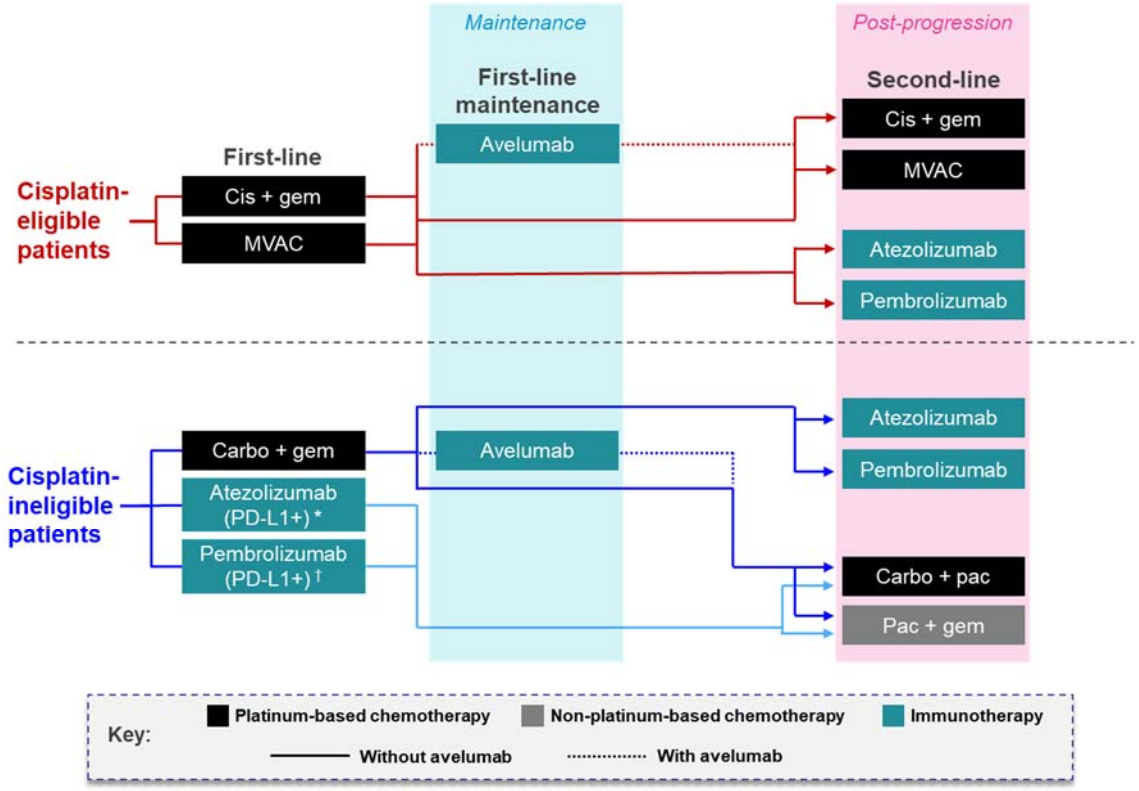
In conclusion, first-line chemotherapy for patients with locally advanced or metastatic UC is associated with short response duration and poor survival, and a clear unmet need exists for maintenance therapy following first-line chemotherapy. Response to first-line therapy is a predictor of long-term outcomes in a number of cancers, including UC;[101-106] therefore, a maintenance therapy that sustains and/or improves response to first-line treatment may significantly improve survival outcomes for patients with locally advanced or metastatic UC.[47] In addition, second- and subsequent-line treatment options are limited and associated with poor outcomes and significant toxicities. This may be particularly detrimental in this patient population, who are generally older and likely to have high rates of comorbidities,[68,107] and may therefore not be suitable for second-line chemotherapy (clinical expert opinion indicates that only 50–60% of patients who receive first-line treatment are eligible for second-line therapy).[108] As such, a maintenance therapy that prevents or delays the need for second-line treatment, and the associated AEs, is therefore also an important unmet need.

B.1.3.7 Place of avelumab in the treatment pathway

Maintenance therapies are already an effective approach in multiple cancers, including lung, colorectal and ovarian cancers, lymphomas, and squamous cell carcinoma of the head and neck.[39-45] However, there are currently no approved maintenance treatment options for patients with locally advanced or metastatic UC. Therefore, a 'watchful waiting' approach must be taken, with patients who experience disease recurrence after first-line therapy managed with second-line treatments (if eligible and fit enough to tolerate further treatment).

Avelumab is the first and only maintenance treatment in the first-line setting to demonstrate a statistically significant improvement in OS for patients with locally advanced or metastatic UC in a Phase 3 trial, sustaining the benefit of first-line platinum-based chemotherapy (see Section B.2.6.1).[47] Avelumab maintenance therapy is expected to provide an additional novel treatment approach, as an alternative to watchful waiting. As such, avelumab may contribute to addressing the critical unmet need for a therapy that improves survival outcomes while maintaining HRQoL for patients with locally advanced or metastatic UC.[47,109]

Figure B.1.3. Proposed treatment pathway for locally advanced or metastatic UC (with avelumab)



Abbreviations: carbo = carboplatin; cis = cisplatin; gem = gemcitabine; MVAC = methotrexate, vinblastine, adriamycin and cisplatin; pac = paclitaxel; PD-L1 = programmed death-ligand 1; UC = urothelial carcinoma
*PD-L1 expression ≥5%; †PD-L1 with a combined positive score ≥10
Source: Merck Sharp & Dohme Ltd, 2019;[77] NICE, 2015;[11] NICE, 2018;[79] NICE, 2018;[80] NICE, 2018;[81] Roche Registration GmbH, 2020[78]

B.1.4 Equality considerations

There are no known equality issues relating to the use of avelumab in patients with locally advanced or metastatic UC.

B.2. Clinical effectiveness

Executive summary

JAVELIN Bladder 100

- The clinical effectiveness of avelumab for the first-line maintenance treatment of locally advanced or metastatic urothelial carcinoma (UC) has been established in the pivotal Phase 3 Study B9991001 (JAVELIN Bladder 100)[47]
- There were four trial sites in the UK (all located in England), and the study enrolled patients representative of those who would receive avelumab as a maintenance treatment in the first-line setting within routine clinical practice in the UK.[110]
- JAVELIN Bladder 100 is currently ongoing; results of the pre-planned interim analysis demonstrate that, compared with best supportive care alone (BSC), avelumab + BSC provides a clinically meaningful benefit to patients with locally advanced or metastatic UC.[47]

Efficacy

- JAVELIN Bladder 100 met its primary objective and demonstrated a significant improvement in overall survival (OS) in all randomised patients:
  - A clinically meaningful and statistically significant improvement in OS was observed, with a 31% reduction in the risk of death in favour of avelumab + BSC (N=700; two-sided p=0.001) compared with BSC alone. The median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus+ BSC arm (N=350), and 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm (N=350).[47]
- Secondary efficacy analyses supported the primary efficacy analysis:
  - Patients assigned to avelumab + BSC had an improvement in progression-free survival (PFS), with a 38% reduction in the risk of progression or death compared with patients assigned to BSC alone (two-sided p<0.0001). The median PFS for avelumab + BSC was 3.7 months (95% CI: 3.5, 5.5) and for BSC alone was 2.0 months (95% CI: 1.9, 2.7)[47,111]
  - Despite no active anti-cancer treatment in the BSC arm, patient reported outcomes (PROs) indicated that overall health status and health-related quality of life in patients treated with avelumab + BSC arm were similar to those assigned to BSC alone.[109]

Safety

- As expected for a trial comparing an immunotherapy with BSC alone, a higher incidence of treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) were observed for avelumab + BSC compared with BSC alone:
  - TEAEs: 98.0% (47.4% Grade ≥3) and 77.7% (25.2% Grade ≥3) in the avelumab + BSC and BSC alone arms, respectively. No individual TEAE (preferred term) had an incidence of ≥20% in the avelumab + BSC arm[47]
  - TRAEs: 77.3% (16.6% Grade ≥3) and 1.2% (0% Grade ≥3) in the avelumab + BSC arm and BSC arm, respectively.[47]

- Immune-related AEs (irAEs) were also higher in the avelumab + BSC arm, compared with BSC alone (29.4% [7.0% Grade ≥3] and 1.4% [0.3% Grade ≥3]), respectively, and infusion-related reactions (IRRs) were reported only in the avelumab + BSC arm (composite term: 21.5% [0.9% Grade ≥3]; preferred term: 10.2% [0.9% Grade ≥3]).[47,110]
  - No Grade 4 or 5 irAEs or IRRs were reported in the study.[47]
- A higher number of fatal TEAEs were reported in the BSC alone arm (7.0%) compared with the avelumab + BSC arm (1.2%), with disease progression being the most common cause of death for both avelumab + BSC (0.9%) and BSC alone (4.6%). Two deaths were considered to be related to avelumab by the investigator (sepsis [0.3%] and ischemic stroke [0.3%]), but were not considered to be treatment-related by the study sponsor.[47,110]
- Overall, the safety profile of avelumab observed in JAVELIN Bladder 100 was tolerable, manageable, and consistent with prior experience in the JAVELIN Solid Tumor and JAVELIN Merkel 200 (N=1,738) studies, along with data from [redacted] patient-years of post-authorisation exposure in patients with Merkel cell carcinoma, UC and advanced renal cell carcinoma (in combination with axitinib).[46,47,54]
  - No new safety concerns were identified in patients with locally advanced or metastatic UC who received maintenance treatment with avelumab.[47]

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify and summarise the available randomised controlled trial (RCT) evidence for the current and future treatment options for previously untreated patients with locally advanced or metastatic UC. Full details of SLR are included in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The efficacy of avelumab has been evaluated in the pivotal Phase 3 JAVELIN Bladder 100 study (Table B.2.1; Section B.2.3).[47]

Table B.2.1. Clinical effectiveness evidence

Study	JAVELIN Bladder 100 (Study B9991001; NCT02603432)				
Study design	Phase 3, randomised, open-label, parallel two-arm, multicentre study				
Population	Locally advanced or metastatic UC that did not worsen during or following completion of first-line platinum-based chemotherapy				
Intervention(s)	Avelumab 10 mg/kg Q2W (4-week cycle) + BSC (N=350)				
Comparator(s)	BSC alone				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	N/A				
Reported outcomes specified in the decision problem	**OS**, **PFS**, response rates, **HRQoL**, **adverse effects of treatment**				
All other reported outcomes	TTR, DOR, DC, SAEs, vital signs, physical examination, ECOG PS, ECG, laboratory assessments, PK, ADA, biomarkers				

Abbreviations: ADA = anti-drug-antibodies; DC = disease control; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PS = performance status; PROs = patient-reported outcomes; SAEs = serious adverse events; TTR = time to tumour response; UC = urothelial carcinoma
Source: Pfizer Inc., 2015;[112] Powles et al., 2020[47]

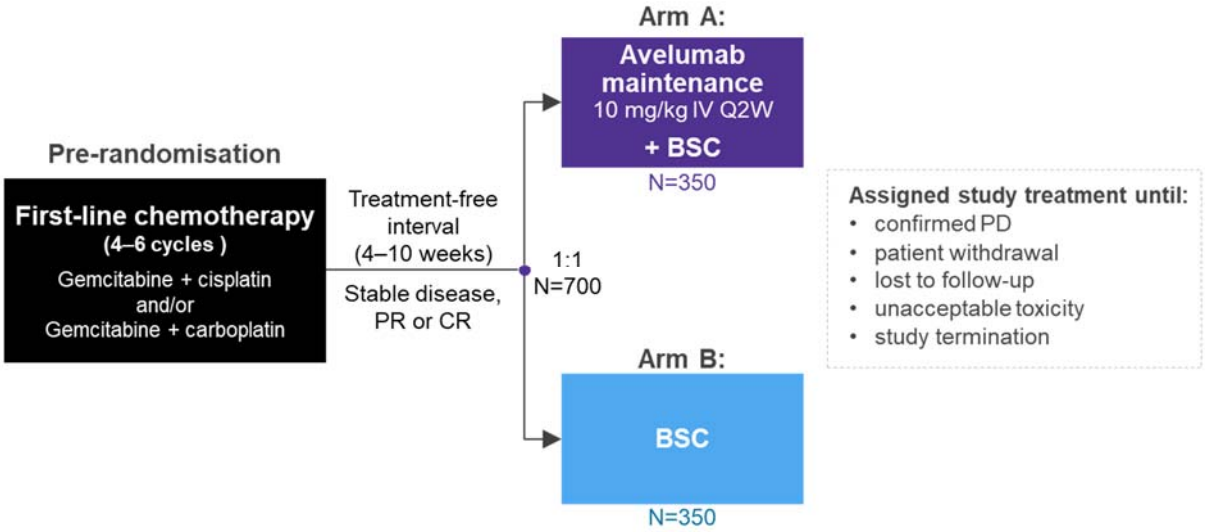
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study design and objectives

JAVELIN Bladder 100 is an ongoing Phase 3, randomised, open-label, parallel two-arm study of avelumab + best supportive care (BSC) versus BSC alone as maintenance treatment in the first-line setting for patients with locally advanced or metastatic UC, whose disease did not progress following first-line platinum-based chemotherapy (gemcitabine + cisplatin and/or gemcitabine + carboplatin). The study was designed with two co-primary populations: 1) all randomised patients and 2) patients with PD-L1-positive tumours (including infiltrating immune cells)[47,112] The study objective was to demonstrate the benefit of maintenance treatment with avelumab + BSC in prolonging OS in patients with locally advanced or metastatic UC.[112]

Summaries of JAVELIN Bladder 100 study design and methodology are presented in Figure B.2.1 and Table B.2.2, respectively.

Figure B.2.1. JAVELIN Bladder 100 study design



Abbreviations: BSC = best supportive care; CR = complete response; IV = intravenous; kg = kilogram; mg = milligram; N = number of patients evaluable; PD = progressive disease; PR = partial response; Q2W = every 2 weeks
*BSC included care as deemed appropriate by the treating physician, including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), but not active anti-tumour therapy
Source: Powles et al., 2020;[111] Powles et al., 2020[47]

Table B.2.2. Summary of methodology of JAVELIN Bladder 100

Study design	Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised (1:1) study
Locations (number of patients recruited)	700 subjects were randomised across 29 countries: Canada (15), United States (19), Hong Kong (2), India (6), Japan (73), Korea (45), Taiwan (21), Australia (59), New Zealand (12), Czech Republic (1), Hungary (1), Poland (5), Russian Federation (17), Serbia (10), Argentina (4), Brazil (13), Mexico (7), Israel (7), Belgium (24), Denmark (23), France (85), Greece (25), Italy (62), Netherlands (15), Norway (7), Portugal (6), Spain (110), Sweden (7), United Kingdom (19)
Study status	Ongoing • First subject first visit: 28 April 2016 • Data cut-off date: 21 October 2019 (IA)
Key eligibility criteria	• Aged ≥18 years (≥20 years in Japan) • Histologically confirmed unresectable locally advanced or metastatic UC • Prior first-line chemotherapy consisting of 4–6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin (no other chemotherapy regimens allowed) • Stage IV disease at the start of first-line chemotherapy and measurable disease (according to RECIST v1.1) prior to the start of first-line chemotherapy • Absence of PD according to RECIST v1.1 • Life expectancy ≥3 months • ECOG PS 0 or 1 • Adequate bone marrow, renal, and liver functions
Study treatments	Arm A: avelumab + BSC (n=350) Arm B: BSC alone (n=350)
Concomitant medication	Permitted:

	• Treatments intended solely for BSC • Recommended medications to treat infusion-related reactions, hypersensitivity reactions and flu-like symptoms, tumour lysis syndrome, and irAE • Growth factors (erythropoietin and darbepoietin alpha only) • Inactive influenza vaccine Disallowed: • Anti-cancer therapy with an agent other than avelumab within arm A • Anti-tumour radiotherapy • Any vaccine therapies for the prevention of infectious disease within 4 weeks of start of study treatment (except administration of the inactive influenza vaccine) • Bisphosphonate or denosumab (unless initiated >14 days prior to the first dose of study treatment) • Growth factors (specifically, G-CSF and GM-CSF) • Herbal remedies with immune-stimulating properties (e.g. mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin)
Primary outcomes	• OS in all randomised patients • OS in patients with PD-L1-positive tumours
Secondary outcomes	Based on BICR assessment according to RECIST v1.1: • PFS • OR • TTR • DOR • DC
PROs	• NCCN FBISI-18 • EQ-5D-5L
Safety outcomes	• AEs • SAEs
Pre-planned subgroups	OS, PFS, and OR by: • Best response to first-line chemotherapy (CR or PR vs stable disease) • Site of metastasis (visceral vs non-visceral) • Age (<65 years, ≥65 years) • Gender (male, female) • Race (white, Asian, other) • Pooled geographic region (Europe, North America, Asia, Australasia, Rest of the World) • PD-L1 status at baseline (positive, negative, unknown) • First-line chemotherapy regimen (gemcitabine + cisplatin, gemcitabine + carboplatin, gemcitabine + cisplatin and gemcitabine + carboplatin) • ECOG performance status (0, ≥1) • Creatinine clearance at baseline (≥ 60 ml/min, <60 ml/min) • Liver lesions at baseline (yes, no) • Lung lesions at baseline (yes, no)

Abbreviations: AE = adverse event; BSC = best supportive care; BICR = blinded independent central review; DC = disease control; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQoL 5-Dimension 5-Level; FBISI-18 = Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index; G-CSF = granulocyte colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IA= interim analysis; irAE = immune-related adverse event; NCCN = National Comprehensive Cancer Network; OS = overall survival; OR = objective response; PD = progressive disease; PFS = progression-free survival; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TTR = time to tumour response; UC = urothelial carcinoma; vs= versus
Source: Pfizer Inc., 2015;[112] Pfizer Inc., 2019;[113] Powles et al., 2020[47]

B.2.3.2 Eligibility criteria

Patients included in the study met the following inclusion criteria:

- A histologically confirmed diagnosis of unresectable locally advanced or metastatic UC, with documented Stage IV disease at the start of first-line chemotherapy and measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) prior to the start of first-line chemotherapy
- Prior first-line chemotherapy consisting of 4–6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin (no other chemotherapy regimens were allowed), with the last dose of chemotherapy received no less than 4 weeks, and no more than 10 weeks, prior to randomisation
- Absence of progressive disease (PD) according to RECIST v1.1 (i.e. an ongoing complete response [CR], partial response [PR] or stable disease) following first-line chemotherapy
- Aged ≥18 years (≥20 years in Japan)
- Estimated life expectancy of at least 3 months
- ECOG PS of 0 or 1
- Adequate bone marrow, renal, and liver functions.[47,112]

Patients with any of the following characteristics/conditions were excluded from the study:

- Patients whose disease progressed (according to RECIST v1.1) on or after first-line chemotherapy for UC
- Prior adjuvant or neoadjuvant systemic therapy within 12 months of randomisation
- Prior immunotherapy with interleukin-2, interferon-α, or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or CTLA-4 (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
- Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to randomisation. Prior palliative radiotherapy is permitted, provided it has been completed at least 48 hours prior to randomisation
- Patients with known symptomatic central nervous system (CNS) metastases requiring steroids. Patients with previously diagnosed CNS metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to randomisation, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.[47,112]

B.2.3.3 Study treatment

B.2.3.3.1 Allocation to treatment

Patients were randomised in a 1:1 ratio to receive avelumab + BSC or BSC alone. Randomisation was stratified by best response to first-line chemotherapy (CR/PR versus stable disease), and metastatic disease site (visceral versus non-visceral) at the time of initiating first-line chemotherapy.[47,112]

B.2.3.3.2 Treatments administered

Avelumab was administered at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks. Patients continued to receive avelumab until confirmed disease progression, patient withdrawal, loss to follow-up, or unacceptable toxicity.[47,112]

BSC included care as deemed appropriate by the treating physician. This could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), but not active anti-tumour therapy. However local radiotherapy of isolated lesions with palliative intent is acceptable.[47,112]

B.2.3.3.3 Dose modification

No avelumab dose modifications were permitted, but infusions could be omitted due to persisting toxicity.[47,112]

B.2.3.3.4 Concomitant therapies

A summary of allowed and disallowed concomitant therapies is shown in Table B.2.3.

Table B.2.3. Allowed and disallowed concomitant therapies

Allowed	• Treatments intended solely for BSC are allowed, including: o Antibiotics o Nutritional support o Correction of metabolic disorders (e.g. megestrol for anorexia) o Local radiotherapy of isolated lesions with palliative intent) o Antiemetics o Analgesics o Anticoagulant therapy (Heparin) • Recommended medications to treat infusion-related reactions, hypersensitivity reactions and flu-like symptoms, tumor lysis syndrome, and irAE: o Short-term administration of systemic steroids (e.g. for allergic reactions or the management of irAEs) o Topical, oral, intravenous, or inhaled steroids o Antihistamines o NSAIDs • Growth factors: o Erythropoietin o Darbepoietin alpha only • Only a single vaccine was permitted (inactive influenza vaccine)
Disallowed	• Anti-cancer therapy with an agent other than avelumab within arm A • Anti-tumour radiotherapy • Any vaccine therapies for the prevention of infectious disease within 4 weeks of start of study treatment (except administration of the inactive influenza vaccine) • Bisphosphonate or denosumab (unless initiated >14 days prior to the first dose of study treatment) • Growth factors: o G-CSF o GM-CSF • Herbal remedies with immunostimulating properties (e.g. mistletoe extract) or known to potentially interfere with major organ function (e.g. hypericin)

BSC = best supportive care; G-CSF = granulocyte colony stimulating factor; GM-CSF = granulocyte macrophage colony stimulating factor; irAE = immune-related adverse event; NSAID = Non-steroidal anti-inflammatory drugs
Source: Pfizer Inc., 2015[112]

B.2.3.4 Assessments and outcomes

B.2.3.4.1 Survival status

Survival status was monitored during study treatment and every 30 days (±3 days) during an initial 90-day follow-up period. Subsequently, survival information was collected every 3 months (±14 days) until death, end of the study, or patient withdrawal of consent, whichever came first, regardless of initiation of new anti-cancer therapy(ies).[112]

B.2.3.4.2 Tumour assessments

Anti-tumour activity was assessed by radiological tumour assessments according to RECIST v1.1 for secondary endpoints. Imaging was conducted at baseline, at 8 weeks after randomisation, then every 8 weeks for up to 1 year from randomisation, and every 12 weeks thereafter until documented disease progression (assessed by blinded independent central review [BICR]) regardless of initiation of subsequent anti-cancer therapy.[112]

B.2.3.4.3 Efficacy outcomes

The primary efficacy endpoint was OS. Secondary efficacy endpoints included:

- PFS based on BICR assessment according to RECIST v1.1
- Objective response (OR), defined as CR or PR, based on BICR assessment according to RECIST v1.1
- Time to tumour response (TTR) based on BICR assessment according to RECIST v1.1
- Duration of response (DOR) based on BICR assessment according to RECIST v1.1
- Disease control (DC), defined as CR, PR, stable disease or non-CR/non-PR, based on BICR assessment according to RECIST v1.1
- Patient reported outcomes (PROs), including:
  - Bladder cancer symptoms, functioning, global QoL and time to deterioration (TTD) using the NCCN Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index (FBlSI-18)
  - Patient-reported health status using the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire.[47,112]

B.2.3.4.4 Safety outcomes

Safety outcomes included AEs and SAEs. AEs (serious and non-serious) were recorded from the time a patient took at least one dose of study treatment (avelumab + BSC arm) or from Cycle 1 Day 1 (BSC alone arm) through to, and including, 90 calendar days after the last administration of study treatment (avelumab + BSC arm) or 90 days after the end-of-treatment visit (BSC alone arm).[47,112]

B.2.3.5 Study population

B.2.3.5.1 Disposition

Between 11 May 2016 and 4 June 2019, 700 patients were randomised (350 to the avelumab + BSC arm and 350 to the BSC alone arm).[47]

As of the data cut-off date (21 October 2019), 265 (75.7%) patients had discontinued in the avelumab + BSC arm and 324 (92.6%) patients had discontinued in the BSC arm. The most frequent cause of discontinuation was disease progression; 189 (54.0%) patients in the avelumab + BSC arm and 263 (75.1%) patients in the BSC arm discontinued due to PD.[110,111] Patient disposition at the end of treatment is shown in Table B.2.4.

Table B.2.4. Patient disposition at end of treatment (FAS)

Endpoint	All patients (N=700)	
	Avelumab + BSC (N=350)	BSC (N=350)
Discontinued, n (%)	265 (75.7)	324 (92.6)
Death	5 (1.4)	14 (4.0)
PD	189 (54.0)	263 (75.1)
AE	39 (11.1)	2 (0.6)
Non-compliance with study drug	1 (0.3)	0 (0.0)
Physician's decision	5 (1.4)	7 (2.0)
No longer meets eligibility criteria	3 (0.9)	0 (0.0)
Global deterioration of health status	4 (1.1)	6 (1.7)
Withdrawal by patient	16 (4.6)	29 (8.3)
Lost to follow-up	2 (0.6)	2 (0.6)
Ongoing, n (%)	85 (24.3)	26 (7.4)

Abbreviations: AE = adverse event; BSC = best supportive care; FAS = full analysis set; n = number of patients in the category; N = number of patients evaluable; PD = progressive disease
Source: Pfizer Inc., 2020[110]

B.2.3.5.2 Data sets analysed

A summary of analysis data sets is provided in Table B.2.5.

Table B.2.5. Analysis data sets

Analysis set	Avelumab + BSC	BSC alone	Total
FAS, n	350	350	700
SAS, n (%)	344 (98.3)	345 (98.6)	689 (98.4)
PP analysis set, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: FAS = full analysis set; n = number of patients in the category; OS = overall survival; PFS = progression-free survival; PP= per protocol; SAS = safety analysis set
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.2.3.5.3 Demographics and baseline characteristics

Demographics and baseline characteristics were balanced between the two treatment arms. At baseline, the majority of patients entered the study following a CR or PR to first-line chemotherapy (72.1% [n=505] of all patients), while the remaining had stable disease (27.9% [n=195] of all patients).[47] The median time from diagnosis to randomisation in JAVELIN Bladder 100 was [redacted] months and [redacted] months in the avelumab + BSC and BSC alone arms, respectively.[110]

Demographic, baseline and disease characteristics are summarised in Table B.2.6

Table B.2.6. Demographics, baseline and disease characteristics (FAS)

Endpoint	All patients (N=700)	
	Avelumab + BSC(N=350)	BSC (N=350)
Age, years		
Median (range)	68.0 (37.0, 90.0)	69.0 (32.0, 89.0)
Mean (SD)	[redacted]	[redacted]
<65 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
Gender, n (%)		
Male	266 (76.0)	275 (78.6)
Female	84 (24.0)	75 (21.4)
Race, n (%)		
Asian	75 (21.4)	81 (23.1)
Black	2 (0.6)	0 (0.0)
White	232 (66.3)	238 (68.0)
Other	21 (6.0)	15 (4.3)
Unknown	20 (5.7)	16 (4.6)
Geographic region, n (%)		
North America	12 (3.4)	22 (6.3)
Europe	214 (61.1)	203 (58.0)
Asia	73 (20.9)	74 (21.1)
Australasia	34 (9.7)	37 (10.6)
Rest of the World	17 (4.9)	14 (4.0)
Median time since initial diagnosis (range), months	[redacted]	[redacted]
First-line chemotherapy regimen, n (%)		
Gemcitabine + cisplatin	183 (52.3)	206 (58.9)
Gemcitabine + carboplatin	147 (42.0)	122 (34.9)
Gemcitabine + cisplatin/gemcitabine + carboplatin	20 (5.7)	20 (5.7)
Not reported	0 (0.0)	2 (0.6)
Best response to first-line chemotherapy		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	97 (27.7)	98 (28.0)
Site of metastasis		
Visceral	191 (54.6)	191 (54.6)
Non-visceral	159 (45.4)	159 (45.4)
Histopathological classification		
Carcinoma	306 (87.4)	292 (83.4)
Carcinoma with squamous	16 (4.6)	26 (7.4)
Carcinoma with glandular	6 (1.7)	9 (2.6)
Carcinoma with variant	22 (6.3)	22 (6.3)
Other	0 (0.0)	1 (0.3)
ECOG PS		
0	213 (60.9)	211 (60.3)
1	136 (38.9)	136 (38.9)
2	1 (0.3)	0 (0.0)
3	0 (0.0)	3 (0.9)
PD-L1 status		
Positive	189 (54.0)	169 (48.3)
Negative	139 (39.7)	131 (37.4)
Unknown	22 (6.3)	50 (14.3)

Abbreviations: BSC = best supportive care; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; n = number of patients in the category; N = number of patients evaluable; PD-L1 = programmed death-ligand 1; PR = partial response; PS = performance status; SD = standard deviation
Source: Pfizer Inc., 2020;[110,114] Powles et al., 2020[47]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1.1 Statistical hypotheses

To maintain a one-sided overall significance level ≤0.025, α=0.015 was allocated to the OS comparison in all randomised patients and α=0.01 to the OS comparison in patients with PD-L1-positive tumours. The study will be considered positive if the stratified log-rank test for OS is significant at the time of analysis for either of the two co-primary populations. The significance levels for each test also considered the group sequential nature of the design.[110,112]

An interim analysis (IA) of OS in both co-primary populations was planned after ≥315 of all randomised patients had died (74% of the total OS events needed), including ≥146 patients with PD-L1-positive tumours (66.7% of the total OS events expected in the PD-L1-positive population).[110,112] The data cut-off date for the IA was 21 October 2019, with a median follow-up time for OS of 19.6 and 19.2 months, for avelumab + BSC and BSC alone, respectively.

B.2.4.2 Determination of sample size

Sample sizes were calculated to appropriately power the study. For all patients, 425 OS events were required to have ≥93% power to detect a hazard ratio (HR) of 0.7 using a one-sided log-rank test at a significance level of 0.015, and a two-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.

For patients with PD-L1-positive tumours, 219 OS events would provide 80% power to detect a HR of 0.65 using a one-sided log-rank test at a significance level of 0.01, and a two-look group sequential design as per the all-patients analysis. The study will be considered positive if the stratified log-rank test for OS is significant at the time of analysis for either of the two co-primary populations.[110,112]

B.2.4.3 Efficacy analyses

The full analysis set (FAS) included all randomised patients. Patients were classified according to the study treatment assigned at randomisation. The FAS was the primary analysis set for the analyses of efficacy endpoints.[112]

B.2.4.3.1 Primary efficacy analyses

B.2.4.3.1.1 Overall survival

The primary endpoint was OS in all randomised patients and in patients with PD-L1-positive tumours. OS was defined as the time from the date of randomisation to the date of death due to any cause. Patients last known to be alive were censored at date of last contact. The study was considered positive if the stratified log-rank test was significant at the respective α levels for either population.[110]

One-sided log tests, stratified by randomisation factors, were performed with overall significance levels preserved at their respective levels (one-sided 0.015 for all patients and one-sided 0.01 for patients with PD-L1-positive tumours). The duration of OS was summarised

by treatment arm using the Kaplan-Meier method, and a Cox proportional hazards model was fitted to compute the hazard ratios and the corresponding CIs. In order to account for the group-sequential design in this study, the repeated CI method was used to construct the two-sided repeated CI for the hazard ratios.[110]

B.2.4.3.2 Secondary efficacy analyses

B.2.4.3.2.1 Progression-free survival

PFS was defined as the time from the date of randomisation to the date of the first documentation of PD or death due to any cause, whichever occurred first. PFS data were censored on the date of the last adequate tumour assessment for patients who did not have an event (PD or death), for patients who started new anti-cancer therapy prior to an event, or for patients with an event after 2 or more missing tumour assessments.[110]

A one-sided stratified log test was used to compare the PFS time between the experimental arm and the control arm. PFS time was summarized by treatment arm using the Kaplan-Meier method. A Cox proportional hazards model was fitted to compute the hazard ratios and the corresponding CIs.[110]

B.2.4.3.2.2 Objective response

The objective response rate (ORR) was defined as the proportion of patients with an objective response (best overall response [BOR] of CR or PR according to RECIST v1.1), and was calculated, for each treatment arm, along with the two-sided 95% CI using the Clopper-Pearson method.[110]

Assessments performed from randomisation until the first documentation of PD were considered, including only those performed on or before the start date of any further anti-cancer therapies.[110]

B.2.4.3.2.3 Disease control

DC was defined as BOR of CR, PR, non-CR/non-PD, or stable disease. BOR of stable disease was required to be met at least 6 weeks after the date of randomisation. DC was summarised by frequency counts and percentages.[110]

B.2.4.3.2.4 Time to response and duration of response

For patients with an OR, TTR was defined as the time from randomization to first documentation of OR which was subsequently confirmed and summarised using simple descriptive statistics.[110]

For patients with an OR, duration of response (DOR) was defined as the time from the first documentation of OR to the first documentation of PD or death due to any cause, whichever occurred first. Censoring rules for DOR were similar to those described for PFS. DOR was summarised using Kaplan-Meier methodology.[110]

B.2.4.3.2.5 Patient reported outcomes

The NCCN FBISI-18 and EQ-5D-5L were scored, and missing values in the instruments, were handled according to their respective validation papers and user's guides. Descriptive

analyses and random coefficient models were carried out for the FBISI-18 and its subscales (Disease Related Symptoms – Physical [DRS-P], Disease Related Symptoms – Emotional, Treatment Side-Effects and Function/Well-Being), EQ-5D-5L, and EQ-VAS.[110]

Time to deterioration (TTD) was defined as the time from randomisation to a ≥3-point decrease from baseline in FBISI DRS-P over two consecutive assessments. TTD was analysed by a log-rank test stratified by randomisation stratification factors; also, TTD in each treatment arm was summarised and displayed graphically using the Kaplan-Meier method.[110]

B.2.4.3.3 Safety analyses

All safety analyses were performed using the safety analysis set (SAS; N=689), which included all patients who received at least one dose of avelumab or received only BSC (344 patients in the avelumab + BSC arm and 345 patients in the BSC alone arm). Six patients randomised to the avelumab + BSC arm and 5 patients randomised to the BSC alone arm did not receive study treatment.[110]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table B.2.7. Quality assessment of JAVELIN Bladder 100

Was randomisation carried out appropriately?	Yes. A total of 700 patients were randomised in a 1:1 ratio to treatment with avelumab + BSC, or BSC alone, via an interactive response technology system (interactive web-based response).
Was the concealment of treatment allocation adequate?	Given the route of administration for avelumab, concealment of treatment allocation was not possible. The unblinded nature of the trial led to differential use of second-line therapies, with the potential for bias analogous to cross-over bias seen in other unblinded studies. For PFS, BICR was used to minimise bias (see below).
Were the groups similar at the outset of the study in terms of prognostic factors?	The distribution of demographic, baseline and disease characteristics were similar between treatment arms (including gender, age, race, ethnicity, pooled geographic region, physical measurements [height, weight, and BMI], ECOG PS, best response to first-line chemotherapy, site of metastasis, and histopathological classification).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Although JAVELIN Bladder 100 was an open-label study, BICR was used to minimise bias that could be introduced into the assessment by the investigator, based on the knowledge of treatment assignment at randomisation. To mitigate the potential for bias in determining disease progression, expedited BICR review was performed for investigator-assessed disease progression. All radiographic images were collected and objectively verified by an independent third-party core imaging laboratory. All patients' files and radiologic images are available for source verification and peer review.
Were there any unexpected imbalances in drop-outs between groups?	No. A larger proportion of patients discontinued BSC treatment (92.6%), compared with avelumab + BSC (75.7%). However, this reflected the higher rate of discontinuation due to disease progression in the BSC arm (75.1%), compared with avelumab + BSC (54.0%).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the CSR. Pfizer fulfils its commitment to publicly disclose clinical trial results through posting the results of studies on ClinicalTrials.gov, EudraCT and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner, and are reported regardless of the outcome of the study or the country in which the study was conducted. In addition, Pfizer supports the exercise of academic freedom and has no objection to publication of the results of the study based on information collected or generated by the principal investigator, whether or not the results are favourable to the Pfizer product.
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. Efficacy analyses were performed using the FAS, defined as all randomised patients. Unless otherwise specified, all data were evaluated as observed, and no imputation method for missing values was used.

Abbreviations: BICR = blinded independent central review; CSR = clinical study report; EudraCT = European Clinical Trials Database; FAS = full analysis set; PD-L1 = programmed death-ligand 1

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 JAVELIN Bladder 100

JAVELIN Bladder 100 assessed the efficacy and safety of avelumab maintenance therapy in the first-line setting across two co-primary populations: all randomised patients and patients with PD-L1-positive tumours. In line with the anticipated indication and scope of this appraisal,[115] results for all randomised patients are presented here; results for patients with PD-L1-positive tumours are presented in Appendix E.

At the time of the IA, the study met its primary objective, demonstrating that avelumab + BSC significantly prolongs OS compared with BSC alone, both in all randomised patients (Section B.2.4.3.1.1), and in patients with PD-L1-positive tumours (Appendix E).[47]

B.2.6.1.1 Duration of follow-up

A summary of the median duration of follow-up for OS and PFS analyses at the IA (21 October 2019) is shown in Table B.2.8.

Table B.2.8. Duration of follow-up in all randomised patients (FAS)

Analysis	Avelumab + BSC (N=350)	BSC (N=350)
Median follow-up time for OS, months (95% CI)	19.6 ([redacted])	19.2 ([redacted])
Median follow-up time for PFS, months (95% CI)	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; CI = confidence interval; IA = interim analysis; OS = overall survival; PFS = progression-free survival
Source: Pfizer Inc., 2020[110] Powles et al., 2020[47]

B.2.6.1.2 Overall survival (primary endpoint)

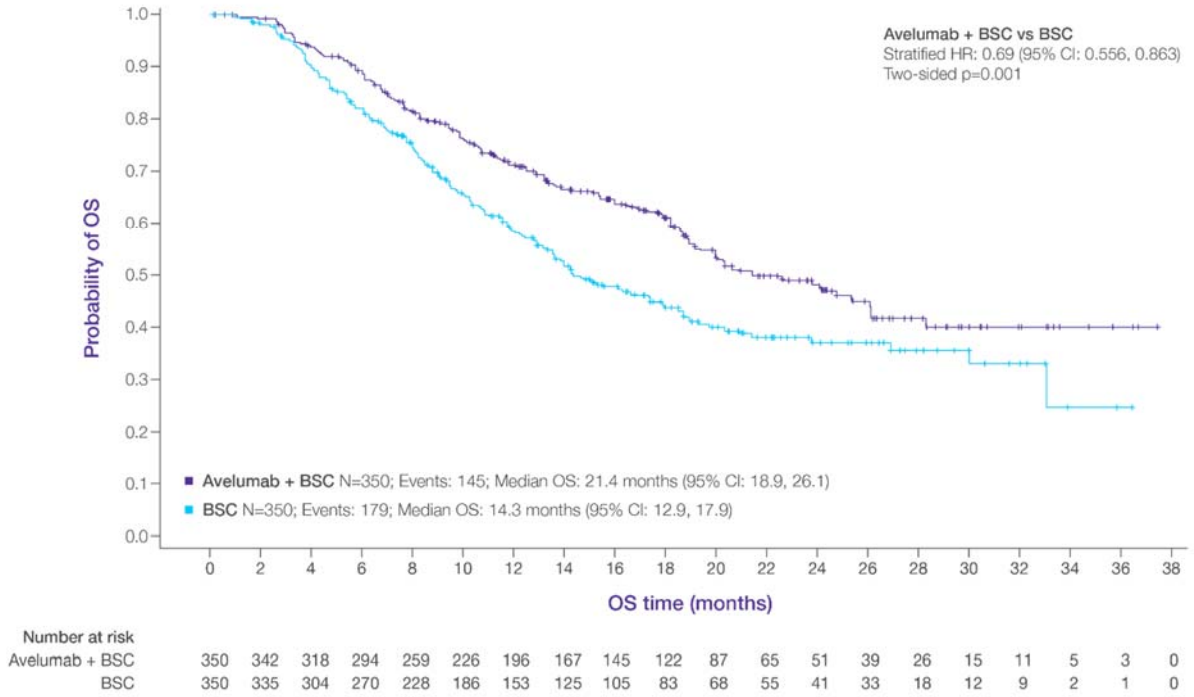
The results of the IA of OS in all randomised patients are summarised in Table B.2.9 and the Kaplan-Meier curves are shown in Figure B.2.2. A clinically meaningful and statistically significant improvement in OS was demonstrated for all patients assigned to avelumab + BSC (FAS), with a 31% reduction in the risk of death compared with patients assigned to BSC alone (HR: 0.69; 95% CI: 0.556, 0.863; two-sided p=0.001). Treatment with avelumab led to a median 7.1-month improvement in OS – the median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab + BSC arm, and 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm (measured from randomisation). The median duration of follow-up for OS was similar between treatment arms: 19.6 months and 19.2 months for avelumab + BSC, and BSC alone respectively.[47,110]

Table B.2.9. Summary of OS in all randomised patients (FAS; primary endpoint)

Endpoint	All patients (N=700)	
	Avelumab + BSC (N=350)	BSC (N=350)
Events, n (%)	145 (41.4)	179 (51.1)
Censored, n (%)	205 (58.6)	171 (48.9)
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Median OS (95% CI), months	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
HR (95% CI)	0.69 (0.556, 0.863)	
Two-sided p-value	0.001	
Probability (95% CI) of being event-free at:		
6 months	[redacted]	[redacted]
12 months	0.713 (0.660, 0.760)	0.584 (0.527, 0.637)
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; n = number of patients in the category; N = number of patients evaluable; NR = not reached; OS = overall survival
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

Figure B.2.2. Kaplan-Meier plot of OS in all randomised patients (FAS; primary endpoint)



Abbreviations: BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; OS = overall survival; vs = versus
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.2.6.1.3 Progression-free survival (secondary endpoint)

A summary of PFS (based on BICR assessment) in all randomised patients is presented in Table B.2.10 and the Kaplan-Meier curves are shown in Figure B.2.3. At the time of the IA,

patients assigned to avelumab + BSC (FAS) had an improvement in PFS, with a 38% reduction of the risk of progression or death compared with patients assigned to BSC alone (HR: 0.62; 95% CI: 0.519, 0.751; two-sided p<0.0001). The median PFS for avelumab + BSC was 3.7 months (95% CI: 3.5, 5.5) and for BSC alone was 2.0 months (95% CI: 1.9, 2.7). The median duration of follow-up was 16.6 months and 19.4 months for avelumab + BSC, and BSC alone respectively.[47,110]

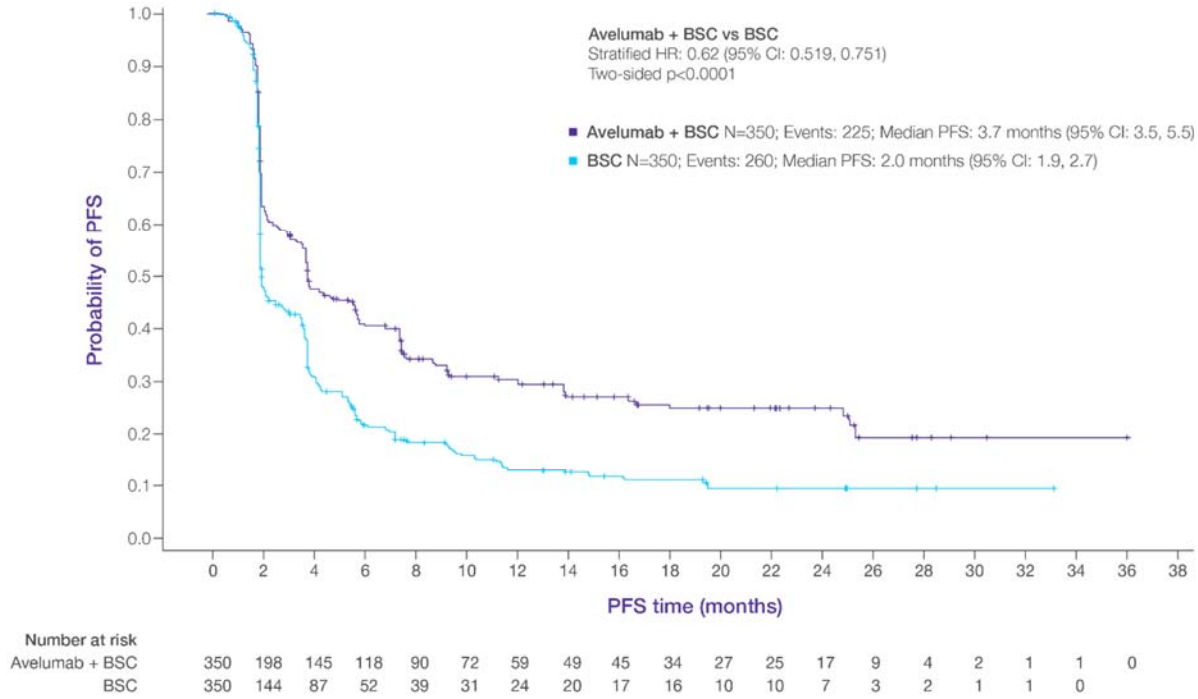
Table B.2.10. Summary of PFS (based on BICR assessment) in all randomised patients (FAS; secondary endpoint)

Endpoint	All patients (N=700)	
	Avelumab + BSC (N=350)	BSC (N=350)
Events, n (%)	225 (64.3)	260 (74.3)
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored, n (%)	125 (35.7)	90 (25.7)
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumour assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Median PFS (95% CI), months	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)
HR (95% CI)	0.62 (0.519, 0.751)	
Two-sided p-value	<0.0001	
Probability (95% CI) of being event-free at:		
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
15 months	[redacted]	[redacted]

Abbreviations: BICR = blinded independent central review; BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; PFS = progression-free survival

Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

Figure B.2.3. Kaplan-Meier plot of PFS (based on BICR assessment) in all randomised patients (FAS; secondary endpoint)



Abbreviations: BICR = blinded independent central review; BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; PFS = progression-free survival; vs = versus
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.2.6.1.4 Objective response (secondary endpoint)

The results of the analysis of BOR and OR (measured from randomisation) based on BICR assessment according to RECIST v1.1 in all randomised patients are summarised in Table B.2.11. The ORR for avelumab + BSC was 9.7%, compared with 1.4% for BSC alone (odds ratio: 7.46; 95% CI: 2.824, 24.445; two-sided p<0.0001).[47,116] At the time of the IA the median DOR for patients who responded was [redacted].[110]

Table B.2.11. Summary of response (based on BICR assessment) in all randomised patients (FAS; secondary endpoint)

Endpoint	All patients (N=700)	
	Avelumab + BSC (N=350)	BSC (N=350)
Confirmed BOR, n (%)		
CR	21 (6.0)	3 (0.9)
PR	13 (3.7)	2 (0.6)
Stable disease	44 (12.6)	46 (13.1)
Non-CR/Non-PD	66 (18.9)	45 (12.9)
PD	130 (37.1)	169 (48.3)
NE	76 (21.7)	85 (24.3)
OR, n (%)	34 (9.7)	5 (1.4)
95% CI	6.8, 13.3	0.5, 3.3
DC, n (%)	144 (41.1)	96 (27.4)
95% CI	[redacted]	[redacted]
Median DOR (95% CI), months	[redacted]	[redacted]

Abbreviations: BICR = blinded independent central review; BOR = best overall response; BSC = best supportive care; CI = confidence interval; CR = complete response; DC = disease control (CR, PR, stable disease, and non-CR/non-PD); FAS = full analysis set; N = number of patients evaluable; NR = not reached; OR = objective response (CR and PR); PD = progressive disease; PR = partial response
Source: Pfizer Inc., 2020[110] Powles et al., 2020[47,111]

B.2.6.1.5 Patient-reported outcomes

Despite no active anti-cancer treatment in the BSC arm, PROs indicated that overall health status and HRQoL in patients treated with avelumab + BSC were similar to those assigned to BSC alone.[109]

In all randomised patients, FBISI-18 scores were not significantly different in the avelumab + BSC arm, compared to BSC alone, across physical and emotional disease-related symptoms, treatment side effects, and functional wellbeing domains. FBISI-18 scores were similar between the avelumab + BSC arm and BSC alone arm in all randomised patients.[109]

As with FBISI-18 scores, EQ-5D-5L scores were not significantly different for patients treated with avelumab + BSC compared to those treated with BSC alone, in all randomised patients.[109]

B.2.6.1.6 Other outcomes

The OS benefit of avelumab treatment versus BSC was observed despite more patients in the BSC alone arm continuing on to subsequent anti-cancer therapies (42.3% versus 61.7%, respectively; Table B.2.12), and a markedly higher proportion of patients receiving follow-on PD-1 or PD-L1 immunotherapy (6.3% versus 43.7% for avelumab _+ BSC and BSC alone, respectively).[111]

Table B.2.12. Follow-up anti-cancer drug therapies in all randomised patients (FAS)

Endpoint	All patients (N=700)	
	Avelumab + BSC (N=350)	BSC (N=350)
Patients with any follow-up anti-cancer drug therapies	148 (42.3)	216 (61.7)
Any PD-1 or PD-L1 inhibitor	22 (6.3)	153 (43.7)
FGFR inhibitor	9 (2.6)	8 (2.3)
Any other drug therapy	140 (40.0)	119 (34.0)

Abbreviations: BSC = best supportive care; FAS = full analysis set; FGFR = fibroblast growth factor receptor; N = number of patients evaluable; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[111]

In the BSC arm, the proportion of patients who received immunotherapy (70.8% of those who received a second-line therapy)[111] was similar to that observed in UK clinical practice (76.9%). Furthermore, the overall number of patients moving onto subsequent anti-cancer therapies is considerably lower in UK clinical practice, with approximately 41.9% of patients receiving a second-line therapy following a first-line platinum-based chemotherapy.[85,86]

B.2.6.2 Efficacy conclusions

The IA results of the pivotal Phase 3 JAVELIN Bladder 100 study demonstrate that avelumab + BSC clinically and statistically improved OS compared with BSC in patients with locally advanced or metastatic UC whose disease did not progress after first-line platinum-based chemotherapy. A clinically meaningful and statistically significant improvement in OS was demonstrated for all patients assigned to avelumab + BSC, with a 31% reduction in the risk of death compared with patients assigned to BSC alone (HR: 0.69; 95% CI: 0.556, 0.863; two-sided p=0.001). Treatment with avelumab led to a median 7.1-month improvement in OS – the median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab + BSC arm, and 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm (measured from randomisation). Importantly, avelumab was effective in improving survival outcomes regardless of PD-L1 expression.[47,110]

Secondary efficacy analyses supported the outcome of the primary efficacy analysis. In all randomised patients, avelumab + BSC had a clinically meaningful improvement in PFS, with a 38% reduction of the risk of progression or death compared with BSC alone (HR: 0.62; 95% CI: 0.519, 0.751; two-sided p<0.0001). The median PFS for avelumab + BSC was 3.7 months (95% CI: 3.5, 5.5) and for BSC alone was 2.0 months (95% CI: 1.9, 2.7).[47,110] Taken together, these data demonstrate that maintenance therapy in the first-line setting with avelumab is an effective and novel strategy to improve clinical outcomes in patients with locally advanced or metastatic UC.

B.2.7 Subgroup analysis

B.2.7.1 Methodology and statistical analysis

OS, PFS and ORR were assessed in the following pre-specific subgroups:

- Randomisation stratification factors
  - Best response to first-line chemotherapy (CR or PR versus stable disease)
  - Site of metastasis (visceral vs non-visceral)
- Age (< 65 years, ≥ 65 years)

- Gender (male, female)
- Race (white, Asian, other)
- Pooled geographic region (Europe, North America, Asia, Australasia, Rest of the World)
- PD-L1 status at baseline (positive, negative, unknown)
- First-line chemotherapy regimen (gemcitabine + cisplatin, gemcitabine + carboplatin, gemcitabine + cisplatin and gemcitabine + carboplatin)
- ECOG performance status (0, ≥1)
- Creatinine clearance at baseline (≥60 ml/min, <60 ml/min)
- Liver lesions at baseline (yes, no)
- Lung lesions at baseline (yes, no)[110,113]

Treatment arms were compared for OS and PFS (based on BICR assessment) for each subgroup level and the unstratified HR and its corresponding 95% CI were computed per subgroup level. All subgroup analyses were exploratory and no adjustment for multiplicity was performed. To assess the heterogeneity of treatment effects across the subgroup levels, an interaction test of treatment by subgroup was also performed for OS and PFS (based on BICR assessment). Hazard ratios and associated CIs were calculated using the Cox proportional hazards model.[110]

B.2.7.2 Results of subgroup analyses

Results of the subgroup analyses are presented in Appendix E. Notably, avelumab + BSC had a beneficial effect across all pre-specified subgroups and efficacy endpoints, indicating that the results of JAVELIN Bladder 100 were not driven by any particular subgroup, and that avelumab is effective in treating a diverse selection of patients.[116]

B.2.7.2.1 Overall survival

OS was consistently longer for avelumab + BSC compared with BSC alone, across all pre-specified subgroups. Interaction tests revealed that there was not a significant difference in treatment effect across subgroups (see Appendix E).[116]

B.2.7.2.2 Progression-free survival

As with OS, PFS (based on BICR assessment) was longer for avelumab + BSC compared with BSC alone across all prespecified subgroups (see Appendix E).[116]

B.2.7.2.3 Objective response

For subgroups with at least one responder (BOR of CR or PR) in both treatment arms, the ORR (based on BICR assessment) was higher for avelumab + BSC compared with BSC alone across all prespecified subgroups (see Appendix E).[116]

B.2.8 Meta-analysis

All efficacy data supporting the use of avelumab for the first-line treatment of patients with locally advanced or metastatic UC are provided by a single study (JAVELIN Bladder 100). Therefore, a meta-analysis is not required.

B.2.9 Indirect and mixed treatment comparisons

In the absence of other first-line maintenance treatments for locally advanced or metastatic UC, neither an indirect nor a mixed treatment comparison can be made.

B.2.10 Adverse reactions

B.2.10.1 JAVELIN Bladder 100

Overall, the safety profile of avelumab was generally tolerable, manageable, and consistent with prior experience in locally advanced or metastatic UC and other solid tumours.[47,117] No new safety concerns were identified and the AE profile is similar to those observed for immune checkpoint inhibitors previously approved for first and second-line treatment of locally advanced or metastatic UC.[46,76-78]

B.2.10.1.1 Safety population

The safety population (N=689) included all patients who received at least one dose of avelumab or received only BSC (344 patients in the avelumab + BSC arm and 345 patients in the BSC alone arm).[47]

B.2.10.1.2 Extent of exposure

The extent of exposure to avelumab and BSC is summarised in Table B.2.13. The median duration of treatment was longer in the avelumab + BSC arm (24.9 weeks, compared with 13.1 weeks for BSC alone), driven by the shorter time to progression in the BSC alone arm. The median relative dose intensity for avelumab was [redacted]. Six patients randomised to the avelumab + BSC arm and 5 patients randomised to the BSC alone arm did not receive study treatment.[47,110]

Table B.2.13. Exposure to study treatment (SAS)

	Avelumab + BSC (N=344)	BSC (N=345)
Duration of treatment, weeks		
Mean (SD)	[redacted]	[redacted]
Median (range)	24.9 (2.0, 159.9)	13.1 (0.1, 155.6)
Dose intensity (mg/kg/4-week cycle)		
Mean (SD)	[redacted]	N/A
Median (range)	[redacted]	N/A
Relative dose intensity (%)		
Mean (SD)	[redacted]	N/A
Median (range)	[redacted]	N/A

Abbreviations: BSC = best supportive care; kg = kilogram; mg = milligram; N = number of patients evaluable; N/A = not applicable; SAS = safety analysis set; SD = standard deviation
Source: Pfizer Inc., 2020[110] Powles et al., 2020[47]

B.2.10.1.3 Adverse events

The frequency of patients with treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) is summarised in Table B.2.14. The incidence of TEAEs and TRAEs was higher for avelumab + BSC compared with BSC alone (98.0% and 77.7%, respectively, for TEAEs; 77.3% and 1.2%, respectively for TRAEs). Patients in the avelumab + BSC arm also

experienced Grade ≥3 TEAEs and TRAEs at a higher frequency compared with those in the BSC alone arm (47.4% and 25.2%, respectively, for TEAEs; 16.6% and 0%, respectively for TRAEs). The incidence of fatal TEAEs was 1.2% for avelumab + BSC and 7.0% for BSC alone. There were no fatal TRAEs during the on-treatment period in the BSC alone arm, compared with an incidence of 0.3% for avelumab + BSC (one patient with a fatal TRAE of sepsis).[47,110]

Table B.2.14. Summary of AEs (SAS)

	TEAEs		TRAEs	
	Avelumab + BSC (N=344)	**BSC (N=345)**	**Avelumab + BSC (N=344)**	**BSC (N=345)**
AEs, n (%)	337 (98.0)	268 (77.7)	266 (77.3)	4 (1.2)
Grade ≥3	163 (47.4)	87 (25.2)	57 (16.6)	0 (0.0)
Serious	96 (27.9)	69 (20.0)	31 (9.0)	0 (0.0)
Leading to discontinuation	41 (11.9)	0 (0.0)	33 (9.6)	0 (0.0)
Leading to death	4 (1.2)	24 (7.0)	1 (0.3)	0 (0.0)

Abbreviations: AE = adverse event; BSC = best supportive care; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set; TEAE = treatment-emergent adverse event
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.2.10.1.4 Commonly reported adverse events

The most common TEAEs are summarised in Table B.2.15. The incidence of TEAEs was 98.0% in the avelumab + BSC arm, compared with 77.7% in the BSC alone arm. In the avelumab + BSC arm, no individual AE occurred at a frequency of ≥20%.[47]

Table B.2.15. Most common TEAEs (any grade in ≥10% of patients or Grade ≥3 in ≥5% of patients in any group; SAS)

Preferred term	Avelumab + BSC (N=344)		BSC (N=345)	
	All grades	Grade ≥3	All grades	Grade ≥3
Events, n (%)	337 (98.0)	163 (47.4)	268 (77.7)	87 (25.2)
Fatigue	61 (17.7)	6 (1.7)	24 (7.0)	2 (0.6)
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0 (0.0)
UTI	59 (17.2)	15 (4.4)	36 (10.4)	9 (2.6)
Diarrhoea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0 (0.0)
Asthenia	56 (16.3)	0 (0.0)	19 (5.5)	4 (1.2)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0 (0.0)
Back pain	55 (16.0)	4 (1.2)	34 (9.9)	8 (2.3)
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0 (0.0)
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)
Cough	44 (12.8)	1 (0.3)	16 (4.6)	0 (0.0)
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0 (0.0)
Rash	40 (11.6)	1 (0.3)	4 (1.2)	0 (0.0)
Anaemia	39 (11.3)	13 (3.8)	23 (6.7)	10 (2.9)
Haematuria	36 (10.5)	6 (1.7)	37 (10.7)	5 (1.4)
IRR	35 (10.2)	3 (0.9)	0 (0.0)	0 (0.0)

Abbreviations: BSC = best supportive care; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set; TEAE = treatment-emergent adverse event; UTI = urinary tract infection
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

The most common TRAEs are summarised in Table B.2.16. A higher incidence of TRAEs were observed in patients that received avelumab + BSC. In the avelumab + BSC arm, Grade ≤2 TRAEs were reported more frequently than TRAEs of Grade ≥3 (77.3% and 16.6%, respectively). In the BSC alone arm, the incidence of TRAEs was 1.2%, with no Grade ≥3 events. Within the avelumab + BSC arm, 9.6% of patients discontinued treatment due to TRAEs (see Table B.2.21) and 31 (9.0%) patients experienced serious TRAEs. Those reported in ≥2 patients were IRR (n=4 [1.2%]), blood creatine phosphokinase increased (n=2 [0.6%]) and colitis (n=2 [0.6%]). There were no discontinuations due to TRAEs or serious TRAEs in the BSC alone arm.[47,110]

Table B.2.16. Most common TRAEs (any grade in ≥5% of patients or Grade ≥3 in ≥2% of patients in any group; SAS)

Preferred term	Avelumab + BSC (N=344)		BSC (N=345)	
	All grades	Grade ≥3	All grades	Grade ≥3
Events, n (%)	266 (77.3)	57 (16.6)	4 (1.2)	0 (0.0)
Pruritus	47 (13.7)	1 (0.3)	0 (0.0)	0 (0.0)
Hypothyroidism	36 (10.5)	1 (0.3)	0 (0.0)	0 (0.0)
Diarrhoea	35 (10.2)	0 (0.0)	0 (0.0)	0 (0.0)
IRR	35 (10.2)	3 (0.9)	0 (0.0)	0 (0.0)
Asthenia	34 (9.9)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	33 (9.6)	1 (0.3)	0 (0.0)	0 (0.0)
Rash	25 (7.3)	1 (0.3)	0 (0.0)	0 (0.0)
Chills	24 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	24 (7.0)	1 (0.3)	0 (0.0)	0 (0.0)
Arthralgia	23 (6.7)	1 (0.3)	0 (0.0)	0 (0.0)
Pyrexia	23 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperthyroidism	21 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dry skin	18 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)
Amylase increased	15 (4.4)	7 (2.0)	0 (0.0)	0 (0.0)
Lipase increased	13 (3.8)	10 (2.9)	0 (0.0)	0 (0.0)

Abbreviations: BSC = best supportive care; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.2.10.1.5 Serious adverse events

The most common serious TEAEs (reported in ≥2 patients in any treatment group) are summarised in Table B.2.17. The overall incidence of serious TEAEs was higher in the avelumab + BSC arm compared with the BSC alone arm (27.9% and 20.0%, respectively).[47,110]

Table B.2.17. Most common serious TEAEs (any grade in ≥2 patients in any group; SAS)

Preferred term	Avelumab + BSC (N=344)	BSC (N=345)
Events, n (%)	96 (27.9)	69 (20.0)
UTI	16 (4.7)	7 (2.0)
Acute kidney injury	6 (1.7)	6 (1.7)
Haematuria	5 (1.5)	2 (0.6)
IRR	4 (1.2)	0 (0.0)
Pain	4 (1.2)	1 (0.3)
Sepsis	4 (1.2)	1 (0.3)
Atrial fibrillation	3 (0.9)	1 (0.3)
Back pain	3 (0.9)	1 (0.3)
Disease progression	3 (0.9)	16 (4.6)
Hydronephrosis	3 (0.9)	1 (0.3)
Ileus	3 (0.9)	1 (0.3)
Pyelonephritis	3 (0.9)	3 (0.9)
Vomiting	3 (0.9)	0 (0.0)
Blood CPK increased	2 (0.6)	0 (0.0)
Colitis	2 (0.6)	0 (0.0)
Constipation	2 (0.6)	0 (0.0)
Dyspnoea	2 (0.6)	1 (0.3)
Kidney infection	2 (0.6)	0 (0.0)
Myocardial infarction	2 (0.6)	0 (0.0)

Preferred term	Avelumab + BSC (N=344)	BSC (N=345)
Pyrexia	2 (0.6)	1 (0.3)
Vascular device infection	2 (0.6)	0 (0.0)
Abdominal pain	1 (0.3)	3 (0.9)
Anaemia	1 (0.3)	2 (0.6)
Basal cell carcinoma	1 (0.3)	2 (0.6)
Urosepsis	1 (0.3)	2 (0.6)
Syncope	0 (0.0)	2 (0.6)
Tumour pain	0 (0.0)	2 (0.6)
Urinary tract obstruction	0 (0.0)	2 (0.6)

Abbreviations: BSC = best supportive care; CPK = creatine phosphokinase; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set; TEAE = treatment-emergent adverse event; UTI = urinary tract infection
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

The most common serious TRAEs (reported in ≥2 patients in any treatment group) are summarised in Table B.2.18. Within the avelumab + BSC arm, 31 (9.0%) patients experienced serious TRAEs. Those reported in ≥2 patients were IRR (n=4 [1.2%]), blood creatine phosphokinase increased (n=2 [0.6%]) and colitis (n=2 [0.6%]). There were no serious TRAEs in the BSC alone arm.[47,110]

Table B.2.18. Most common serious TRAEs (any grade in ≥2 patients in any group; SAS)

Preferred term	Avelumab + BSC (N=344)	BSC (N=345)
Events, n (%)	31 (9.0)	0 (0.0)
IRR	4 (1.2)	0 (0.0)
Blood CPK increased	2 (0.6)	0 (0.0)
Colitis	2 (0.6)	0 (0.0)

Abbreviations: BSC = best supportive care; CPK = creatine phosphokinase; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set; TRAE = treatment-related adverse event
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.2.10.1.6 Deaths

A summary of deaths is presented in Table B.2.19. The most common cause of death was disease progression in both treatment arms ([redacted] and [redacted] for the avelumab + BSC and BSC alone arms, respectively).[110]

Table B.2.19. Summary of deaths (SAS)

	Avelumab + BSC (N=344)	BSC (N=345)
Deaths, n (%)	[redacted]	[redacted]
Disease progression		
Study treatment toxicity	2 (0.6)	0 (0.0)
AE not related to study treatment	[redacted]	[redacted]
Other		
Unknown		
Deaths within 30 days after last dose of study treatment, n (%)		
Disease progression		
Study treatment toxicity		
AE not related to study treatment		

Abbreviations: AE = adverse event; BSC = best supportive care; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

A summary of TEAEs leading to death during the on-treatment period (within 30 days of ending study treatment, or on initiation of subsequent anti-cancer drug therapy) is presented in Table B.2.20. Grade 5 TEAEs occurred in 1.2% of patients in the avelumab + BSC arm and 7.0% of patients in the BSC alone arm. Other than disease progression, sepsis was the only fatal TEAE that lead to death in the avelumab + BSC arm during the on-treatment period (n=1 [0.3%]).[47,110]

Table B.2.20. Summary of TEAEs leading to death (SAS)

System Order Class/Preferred Term	Avelumab + BSC (N=344)	BSC (N=345)
Events, n (%)	4 (1.2)	24 (7.0)
General disorders and administration site conditions, n (%)	[redacted]	[redacted]
Disease progression		
Infections and infestations, n (%)		
Sepsis	1 (0.3)	0 (0.0)
Biliary sepsis	[redacted]	[redacted]
Urosepsis		
Cardiac disorders, n (%)		
Cardiogenic shock		
Neoplasms benign, malignant and unspecified, n (%)		
Bladder cancer		
Malignant neoplasm progression		
Metastatic carcinoma of the bladder		
Neoplasm progression		
Respiratory, thoracic and mediastinal disorders, n (%)		
COPD		

Abbreviations: BSC = best supportive care; COPD = chronic obstructive pulmonary disease; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set; TEAE = treatment-emergent adverse event
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

Two deaths in the avelumab + BSC arm were attributed to study treatment toxicity by the investigator – sepsis (n=1 [0.3%]), 29 days after the last dose of avelumab, and one death (0.3%) due to ischemic stroke after the end of the on-treatment period, 100 days after a single dose of avelumab. Both deaths were considered to be unrelated to avelumab by the sponsor.[47,110]

B.2.10.1.7 Adverse events leading to treatment discontinuation

A summary of TEAEs and TRAEs leading to discontinuation of avelumab is provided in Table B.2.21. TEAEs leading to discontinuation were reported in 11.9% of patients in the avelumab + BSC arm.[47] The most frequent TEAEs leading to discontinuation of avelumab were [redacted][110]

Table B.2.21. Summary of TEAEs and TRAEs leading to treatment discontinuation (SAS)

System Order Class/Preferred Term	TEAEs		TRAEs	
	Avelumab + BSC (N=344)	BSC (N=345)	Avelumab + BSC(N=344)	BSC (N=345)
Events, n (%)	41 (11.9)	0 (0.0)	33 (9.6)	0 (0.0)
Investigations	[redacted]			
Lipase increased				
Troponin T increased				
ALT increased				
Amylase increased				
AST increased				
Blood ALP increased				
GGT increased				
Neutrophil count decreased				
Platelet count decreased				
Gastrointestinal disorders				
Colitis				
Autoimmune pancreatitis				
Gastric ulcer				
Pancreatitis				
Vomiting				
General disorders and administration site conditions				
Disease progression				
Fatigue				
Malaise				
Injury, poisoning and procedural complications				
IRR				
Musculoskeletal/connective tissue disorders				
Muscular weakness				
Myositis				
Rheumatoid arthritis				
Renal and urinary disorders				
Nephritis				
Tubulointerstitial nephritis				
Ureteric obstruction				
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease				
Pneumonitis				
Cardiac disorders				
Acute myocardial infarction				
Myocardial infarction				
Endocrine disorders				
Autoimmune thyroiditis				
Hyperthyroidism				
Hepatobiliary disorders				
Autoimmune hepatitis				

System Order Class/Preferred Term	TEAEs		TRAEs	
	Avelumab + BSC (N=344)	BSC (N=345)	Avelumab + BSC(N=344)	BSC (N=345)
Hepatotoxicity	[redacted]			
Infections and infestations				
Sepsis				
Blood and lymphatic system disorders				
Anaemia				
Metabolism and nutrition disorders				
Hypokalaemia				
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Oesophageal squamous cell carcinoma				
Nervous system disorders				
Toxic neuropathy				
Skin and subcutaneous tissue disorders				
Pruritus				
Rash maculo-papular				

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSC = best supportive care; GGT = gamma-glutamyl transferase; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set; TEAE = treatment-emergent adverse event
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.2.10.1.8 Adverse events leading to dose interruption or modification

TEAEs leading to interruption of avelumab treatment were reported in 140 patients (40.7%).[47] The most frequent TEAE leading to avelumab interruption was [redacted]. [redacted] patient experienced a TEAE of [redacted] that led to a starting dose reduction of avelumab (not permitted by the protocol). There were [redacted] TEAEs leading to both dose reduction and interruption of avelumab treatment.[110]

B.2.10.1.9 Adverse events of special interest

B.2.10.1.9.1 Immune-related adverse events

A summary of immune-related adverse events (irAEs) is presented in Table B.2.22. As expected for a trial comparing an immunotherapy with BSC alone, there was a higher incidence of irAEs in the avelumab + BSC arm. irAEs were reported for 29.4% of patients in the avelumab + BSC arm and 1.4% of patients in the BSC alone arm. In the avelumab + BSC arm, Grade 3 events were reported for 7.0% of patients and no Grade 4 or Grade 5 events were reported. The highest frequency of irAEs was in the immune-related endocrinopathies cluster, thyroid disorders sub-cluster (12.2%), and the most common irAEs were hypothyroidism (10.2%), rash (4.9%) and hyperthyroidism (4.7%). In total, [redacted] patients with an irAE were administered medication ([redacted] [N=[redacted]] in the avelumab + BSC arm and [redacted] [n=[redacted]] in the BSC alone arm). Of these, systemic corticosteroids were administered to [redacted] (n=[redacted]) of patients in the avelumab + BSC arm, compared with [redacted] (n=[redacted]) in the BSC alone arm. High-dose corticosteroids (≥40 mg total daily prednisolone dose equivalent) were administered to 9.0% (n=31) of patients with an irAE in the avelumab + BSC arm, and no patients in the BSC alone arm.[111,118]

Table B.2.22. Summary of irAEs (SAS)

Cluster/Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All grades	Grade ≥3	All grades	Grade ≥3
Events, n (%)	101 (29.4)	24 (7.0)	5 (1.4)	1 (0.3)
Immune-related endocrinopathies: thyroid disorders	[redacted]	[redacted]	2 (0.6)	0 (0.0)
Hypothyroidism	35 (10.2)	1 (0.3)	1 (0.3)	0 (0.0)
Hyperthyroidism	16 (4.7)	0 (0.0)	1 (0.3)	0 (0.0)
Autoimmune thyroiditis	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmune hypothyroidism	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood thyroid stimulating hormone increased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroiditis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroxine free decreased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-related rash	[redacted]	[redacted]	1 (0.3)	0 (0.0)
Rash	17 (4.9)	1 (0.3)	0 (0.0)	0 (0.0)
Rash maculo-papular	8 (2.3)	1 (0.3)	0 (0.0)	0 (0.0)
Pruritus	7 (2.0)	0 (0.0)	1 (0.3)	0 (0.0)
Erythema	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Purpura	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Rash erythematous	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Drug eruption	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Erythema multiforme	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Lichen planus	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rash papular	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rash pruritic	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other irAE: other	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Psoriasis	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Vitiligo	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Arthritis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis psoriasiform	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Oligoarthritis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Polyarthritis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid arthritis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Immune-related pneumonitis	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Pneumonitis	5 (1.5)	1 (0.3)	0 (0.0)	0 (0.0)
Interstitial lung disease	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-related nephritis and renal dysfunction	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Nephritis	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure	3 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)
Tubulointerstitial nephritis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-related colitis	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Colitis	3 (0.9)	2 (0.6)	0 (0.0)	0 (0.0)
Diarrhoea	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Enteritis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Proctitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-related hepatitis	[redacted]	[redacted]	0 (0.0)	0 (0.0)
ALT increased	3 (0.9)	3 (0.9)	0 (0.0)	0 (0.0)
AST increased	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)
Autoimmune hepatitis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Hepatotoxicity	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Immune-related endocrinopathies: adrenal insufficiency	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Adrenal insufficiency	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)

Cluster/Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All grades	Grade ≥3	All grades	Grade ≥3
Immune-related endocrinopathies: type 1 diabetes mellitus	[redacted]	[redacted]	1 (0.3)	1 (0.3)
Hyperglycaemia	3 (0.9)	3 (0.9)	0 (0.0)	0 (0.0)
Diabetes mellitus	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Immune-related pancreatitis	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Autoimmune pancreatitis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Pancreatitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other irAE: myositis	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Myositis	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)
Other irAE: Guillain-Barre syndrome	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Miller Fisher syndrome	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Other irAE: uveitis	[redacted]	[redacted]	1 (0.3)	0 (0.0)
Uveitis	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSC = best supportive care; irAE = immune-related adverse event; n = number of patients in the category; N = number of patients evaluable;SAS = safety analysis set
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

[redacted] patients in the avelumab + BSC arm discontinued study treatment due to an irAE. The most frequent irAE leading to discontinuation of avelumab was [redacted].[110]

A summary of serious irAEs is presented in Table B.2.23. Within the avelumab + BSC arm, [redacted] of patients experienced a serious irAE. The most frequent serious irAE was [redacted].[110]

Table B.2.23. Summary of serious irAEs (SAS)

Cluster/Preferred Term	Avelumab + BSC (N=344)	BSC (N=345)
Events, n (%)	[redacted]	1 (0.3)
Immune-related colitis	[redacted]	0 (0.0)
Colitis	[redacted]	0 (0.0)
Enteritis	[redacted]	0 (0.0)
Immune-related nephritis and renal dysfunction	[redacted]	0 (0.0)
Nephritis	[redacted]	0 (0.0)
Renal failure	[redacted]	0 (0.0)
Tubulointerstitial nephritis	[redacted]	0 (0.0)
Immune-related endocrinopathies: thyroid disorders	[redacted]	0 (0.0)
Hyperthyroidism	[redacted]	0 (0.0)
Hypothyroidism	[redacted]	0 (0.0)
Immune-related hepatitis	[redacted]	0 (0.0)
Autoimmune hepatitis	[redacted]	0 (0.0)
Hepatotoxicity	[redacted]	0 (0.0)
Immune-related pneumonitis	[redacted]	0 (0.0)
Interstitial lung disease	[redacted]	0 (0.0)
Pneumonitis	[redacted]	0 (0.0)
Immune-related pancreatitis	[redacted]	0 (0.0)
Autoimmune pancreatitis	[redacted]	0 (0.0)
Immune-related rash	[redacted]	0 (0.0)
Drug eruption	[redacted]	0 (0.0)
Other irAE: Guillain-Barre syndrome	[redacted]	0 (0.0)
Miller Fisher syndrome	[redacted]	0 (0.0)
Other irAE: myositis	[redacted]	0 (0.0)
Myositis	[redacted]	0 (0.0)

Cluster/Preferred Term	Avelumab + BSC (N=344)	BSC (N=345)
Immune-related endocrinopathies: type 1 diabetes mellitus	[redacted]	1 (0.3)
Diabetes mellitus	[redacted]	1 (0.3)

Abbreviations: BSC = best supportive care; irAE = immune-related adverse event; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set
Source: Pfizer Inc., 2020[110]

B.2.10.1.9.2 Infusion-related reactions

A summary of infusion-related reactions (IRRs) is presented in Table B.2.24. As the sole intravenously administered treatment arm, IRRs were observed only in patients treated with avelumab + BSC (21.5% [composite term]). Of these patients, 0.9% experienced a Grade 3 IRR. [redacted] Grade 4 or Grade 5 IRRs were reported. When patients first experienced an IRR, it was typically following the first or second infusion of avelumab, with only [redacted] patients who received avelumab having their first IRR at a later infusion.[47,110]

Table B.2.24. Summary of IRRs (SAS)

Preferred term	Avelumab + BSC (N=344)		BSC (N=345)	
	All grades	Grade ≥3	All grades	Grade ≥3
Events, n (%)	74 (21.5)	3 (0.9)	0 (0.0)	0 (0.0)
IRR	35 (10.2)	3 (0.9)	0 (0.0)	0 (0.0)
Chills	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Pyrexia	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Back pain	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Hypersensitivity	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Dyspnoea	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Hypotension	[redacted]	[redacted]	0 (0.0)	0 (0.0)

Abbreviations: BSC = best supportive care; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

[redacted] in the avelumab + BSC arm experienced serious IRRs. All [redacted] events were IRR (preferred term) and all patients were discontinued from study treatment.[110]

B.2.10.2 Safety conclusions

As expected, with a control arm including BSC alone, there was, in general, a higher incidence of TEAEs in the avelumab + BSC arm of JAVELIN Bladder 100 than in the BSC alone arm (98.0% and 77.7%, respectively). Grade ≥3 TEAEs were also more frequently reported in patients treated with avelumab + BSC (47.4% and 25.2%, respectively). However, no TEAEs were reported at a frequency >20% in the avelumab + BSC arm; the most common TEAEs (≥10% for any grade or ≥5% for Grade ≥3) included fatigue, pruritus, UTI, diarrhoea, arthralgia, asthenia, constipation, back pain, nausea, pyrexia, decreased appetite, cough, vomiting, hypothyroidism, rash, anaemia, haematuria, and IRR.[47,110]

SAEs occurred in 27.9% of patients in the avelumab + BSC arm and 20% of patients in the BSC alone arm. The most common cause of death was disease progression in both treatment arms (38.7% vs 45.5%, respectively). Two (0.6%) fatal TRAEs were attributed to avelumab toxicity by the investigator (0.6%), however neither death was considered to be related to avelumab by the study sponsor. TEAEs leading to avelumab discontinuation were reported in

11.9% of patients in the avelumab + BSC arm. The primary reason for treatment discontinuation in both treatment arms was disease progression.[110]

There were [redacted] Grade 4 or 5 IRRs in the study. irAEs were observed in 29.4% of patients in the avelumab + BSC arm; Grade 3 irAEs were observed in 7.0% of patients, and there were no Grade 4 or 5 irAEs in the study. IRRs were reported for 21.5% of patients in the avelumab + BSC arm. Grade 3 IRRs were reported in 0.9% of patients.[47,110]

Overall, the safety profile of avelumab observed in JAVELIN Bladder 100 was tolerable, manageable, and consistent with prior experience of avelumab.[46,47,110] No new safety concerns were identified in patients with locally advanced or metastatic UC who received maintenance treatment with avelumab.[110] In addition, data from [redacted] patient-years of post-authorisation exposure in patients with MCC, UC and aRCC (in combination with axitinib) also demonstrate that avelumab is associated with a generally manageable and tolerable safety profile.[54]

B.2.11 Ongoing studies

Other than JAVELIN Bladder 100, there are no ongoing studies of avelumab monotherapy for the treatment of locally advanced or metastatic UC in the first-line maintenance setting.

B.2.12 Innovation

Prior to the recent introduction of immunotherapies in 2017, chemotherapy was the only available systemic treatment for locally advanced or metastatic UC. Immunotherapies have provided novel therapeutic options, which potentiate the anti-tumour immune response through inhibition of the immune-checkpoint proteins PD-1 or PD-L1.[119,120] However, their first-line use is currently restricted to cisplatin-ineligible patients with PD-L1-positive tumours,[121] and the majority of patients do not receive an immunotherapy until second-line, where survival outcomes are particularly poor.[2,38,95] Separately, neither first-line chemotherapy or first-line immunotherapy have offered substantial long-term survival benefit, and the majority of patients do not remain sufficiently healthy to receive second-line treatment.[86]

Maintenance treatment with avelumab following first-line platinum-based chemotherapy is a novel and innovative treatment approach in UC, as demonstrated by the designation of Promising Innovative Medicine status in May 2020 and EAMS scientific opinion in September 2020. Under the current standard of care, patients who remain stable or respond to first-line chemotherapy must wait for disease progression before receiving further anti-tumour treatment (watchful waiting).[2,11,85,86] However, first-line platinum-based chemotherapy regimens have demonstrated median PFS of 5.8–9.9 months,[14,18,20-22,32,37,87] and clinical expert opinion indicates that only 50–60% of patients who receive first-line treatment are eligible for second-line therapy.[108]

A growing body of evidence indicates that there are mechanistic advantages to receiving an immunotherapy immediately after chemotherapy.[122-125] Emerging evidence indicates that chemotherapy could prime the immune system for immunotherapy through a process of immunomodulation.[122] Chemotherapy-associated immunomodulatory effects include upregulation of tumour-recognising MHC class I receptors, increased levels of anti-tumour cytotoxic T- and NK cells, augmented cytolytic activity, and downregulation of the tumour immunosuppressive microenvironment by reduction in regulatory T-cells (Tregs).[122-124] Furthermore, although patients with UC typically respond to first-line chemotherapy, the low probability of durable response could in part be due to untreated residual disease.[37,38] Administration of avelumab immediately after first-line chemotherapy offers the advantage of targeting minimum residual disease. Smaller, debulked tumours have fewer cancer cells to target with reduced clonal complexity, and are likely to be more accessible to subsequent therapies.[125]

Through their complementary mechanisms of action, the sequential administration of induction chemotherapy followed by avelumab maintenance is proven to extend the benefit of first-line platinum-based chemotherapy.[47] Avelumab is the first and only maintenance therapy in Phase 3 development for locally advanced or metastatic UC to demonstrate statistically significant improvements in both OS and PFS.[47,48] The availability of avelumab as a maintenance therapy allows for its use in a well-defined patient group likely to derive the most benefit from treatment before disease progression, after which the capacity for patients to respond to cancer immunotherapy may be compromised. Avelumab therefore represents a step-change in the management of UC. Maintenance therapy with avelumab in the first-line setting is therefore expected to provide an important and efficient new treatment option for patients whose disease has not progressed following first-line platinum-based chemotherapy. As such, it may

contribute to addressing the critical unmet need for a therapy that sustains first-line therapeutic responses and improves survival outcomes, while maintaining HRQoL.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Interim findings from the clinical evidence

Current treatment options for advanced or metastatic UC are limited, with systemic platinum-based chemotherapy regimens being the current standard of care in the UK.[11] Outcomes with first-line chemotherapy regimens are modest, with median PFS and OS ranging from 5.8 to 9.9 months and 9.3 to 18.0 months, respectively (see Table B.1.6).[14,18,20-22,32,37,87] Although atezolizumab and pembrolizumab are recommended for use within the CDF as first-line treatments for cisplatin-ineligible patients with PD-L1-positive tumours,[79,80] outcomes in Phase 2 single-arm studies were similar to those observed with first-line chemotherapy (median OS of 12.3 months and 18.5 months, respectively, and PFS of 4.1 and 4.9 months, respectively [see Table B.1.6]).[90-92] Furthermore, recent Phase 3 data have failed to demonstrate superiority of atezolizumab or pembrolizumab over first-line chemotherapy in extending OS.[93,94]

At the time of the pre-planned IA, JAVELIN Bladder 100 met its primary objective, demonstrating a statistically significant and clinically meaningful 7.1-month improvement in median OS, compared with BSC alone, regardless of PD-L1 status (median OS of 21.4 months and 14.3 months, respectively; HR: 0.69; two-sided p=0.001).[47] In addition, the median PFS for avelumab + BSC was almost doubled compared with BSC alone (median PFS of 3.7 months] and 2.0 months, respectively; HR: 0.62; two-sided p<0.0001).[47,110] Despite no active anti-cancer treatment in the BSC arm, the efficacy benefits of avelumab were achieved with no significant impact on health status or HRQoL according to FBISI-18 and EQ-5D-5L questionnaires.[109] Avelumab has also demonstrated acceptable tolerability and a manageable safety profile, both in JAVELIN Bladder 100,[47] and across [redacted] patient-years of post-authorization exposure in patients with MCC, RCC (in combination with axitinib), and UC (second-line treatment only).[54] In JAVELIN Bladder 100, the incidence of TEAEs was higher for avelumab + BSC compared to BSC alone (98.0% [47.4% Grade ≥3] and 77.7% [25.2% Grade ≥3], respectively). TRAEs were reported in 77.3% of patients treated with avelumab + BSC (16.6% Grade ≥3) and 1.2 % of patients treated with BSC alone (no Grade ≥3 TRAEs observed). Importantly, there were fewer fatal TEAEs in the avelumab + BSC arm compared with the BSC alone arm (1.2% [0.3% fatal TRAE - sepsis] and 7.0% [no fatal TRAEs], respectively).[47,110] No new safety concerns were identified, and the safety profile of avelumab monotherapy was consistent with prior experience.[46,54,110]

In conclusion, clinical evidence from JAVELIN Bladder 100 demonstrates that maintenance treatment with avelumab following first-line platinum-based chemotherapy improves survival and extends time to progression compared with the current standard of care.[46,124] This represents a significant advance in a life-threatening disease with substantial unmet need.[12-21,34,37,87,88,126]

B.2.13.2 Strengths and limitations of the clinical evidence base

Overall, clinical data for avelumab provide an appropriate evidence base for assessment of its clinical and cost-effectiveness for the first-line maintenance treatment of locally advanced or metastatic UC.

The strengths of the clinical evidence base are:

- JAVELIN Bladder 100 is a robust, multicentre RCT which randomised 700 patients with locally advanced or metastatic UC, whose disease had not progressed following first-line platinum-based chemotherapy[47]
- The safety and efficacy of avelumab maintenance was assessed in comparison to that of BSC, the current standard of care in the UK, as per NICE recommendation.[11]
- The trial included four sites in the UK, and enrolled patients representative of those who would receive maintenance treatment with avelumab in the first-line setting in routine clinical practice in the UK[110]
- JAVELIN Bladder 100 assessed the primary outcome of OS in two co-primary populations: 1) all randomised patients, and 2) patients with PD-L1-positive tumours
  - The primary outcome of OS was met in both co-primary populations, with a significant and clinically meaningful improvement in OS compared to BSC
  - Multiple sensitivity analyses of OS were consistent with the primary analysis, demonstrating robustness of the clinical benefit of avelumab
  - The OS benefit for patients in the avelumab plus BSC alone arm was observed despite the large proportion of patients in the BSC alone arm than in the avelumab plus BSC arm who received a follow-up anticancer drug therapy, in general, and anti-PD-1/PD-L1, in particular)[47,110]
- Importantly, OS was consistently longer for avelumab + BSC compared with BSC alone across all pre-specified subgroups[110,116]
- The secondary efficacy endpoint of PFS is relevant to routine clinical practice and supports the outcome of the primary efficacy analysis[47]
- The study also included an assessment of HRQoL, as measured by the generic EQ-5D-5L instrument, and the disease-specific FBISI-18 instrument.[109]

The limitations of the clinical evidence base include:

- JAVELIN Bladder 100 was limited to open-label treatment masking due to clear differences in administration between intravenously-administered avelumab, and BSC alone. However, BICR was used to minimise bias (including expedited BICR review was for investigator-assessed disease progression). All radiographic images were submitted to the BICR for expedited review[110]
- Although weight-based dosing was used in JAVELIN Bladder 100 (10 mg/kg), the recommended avelumab dose is 800 mg Q2W. A flat dose of 800 mg is supported by overlapping PK exposures observed in JAVELIN Bladder 100 (10 mg/kg Q2W), and simulations of monotherapy at 10 mg/kg Q2W or 800 mg Q2W (flat dose). In JAVELIN Bladder 100, patients treated with avelumab + BSC had a median weight at baseline of 72.4 kg, and a mean weight of 75.2 kg (equating to a dosage of 724 mg, and 752 mg, respectively)

B.2.13.3 End-of-life criteria

First-line maintenance treatment with avelumab is indicated for patients with locally advanced or metastatic UC. In this population, OS is typically <24 months, and avelumab + BSC has been shown to extend survival by >3 months. As such, avelumab + BSC meets the end-of-life criteria (see Table B.2.25).

Table B.2.25. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The median survival for adult patients in England diagnosed with Stage III–IV UC between 2013 and 2017 was [redacted] months (95% CI: [redacted], [redacted]).[2]	Section B.1.3.4.1 (page 15)
	The median OS from JAVELIN Bladder 100 for the cohort most relevant to this submission (patients treated with BSC alone) was 14.3 months.[110]	Section B.2.6.1.2 (page 36)
	Across other clinical trials, the median OS in patients treated with first-line chemo- or immunotherapy ranges from 9.3 to 18.5 months.[14,18,20-22,32,37,87,90-92]	Section B.1.3.6 (page 20)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In JAVELIN Bladder 100, treatment with avelumab + BSC led to a statistically significant improvement of 7.1 months in median OS (avelumab + BSC: 21.4 months; BSC alone: 14.3 months).	Section B.2.6.1.2 (page 36)

Abbreviations: BSC = best supportive care; CI = confidence interval; NHS = National Health Service; OS = overall survival

B.3. Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify evidence on the economic outcomes of avelumab and relevant comparators for the treatment of locally advanced or metastatic UC (see Appendix G).

No pre-existing cost-effectiveness analyses of avelumab maintenance therapy for the treatment of patients with locally advanced or metastatic UC were identified. Consequently, a *de novo* cost-effectiveness model was constructed to inform this submission. However, elements from published cost-effectiveness studies identified in the broader locally advanced or metastatic UC population (and other late-stage cancer populations) were considered when developing the model to inform this submission, which are discussed where relevant henceforth.

B.3.2 Economic analysis

B.3.2.1 Population

In accordance with the final scope issued by NICE, the cost-effectiveness analysis considers the use of avelumab maintenance versus watchful waiting in patients with locally advanced or metastatic UC, following a first-line platinum-based chemotherapy regimen. This population reflects the use of avelumab + BSC versus BSC alone within the pivotal JAVELIN Bladder 100 clinical trial (see Section B.2 and Figure B.2.1). The base-case analysis considers the full ITT (FAS) population from JAVELIN Bladder 100.

B.3.2.2 Intervention

The intervention relevant to this appraisal is avelumab (Bavencio®), administered as an IV dose of 800 mg Q2W.[46] While the expected dosing of avelumab (a flat dose of 800 mg) is different to that in the JAVELIN Bladder 100 trial (a weight-based dose of 10 mg/kg), outcomes are not expected to differ by the alternative dosing assumptions and therefore no adjustment to efficacy has been made. This approach has been implemented and accepted by NHS England in a prior avelumab appraisal (avelumab in combination with axitinib for untreated advanced or metastatic renal cell carcinoma), in which the trial dose of 10 mg/kg was considered generalisable to the 800 mg flat dose.[127]

In JAVELIN Bladder 100, patients received avelumab as maintenance until one of the following:

- Documented disease progression
- Patient withdrawal
- Loss of patient to follow up
- Unacceptable toxicity
- Study termination[110]

In clinical practice, treatment with avelumab is anticipated to be given until disease progression, unacceptable toxicity, or at the discretion of the treating clinician regarding the benefits of continued avelumab maintenance in patients without disease progression. This is

generally aligned with the design of JAVELIN Bladder 100, with allowances for clinicians to consider discontinuation of treatment prior to documented disease progression where deemed appropriate. It should be noted however that in JAVELIN Bladder 100, patients were permitted to continue treatment after initial evidence of radiologic disease progression at the discretion of the investigator if the following criteria were met:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression
- No decline in ECOG PS
- Absence of rapid disease progression evident in radiographic imaging
- Absence of progressive tumour at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention[110]

Treatment with avelumab maintenance after disease progression is not anticipated to occur in NHS practice. Based on the use of avelumab in JAVELIN Bladder 100, it was deemed necessary to specify a time to treatment discontinuation (TTD) curve in order to accurately determine the proportion of patients still receiving avelumab maintenance over time (see Section B.3.3), as well as to acknowledge the expectation of discontinuation of avelumab in the longer term. In addition, unit costs related to treatment acquisition, administration, medical management, and the resolution of AEs are discussed in Section B.3.5.

B.3.2.3 Comparator

The comparator relevant to this appraisal is *'Established clinical management without avelumab (including but not limited to routine surveillance, symptom control and pain management [including palliative radiotherapy])'* (see Table B.1.1).

Established clinical management without avelumab is considered 'watchful waiting' throughout the company submission (CS), and is analogous to no active treatment (as per the BSC arm in JAVELIN Bladder 100), reflecting the management of locally advanced or metastatic UC until after disease progression. On the basis of clinical advice, the term 'watchful waiting' is used in preference to BSC in this appraisal to more closely describe the comparator where subsequent active treatments may be offered in the event of progression.

As watchful waiting is not associated with any active treatment costs, the costs associated with watchful waiting are discussed alongside the medical resource use costs incurred by patients managed with avelumab maintenance (see Section B.3.5).

B.3.2.4 Model outcomes

In accordance with the NICE reference case, the model is capable of estimating the total costs, quality-adjusted life years (QALYs) and life-years (LYs) associated with avelumab or watchful waiting. Using these outcomes, an incremental analysis is presented in order to establish the incremental cost-effectiveness ratio (ICER) for avelumab maintenance versus watchful waiting.

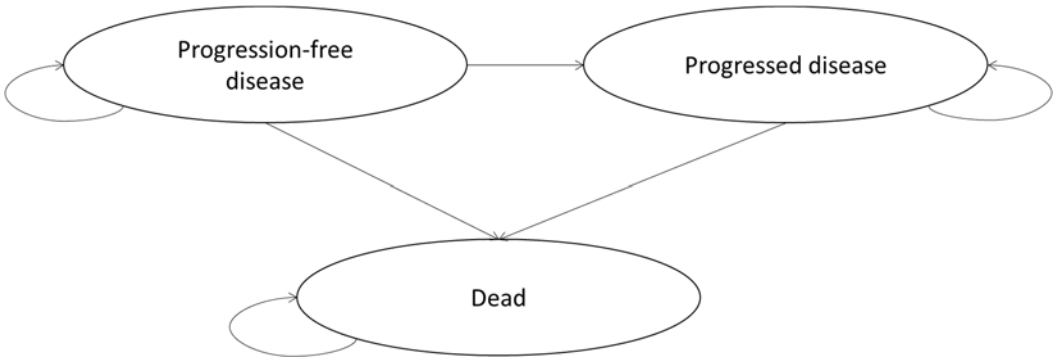
B.3.2.5 Economic model structure

The cost-effectiveness model was developed in Microsoft Excel® using an area-under-the-curve, partitioned-survival analysis (PartSA) structure in both deterministic and probabilistic (Monte Carlo simulation) frameworks. This structure was selected based on:

- The PartSA structure has been used to inform a number of previous NICE appraisals, particularly within the context of a metastatic cancer population
  - At the time of writing, NICE has published guidance for six technology appraisals conducted in a locally advanced or metastatic UC population, all of which adopted a PartSA structure (see Table B.3.1)[79-84]
- Through the use of survival curves, the PartSA structure revolves around the JAVELIN Bladder 100 primary endpoint of OS, as well as PFS (one of the key secondary endpoints)[110]
- The PartSA structure provides an intuitive application of outcomes seen in JAVELIN Bladder 100 without the need to rely upon estimating individual transition probabilities (some of which would be based on small numbers of patients)

The model schematic is presented in Figure B.3.1.

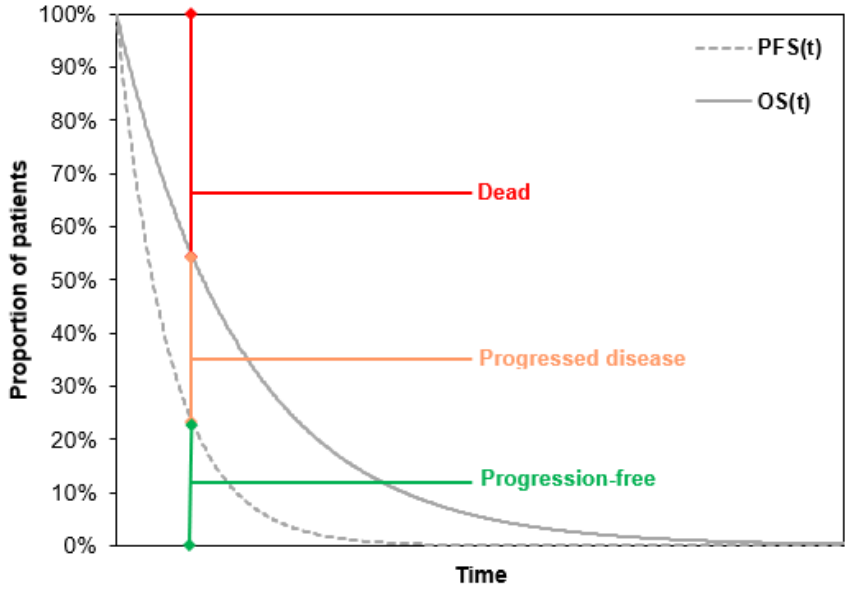
Figure B.3.1. *De novo* model schematic



The model structure has three health states: *progression-free disease, progressed disease and dead*. All patients begin the model in the *progression-free state* and are at risk of progression or death. Death can occur in either the *progression-free or progressed state*, and *dead* is an absorbing state. The occupancy in the progression-free state is calculated as the area under the PFS curve, while the progressed state is calculated as the area between the OS curve and the PFS curve, and dead is calculated as 1-OS. The *progression-free* health state was designed to capture the relatively higher HRQoL while disease is stable (post-chemotherapy with either avelumab or watchful waiting) prior to progression.

The model therefore captures the changes in HRQoL between the progression-free and progressed states. An alternative representation of the economic model structure is provided in Figure B.3.2, which illustrates how the OS and PFS curves are used to inform health state occupancy. Separately to the core model structure (shown in Figure B.3.1 and Figure B.3.2), the costs related to avelumab maintenance treatment (and other associated costs such as administration and the resolution of AEs) are estimated based on a TTD curve.

Figure B.3.2. Summary of how modelled survival curves are used within the *de novo* model



Abbreviations: OS = overall survival; PFS = progression-free survival

The base-case analysis adopts a lifetime horizon of 25 years, which is considered long enough to capture the lifetime of patients with locally advanced or metastatic UC and is similar to prior appraisals.[79-81,84] A cycle length of 7 days has been incorporated, assumed to be sufficiently short to represent the frequency of clinical events, and aligned with the administration of avelumab (Q2W) and subsequent treatments. No half-cycle correction was applied given the short cycle length.

The analysis was constructed from the perspective of the NHS and personal social services (PSS) in England and Wales. Costs were included based on 2018–2019 prices (which were the latest available publication sources at the time of submission). Costs and QALYs are discounted at 3.5% per annum, though LYs are not discounted (for ease of interpretation when considering the extension to life provided by avelumab maintenance).

As there have been no previous assessments conducted by NICE in the maintenance setting in locally advanced or metastatic UC, a summary of the key features of previous NICE assessments in the broader locally advanced or metastatic UC population is provided in Table B.3.1.

Table B.3.1. Key features of published economic analyses in UC

Factor	Previous appraisals						Current appraisal	
	TA272[82]	TA492[79]	TA519[84]	TA522[80]	TA525[81]	TA530[83]	Chosen value	Justification
Time horizon	5 years (lifetime)	20 years (lifetime)	35 years (lifetime)	20 years (lifetime)	20 years (lifetime)	Lifetime	25 years (lifetime)	Time horizon long enough to reflect the lifetime of patients
Model structure	3-state PartSA	3-state PartSA	3-state PartSA	3-state PartSA	3-state PartSA	3-state PartSA	3-state PartSA	Reflects decision problem, used in prior UC submissions
Treatment waning effect?	No	No	No	No	No	No	No	Range of survival models reflects difference in treatment effects over time.
Source of utilities	Mix of pivotal trial and external data	External data	Pivotal trial data	Pivotal trial data	Published literature	Pivotal trial data + external data for AEs	Pivotal trial data + external data for AEs	As per NICE reference case (external sources only considered to address data gaps)
Source of costs	NCC, literature and expert opinion	NCC, literature and expert opinion	NCC, literature and expert opinion	NCC, literature and expert opinion	NCC, literature and expert opinion	NCC, literature and expert opinion	NCC, published literature and expert opinion	Standard cost sources in line with NICE reference case
Discount of 3.5% for utilities and costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NICE reference case
Perspective (NHS/PSS)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NICE reference case

Abbreviations: AE = adverse event; NCC = National Cost Collection (national reference costs for older appraisals); NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PartSA = partitioned-survival analysis; PSS = personal social services; TA = technology appraisal; UC = urothelial carcinoma

B.3.3 Clinical parameters and variables

Data from the pivotal JAVELIN Bladder 100 trial comprise the key evidence base concerning the use of avelumab as maintenance treatment relevant to this appraisal (see Section B.2). Clinical data for the following endpoints/events are used to inform the estimation of costs and effects related to avelumab maintenance (or watchful waiting) within the model:

- Baseline patient characteristics
- Safety
- Efficacy
  - OS (Section B.3.3.3.1)
  - PFS (Section B.3.3.3.2)
  - TTD (Section B.3.3.3.3)

B.3.3.1 Baseline patient characteristics

The baseline characteristics used to inform the economic analysis are presented in Table B.3.2. A more detailed summary of the baseline patient demographics is provided in Section B.2.3.5.3.

Table B.3.2. Baseline patient characteristics used in the model

Parameter	Value	Use in model
Mean age	67.5 years	Used to inform estimation of background mortality and adjustment of utility values over time.
Male	77.3%	
Mean BSA	1.87 m^2	Used to inform estimation of drug costs (those dosed according to BSA, or requiring GFR [i.e. AUC dosing]).
GFR	68.92 ml/min/1.73m^2	

Abbreviations: AUC = area under the curve; BSA = body surface area; GFR = glomerular filtration rate
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

B.3.3.2 Safety

AEs that occurred in JAVELIN Bladder 100 are reported in Section B.2.10. AEs were included within the model if they met any of the following criteria:

- Most common Grade ≥3 TEAEs occurring in ≥1% of patients in either treatment arm
- Most common Grade ≥3 TRAEs occurring in ≥1% of patients in either treatment arm (i.e. avelumab arm only)
- Grade ≥3 irAEs occurring in ≥1% of patients on either treatment arm (i.e. avelumab arm only)

Non-irAEs were only included within the model if they were considered to be the most common AEs (defined as any Grade in ≥5% subjects or Grade ≥3 in ≥2% subjects in any treatment group) in JAVELIN Bladder 100. A summary of the AEs included within the model is provided in Table B.3.3.

Table B.3.3. AE rates in JAVELIN Bladder 100 included in the model

Event	Avelumab, n (%)	Watchful waiting, n (%)
TEAEs		
Anaemia	13 (3.8)	10 (2.9)
Asthenia	0 (0.0)	4 (1.2)
Back pain	4 (1.2)	8 (2.3)
Fatigue	6 (1.7)	2 (0.6)
Haematuria	6 (1.7)	5 (1.4)
Urinary tract infection	15 (4.4)	9 (2.6)
Vomiting	4 (1.2)	2 (0.6)
TRAE		
Amylase increased	7 (2.0)	0 (0.0)
Lipase increased	10 (2.9)	0 (0.0)
AESI: irAEs		
Immune-mediated hepatitis	[redacted]	[redacted]
Immune-mediated rash	[redacted]	[redacted]

Abbreviations: AESI = adverse events of special interest; irAE = immune-related adverse events; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

The associated impacts of AE occurrence on modelled outcomes (i.e. QALYs) and costs are discussed further in Sections B.3.4 and B.3.5, respectively.

B.3.3.3 Efficacy

Parametric survival models were fitted to each of the three time-to-event outcomes used to inform the model (OS, PFS and TTD). The process of selecting the best fitting distribution for extrapolation involved visual inspection of the graphical fit to observed data, goodness-of-fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), and clinical plausibility of long-term projections. Extrapolations were presented to, and subsequently validated by, consultant oncologists based in the UK with experience in treating patients with locally advanced or metastatic UC.

B.3.3.3.1 Overall survival

Survival modelling was required to inform the economic model, due to the specification of a lifetime horizon over which modelled costs and QALYs are required to be estimated. The approach taken is described below:

- Assessment of data from JAVELIN Bladder 100
  - Inspection of Kaplan-Meier curves
  - Production of log-cumulative hazard plots (LCHP) to determine potentially suitable parametric model fits and modelling approaches
- Fitting of potentially suitable models
- Inspection of statistical goodness-of-fit scores for fitted models
- Plausibility of fitted models after the end of follow-up in JAVELIN Bladder 100
- Requirement for any subsequent adjustments to be made

The approach taken to determine the most suitable survival models follows best practice guidance set out in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[128]

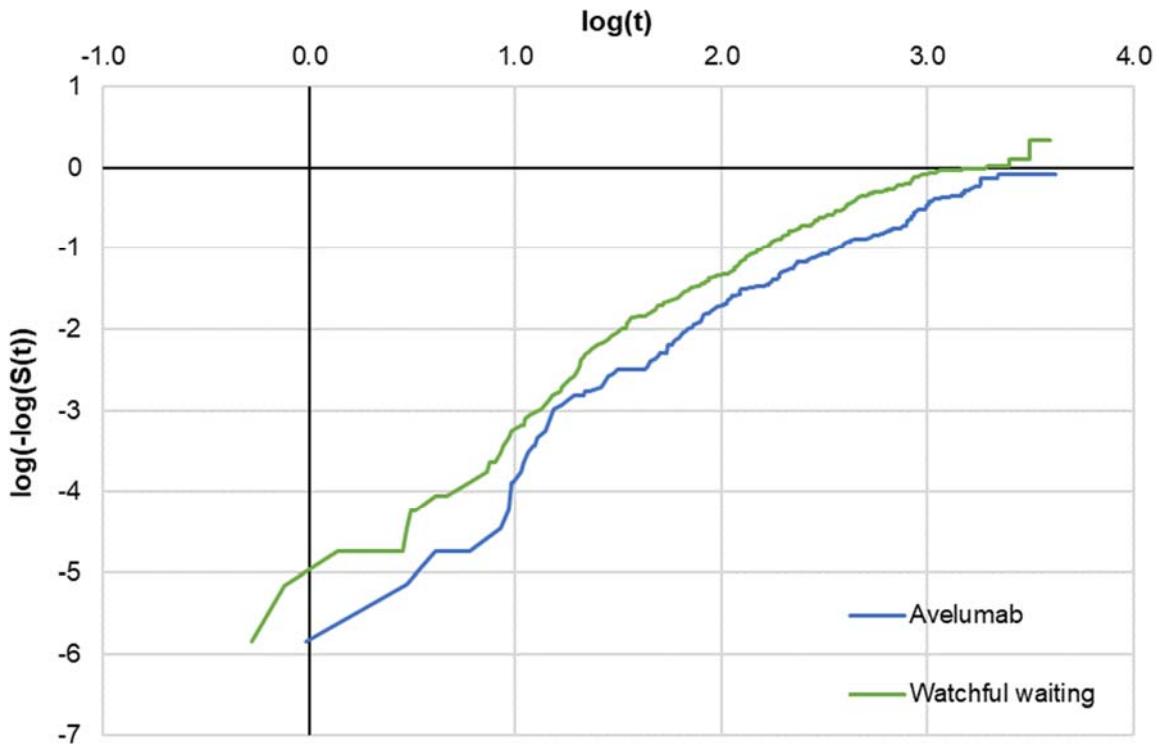
B.3.3.3.1.1 Assessment of data from JAVELIN Bladder 100

A summary of OS from JAVELIN Bladder 100 is provided in Section B.2. As can be seen from the Kaplan-Meier curves, OS data are incomplete and therefore extrapolation of outcomes is required to inform the cost-effectiveness analysis.

Prior to the fitting of parametric models, an LCHP was produced to assess whether the proportional hazards (PH) assumption may be assumed to hold, as well as the appropriateness of the exponential and Weibull parametric models specifically. If the plots exhibit non-linear trends, then both the exponential and Weibull models are unlikely to yield good fits to the Kaplan-Meier curves. In addition, if the plots for each treatment arm are approximately parallel, the ratio of the hazards between the treatment arms may be deemed constant (and thus the PH assumption may be considered met).

From the LCHP (Figure B.3.3), the gradient of each curve changes over time, indicating that the exponential and Weibull models would likely yield a poor fit to the Kaplan-Meier curves. In addition, the curves appear to converge and diverge at various time points over the duration of follow-up, and so the PH assumption may not hold.

Figure B.3.3. Log-cumulative hazard plot for OS



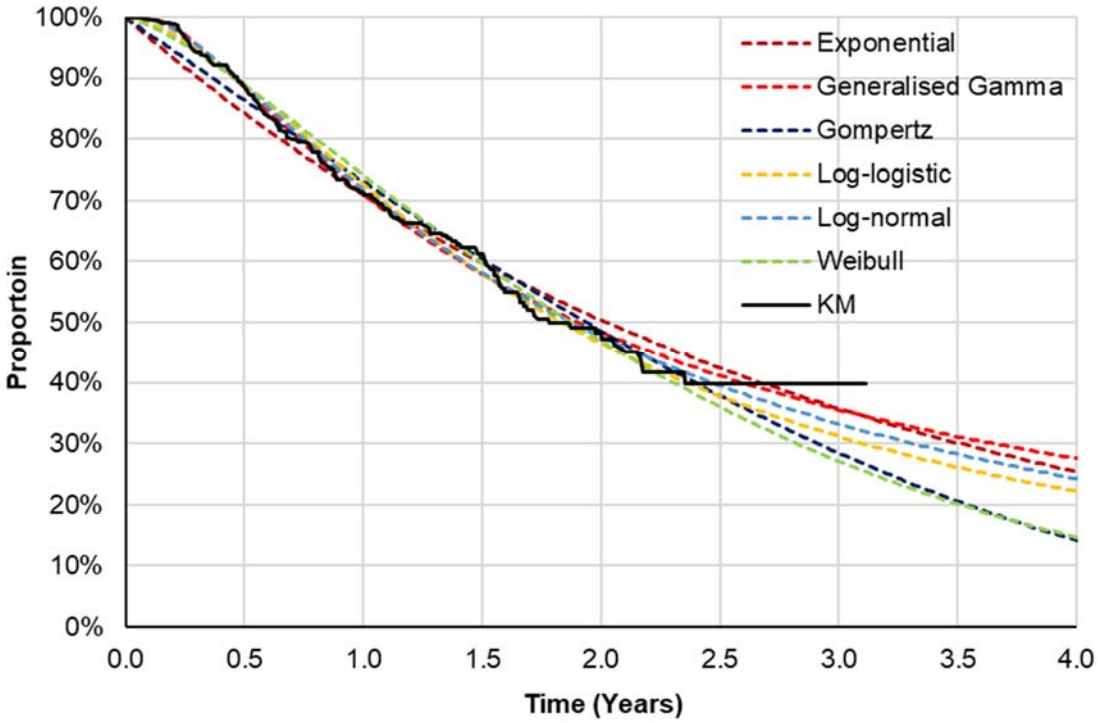
Abbreviations: OS = overall survival; S(t) = Survival at time t.

Based on inspection of the Kaplan-Meier curves and the corresponding LCHP plot, a range of independent models (i.e. models fitted separately for each treatment arm) were considered to provide a sufficient basis for informing the cost-effectiveness analysis.

B.3.3.3.1.2 Fitting of potentially-suitable models

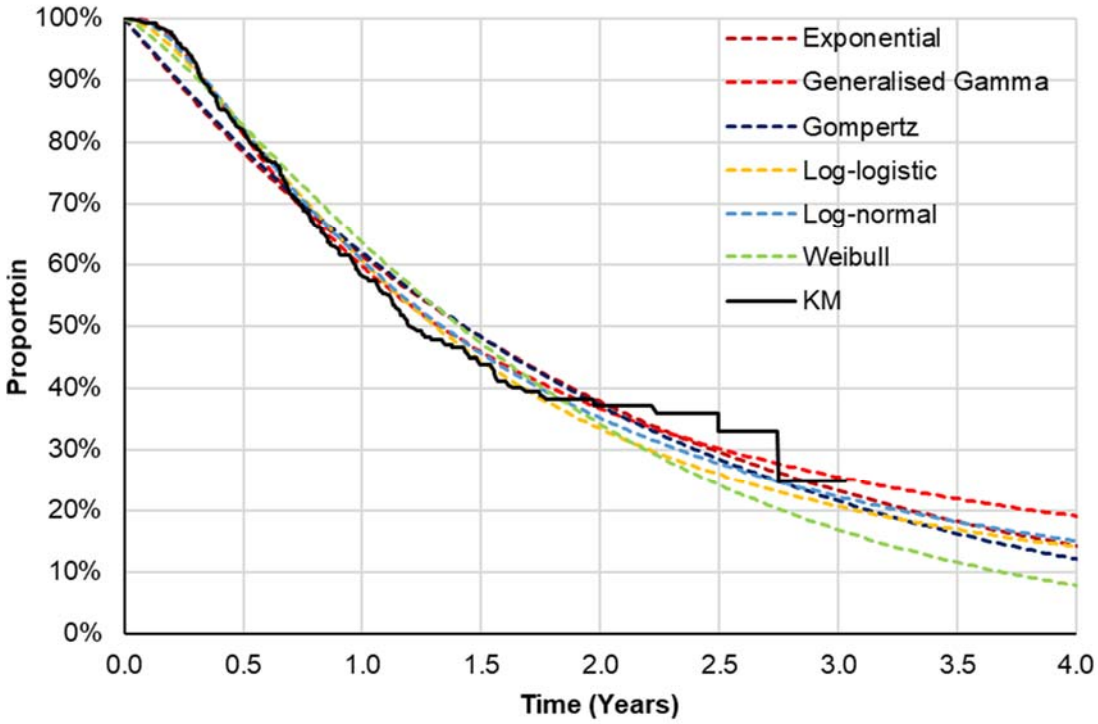
Parametric survival models were fitted in the statistical software program STATA using the streg package. The six standard parametric forms discussed in NICE DSU TSD 14 were fitted for completeness: exponential, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull. Models were fitted independently for each treatment arm, allowing for exploration of the different fits for each group. The model fits are presented in Figure B.3.4 and Figure B.3.5 for avelumab and watchful waiting, respectively. Longer-term extrapolations are presented in Section B.3.3.3.1.4.[129]

Figure B.3.4. Parametric survival model fits for OS (avelumab)



Abbreviations: KM = Kaplan-Meier; OS = overall survival

Figure B.3.5 Parametric survival model fits for OS (watchful waiting)



Abbreviations: KM = Kaplan-Meier; OS = overall survival

Figure B.3.4 and Figure B.3.5 show that the exponential and Gompertz models do not fit the earlier parts of each Kaplan-Meier curve well, or indeed most of the latter parts of the curves. The Weibull model provides a better fit to the earlier portion of both curves, but is later shown to provide a poor fit (especially for the watchful waiting arm). The remaining three models (log-normal, log-logistic, and generalised gamma) better reflect the Kaplan-Meier curves for each arm, providing very similar fits. Therefore, based on visual fit, the log-normal, log-logistic, and generalised gamma models appear to be the most suitable for the purpose of informing the cost-effectiveness analysis.

B.3.3.3.1.3 Inspection of statistical goodness-of-fit scores for fitted models

AIC and BIC scores are useful statistical tests that determine the relative fit of alternative parametric models, as a trade-off between their goodness-of-fit and complexity. While NICE DSU TSD 14 does not specify any fixed rules related to either AIC or BIC scores to overtly reject any specific model, a general 'rule of thumb' is proposed by Burnham & Anderson (2004) regarding AIC scores.[130] Based on the difference in the AIC scores for the 'best-fitting' model (i.e. the lowest AIC) and an alternative model, Burnham & Anderson suggest:

- If the difference is ≤2, the models are essentially equivalent
- If the difference is >2 but <10, the alternative model has less support, but may still provide a reasonable fit
- If the difference is >10, the alternative model has essentially no support and should not be selected

For BIC, a similar rule of thumb is proposed by Rafferty (1995), wherein differences in the BIC score of 0–2, 2–6, 6–10, and ≥10 are referred to as a means of justifying additional model complexity.[131]

These rules of thumb were considered when determining which models were likely to yield the best fit to data from JAVELIN Bladder 100. Statistical goodness-of-fit scores for the independent models are provided in Table B.3.4.

Table B.3.4. Statistical goodness-of-fit scores (OS, independent models)

Model	Avelumab		Watchful waiting	
	AIC	BIC	AIC	BIC
Exponential	690.99	694.84	784.62	788.48
Generalised gamma	665.92	677.49	**749.28**	760.85
Gompertz	688.87	696.59	786.36	794.08
Log-logistic	670.66	678.38	756.55	764.26
Log-normal	**664.87**	**672.59**	750.09	**757.80**
Weibull	677.76	685.47	775.16	782.87

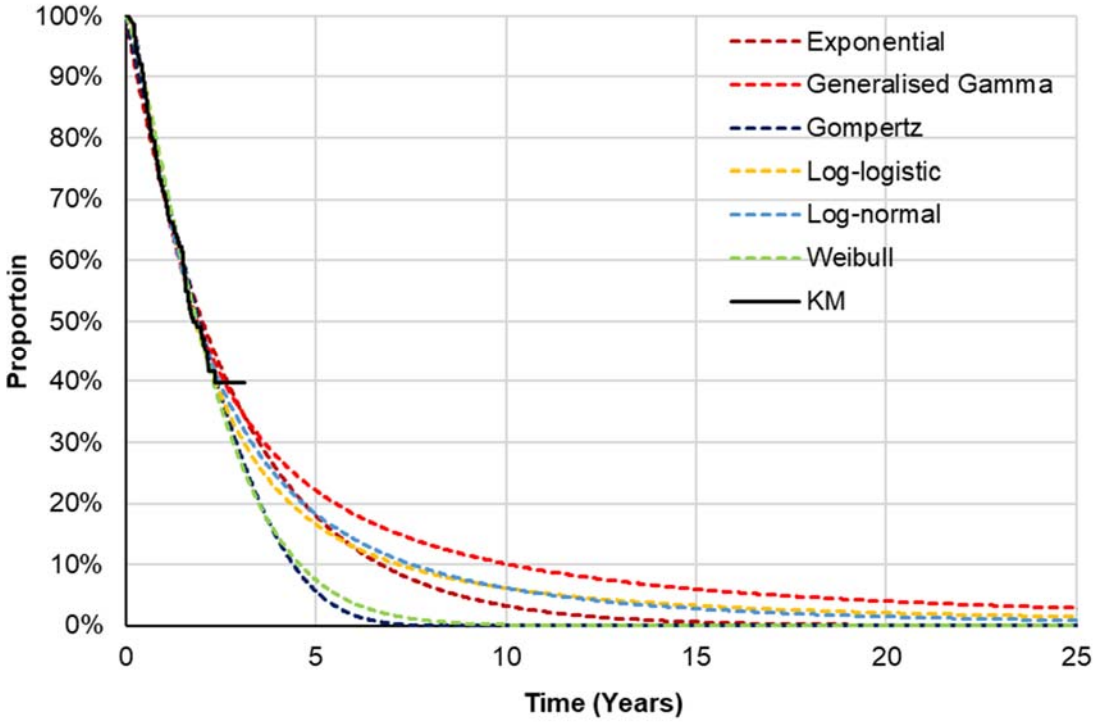
Abbreviations: AIC = Akaike's information criteria; BIC = Bayesian information criteria; OS = overall survival
Note: values shown in bold represent the lower scores (i.e. statistically best-fitting models).

Based on the statistical goodness-of-fit scores (Table B.3.4), it may be inferred that the exponential, Gompertz, and Weibull models provide a relatively poor fit for both treatment arms. The log-normal distribution provides the best-fitting model for the avelumab maintenance arm (based on AIC and BIC), whereas the generalised gamma and log-normal models provide the best AIC and BIC scores for the watchful waiting arm, respectively. However, for the watchful waiting arm, the log-logistic, log-normal, and generalised gamma parameterisations yield similar statistical goodness-of-fit scores, and were therefore not discounted on the basis of AIC and BIC scores alone.

B.3.3.3.1.4 Plausibility of fitted models after the end of follow-up in JAVELIN Bladder 100

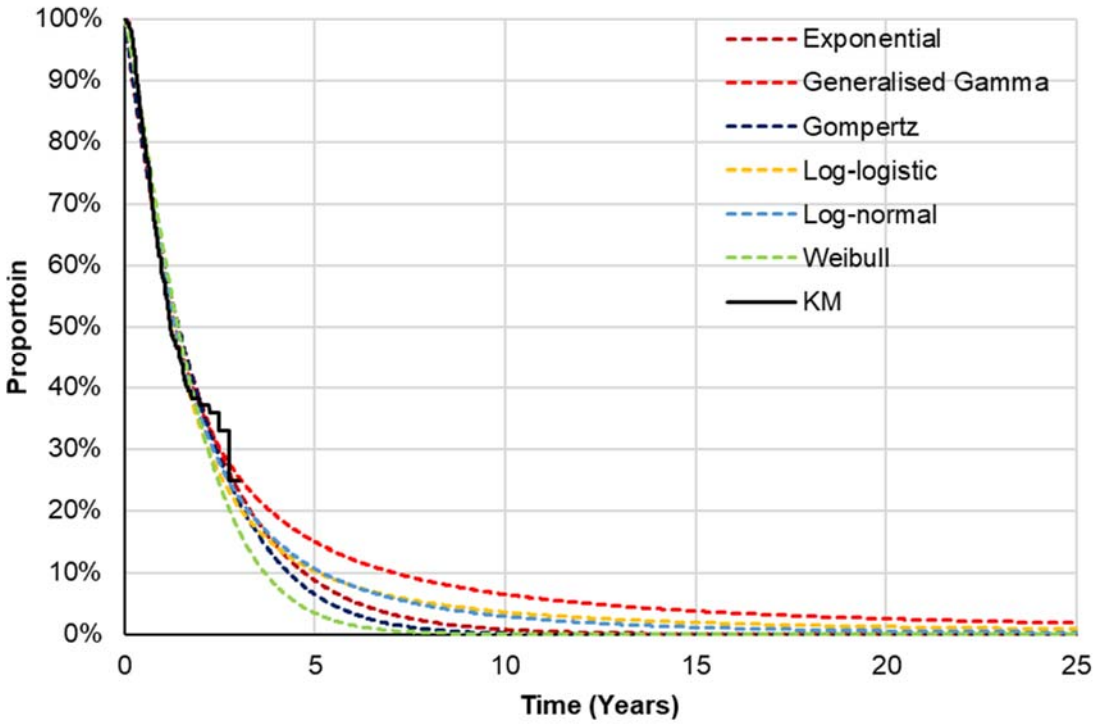
Figure B.3.6 presents the OS parametric survival curves fit to the avelumab arm in JAVELIN Bladder 100 over the model time horizon of 25 years. Figure B.3.7 presents the equivalent model fits for the watchful waiting arm.

Figure B.3.6. Parametric survival model extrapolations for OS (avelumab)



Abbreviations: KM = Kaplan-Meier; OS = overall survival

Figure B.3.7. Parametric survival model extrapolations for OS (watchful waiting)



Abbreviations: KM = Kaplan-Meier; OS = overall survival

Eight consultant oncologists from various hospitals in the UK consulted for this appraisal suggested that 5-year OS for patients managed with avelumab maintenance is expected to be between 20% and 30%, and 10-year OS is expected to be in the region of 10–15%. The only model to predict 10-year OS in the region of 10–15% is the generalised gamma (10.14%). The Gompertz and Weibull models estimated 10-year OS to be near-zero (0.00–0.14%). The remaining models estimated 10-year OS to be 3.26% (exponential), 6.15% (log-logistic) and 6.18% (log-normal).

For the watchful waiting arm, clinicians suggested that 5-year OS is expected to be in the region of 5–15%, and that 10-year OS could be between 2% and 7%, with an estimate of 10% considered optimistic. This feedback suggests that the exponential, Weibull, and Gompertz models may be considered too pessimistic for the watchful waiting arm (10-year OS estimated to be between 0.03% and 0.77%). Conversely, the generalised gamma may be considered optimistic, given that estimates of 5- and 10-year OS (15.00% and 6.48%, respectively) are closer to the upper bounds suggested by the clinicians. The remaining two models (log-normal and log-logistic) provided estimates approximately in the middle of the ranges suggested by the clinicians:

- Log-normal: 5-year OS: 10.71%, 10-year OS: 2.90%
- Log-logistic: 5-year OS: 10.29%, 10-year OS: 3.60%

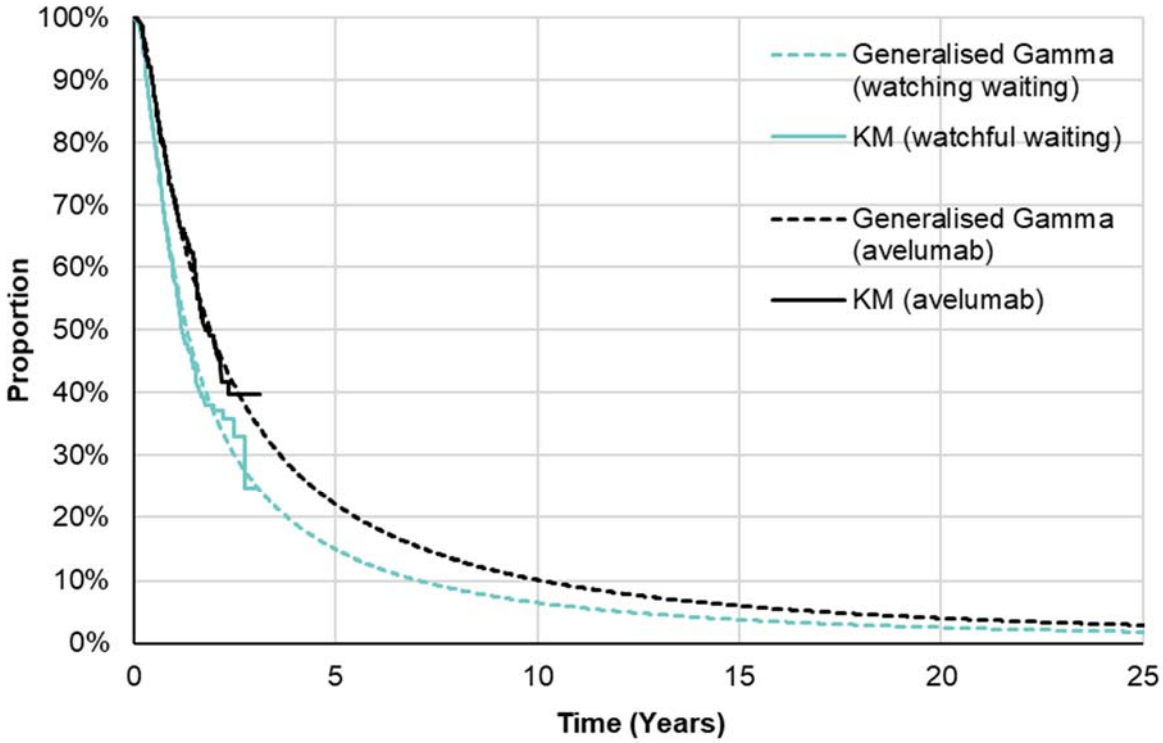
B.3.3.3.1.5 Requirement for any adjustments to be made

To ensure model projections did not lead to an estimated hazard of death that falls beneath that of the age- and sex-adjusted general population, the model 'caps' the estimated probability of death for both treatment arms by an estimated survival curve for the general population. National life tables from the Office for National Statistics were used to produce the general population survival curve.[132]

B.3.3.3.1.6 Summary of base-case model(s)

Figure B.3.8 provides a summary of base-case extrapolations for OS applied within the model.

Figure B.3.8. Base-case extrapolations for OS (avelumab and watchful waiting)



Abbreviations: KM = Kaplan-Meier; OS = overall survival

The generalised gamma model was considered the most suitable extrapolation to inform the avelumab arm, based on it being the only model to provide an estimate of 10-year survival within the bounds estimated by UK consultant oncologists. Furthermore, the AIC difference is less than two which demonstrates that the best fitting and second best-fitting models are essentially equivalent. The BIC difference of <10 further demonstrates that generalised gamma has a reasonable fit compared with the best-fitting model. For the watchful waiting arm, the generalised gamma model provided the best AIC score, and the second-best BIC score, a good visual fit to the Kaplan-Meier curve, and a clinically-plausible extrapolation.

The generalised gamma extrapolation for the watchful waiting arm may be considered optimistic, whereas the corresponding extrapolation for the avelumab arm may be considered pessimistic (based on clinical expert opinion). Therefore, the combination of these extrapolation approaches may under-estimate the true survival benefit attributable to avelumab.

The use of the same parametric model for both treatment arms was also considered appropriate given that each strategy should be associated with a potential flattening of the OS curve (in line with the use of anti-PD-1/PD-L1 therapy either upfront as maintenance, or following disease progression). However, the flattening of the curve for the avelumab arm is noted to occur earlier, given that this strategy reflects earlier use of anti-PD-L1 therapy in all patients in the avelumab arm, versus only a proportion of patients who experience disease progression in the watchful waiting arm.

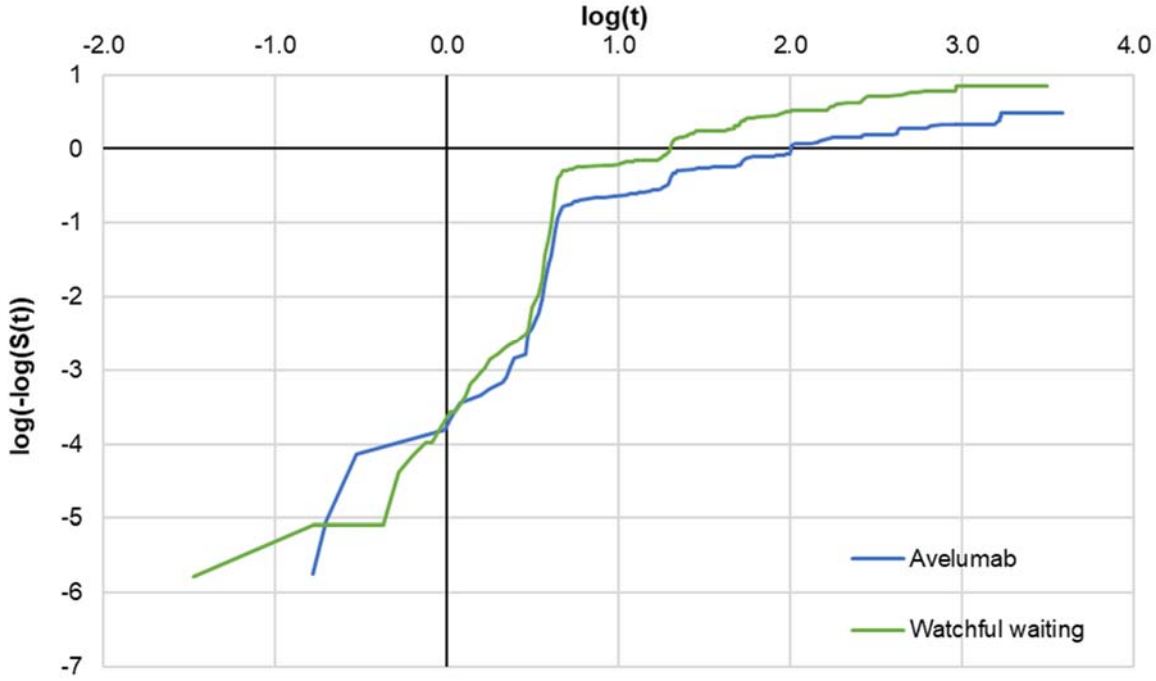
B.3.3.3.2 Progression-free survival

Two alternative approaches were available to inform designation of progression status based on data collected as part of the JAVELIN Bladder 100 trial: (1) investigator-assessed progression (INV), or (2) BICR-assessed progression. In the base-case analysis, BICR-assessed progression is used to inform the model. INV-assessed progression is explored further within sensitivity analysis.

B.3.3.3.2.1 Assessment of data from JAVELIN Bladder 100

As with OS data from JAVELIN Bladder 100, a LCHP was produced for PFS (Figure B.3.9). From the LCHP, it can be seen that the curves cross, and there is no clear evidence of parallel lines over time. Therefore, it was determined that independent model fits were likely to be the most suitable for informing the cost-effectiveness analysis.

Figure B.3.9. Log-cumulative hazard plot for PFS

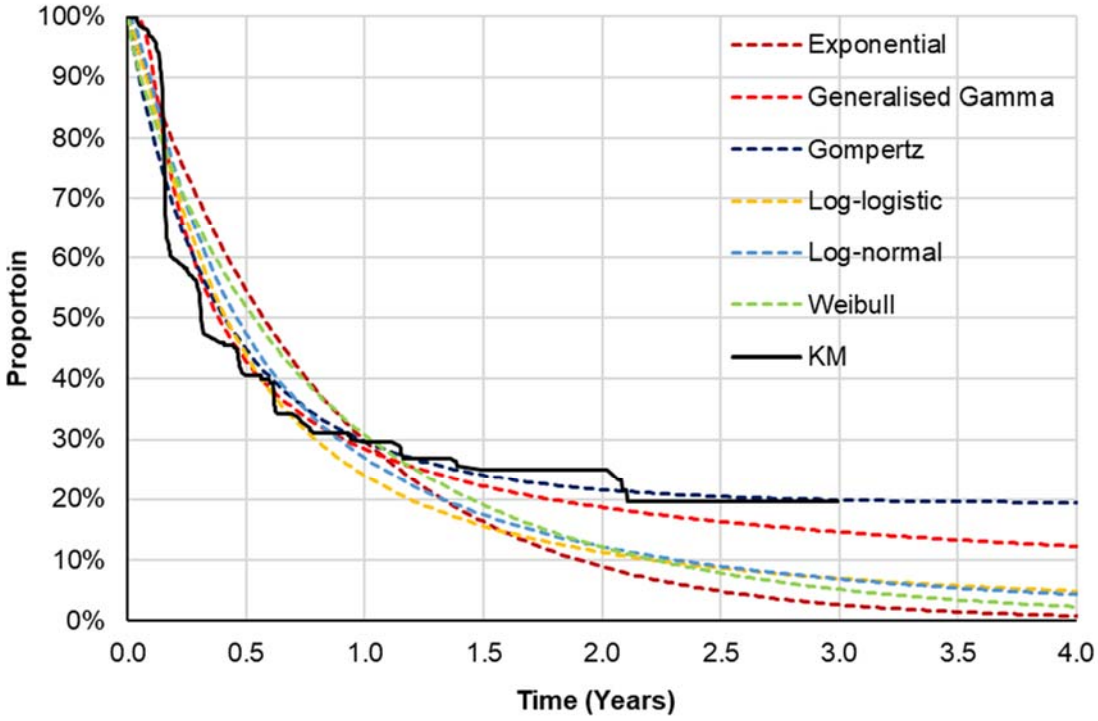


Abbreviations: PFS = progression-free survival; S(t) = Survival at time t

B.3.3.3.2.2 Fitting of potentially-suitable models

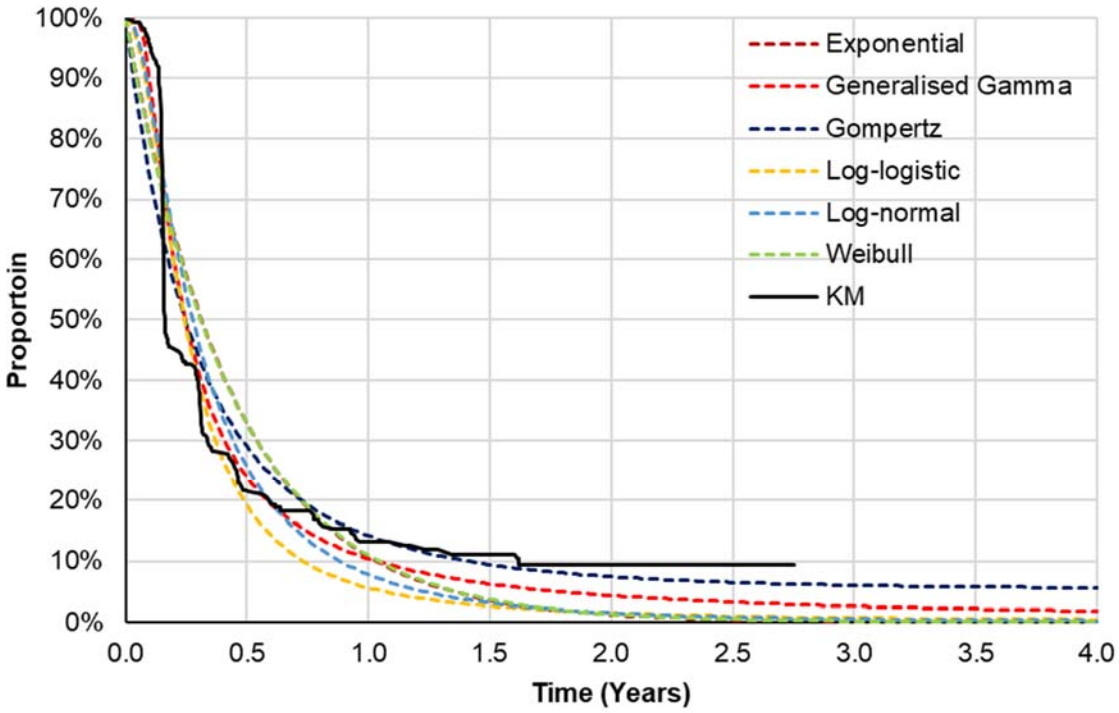
The same six parametric models used for OS were also fitted for the outcome of PFS (Figure B.3.10 and Figure B.3.11 for avelumab and watchful waiting, respectively). Longer-term extrapolations are presented in Section B.3.3.3.2.4.

Figure B.3.10. Parametric survival model fits for PFS (avelumab)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

Figure B.3.11. Parametric survival model fits for PFS (watchful waiting)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

Based on an inspection of the fitted models, it can be seen that none of the models are able to fully reflect the protocol-driven bumps in the PFS curves for both arms; most notably based on the initial drop seen at approximately 2 months in the watchful waiting arm (Figure B.3.11). The Gompertz model provides a good visual fit for each arm, as does the generalised gamma. However, the remaining four models fail to fit to the tail-end of the Kaplan-Meier curves for each arm.

Given that the standard models did not exhibit a good fit to the PFS Kaplan-Meier curves, an alternative approach was explored based on the specification of natural-cubic spline-based parametric models (also known as Royston and Parmar spline models). Spline-based parametric models have been used to inform a number of previous appraisals conducted by NICE, including the previous assessment of avelumab for patients with metastatic MCC (TA517).[133] Spline-based models were fitted using the *stpm2* package in STATA.[134] As described by Royston and Parmar (2002), a transformation $g(S(t))$ of the survival function is modelled as a natural cubic spline function of log time $x = log(t)$.[135] A spline function comprises piecewise polynomials, joined at knots. The term "natural" (or "restricted") is used to describe a spline model where polynomials are constrained to be linear in the two tails (i.e. of order 1 beyond the boundary knots); as this generally provides a reasonable fit to the typically sparse data at the extremes. 'Cubic' describes the specification of a spline model comprising polynomials of order 3 – the simplest polynomial that allows an inflection while smoothing at knot boundaries.[135]

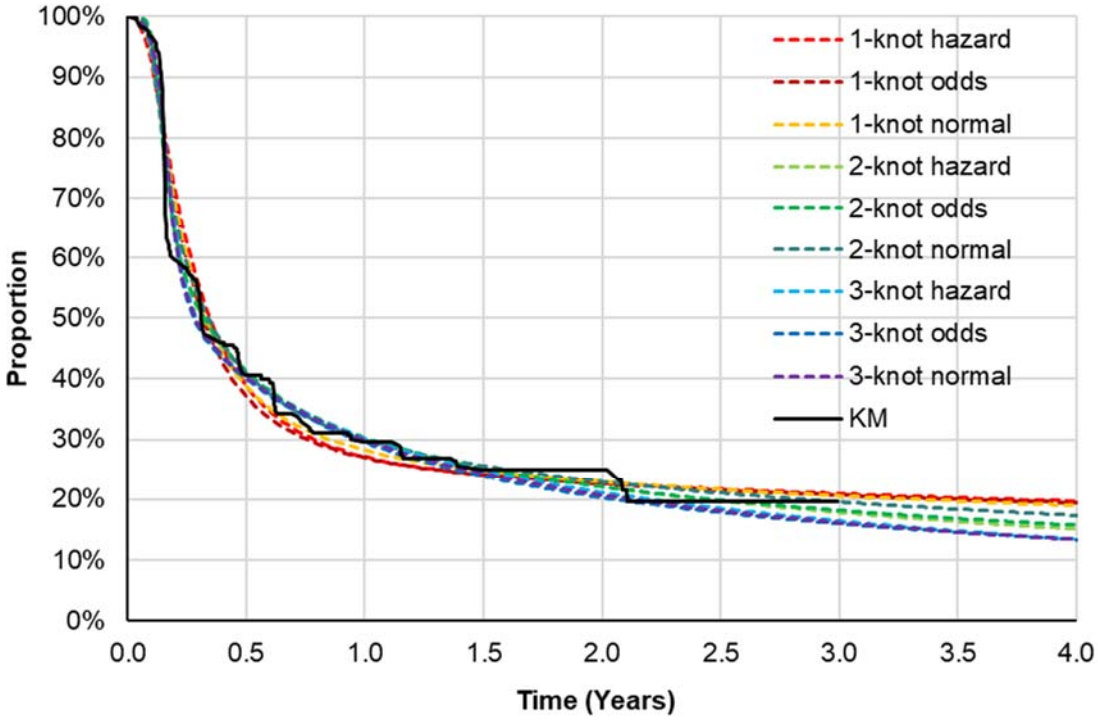
Three potential functional forms or model types were considered:

- 'Hazard', where the 'log cumulative hazard' is modelled as a spline function. This is an extension to a traditional Weibull model
- 'Odds', where the 'log cumulative odds' is modelled as a spline function. This is an extension to a traditional log-logistic model
- 'Normal', where $-\Phi^{-1}(S(t))$ is modelled as a spline function $\Phi^{-1}()$ is the inverse normal distribution function). This is an extension to a traditional log-normal model

Minimum and maximum knots are positioned at the first and last events that were observed, respectively. Models were fitted with one, two, or three intermediate knots. Models with more than three internal knots were not fitted, as literature suggests any more than three intermediate knots (i.e. more than four degrees of freedom) could be potentially unstable.[135] Knot locations were set based on percentiles of the uncensored survival times (as knot location is not considered critical for model fit).[135]

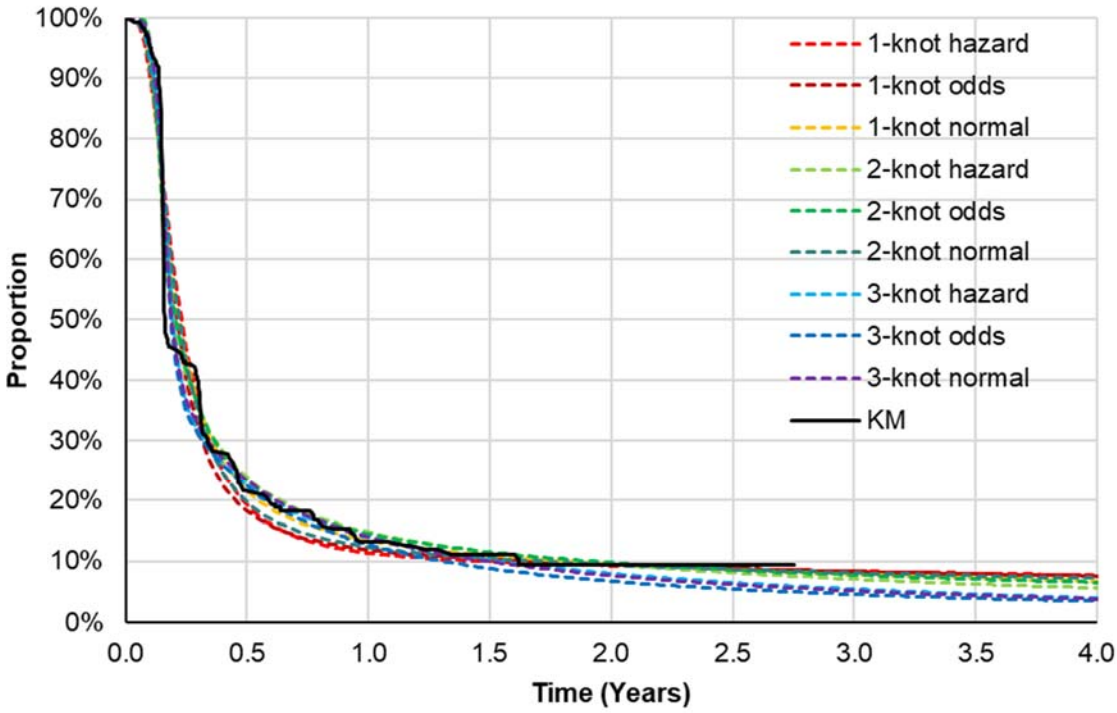
The combination of the three functional forms and different number of internal knots led to a total of nine different spline-based models being fitted. The spline-based model fits are presented in Figure B.3.12 and Figure B.3.13 for avelumab and watchful waiting, respectively.

Figure B.3.12. Spline-based parametric survival model fits for PFS (avelumab)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

Figure B.3.13. Spline-based parametric survival model fits for PFS (watchful waiting)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

Compared with the standard parametric models, the spline-based models exhibit a much better fit to the Kaplan-Meier curve. For this reason, the spline-based models were deemed to

be more suitable for informing the cost-effectiveness analysis than the standard parametric models. However, the standard models were explored in sensitivity analysis for completeness. Each of the nine spline-based models fitted exhibited a similar visual fit to the Kaplan-Meier curve, and so further inspection of the models was considered necessary to determine a model suitable to inform the base-case analysis.

B.3.3.3.2.3 Inspection of statistical goodness-of-fit scores for fitted models

Statistical goodness-of-fit scores for the PFS models are provided in Table B.3.5.

Table B.3.5. Statistical goodness-of-fit scores (PFS)

Model	Avelumab		Watchful waiting	
	AIC	BIC	AIC	BIC
INV-assessed				
Exponential	1,016.90	1,020.76	936.44	940.30
Generalised gamma	903.47	915.04	817.12	828.69
Gompertz	981.61	989.32	907.61	915.33
Log-logistic	964.43	972.15	822.55	830.26
Log-normal	950.54	958.26	834.40	842.12
Weibull	1,014.15	1,021.86	938.41	946.13
1-knot hazard	914.96	926.53	768.86	780.43
1-knot odds	906.96	918.53	755.13	766.70
1-knot normal	899.29	910.86	797.15	808.73
2-knot hazard	884.99	900.42	742.91	758.34
2-knot odds	884.11	899.54	745.14	760.58
2-knot normal	893.73	909.17	780.83	796.26
3-knot hazard	**879.08**	**898.37**	707.23	726.52
3-knot odds	879.89	899.18	682.25	**701.54**
3-knot normal	895.94	915.23	688.10	707.39
BICR-assessed				
Exponential	1,005.23	1,009.09	930.79	934.65
Generalised gamma	841.64	853.22	743.76	755.34
Gompertz	937.21	944.93	888.59	896.31
Log-logistic	929.00	936.71	794.70	802.41
Log-normal	918.03	925.75	809.28	817.00
Weibull	995.02	1,002.73	932.72	940.44
1-knot hazard	835.01	846.58	703.36	714.94
1-knot odds	820.97	832.54	676.31	687.88
1-knot normal	818.49	830.06	698.59	710.16
2-knot hazard	786.94	802.37	645.26	660.70
2-knot odds	787.99	803.43	657.07	672.51
2-knot normal	814.61	830.04	696.77	712.20
3-knot hazard	785.14	804.43	610.76	630.05
3-knot odds	775.59	794.88	**589.38**	**608.67**
3-knot normal	**770.00**	**789.29**	592.75	612.04

Abbreviations: AIC = Akaike's information criteria; BIC = Bayesian information criteria; INV = investigator; BICR = blinded independent central review
Notes: values shown in bold represent the lower scores (i.e. statistically best-fitting models)

Based on the statistical goodness-of-fit scores (Table B.3.5), it may be inferred that the more flexible generalised gamma models provide a clearly superior fit to the Kaplan-Meier curves for both arms, versus the other standard parametric models. However, the spline-based

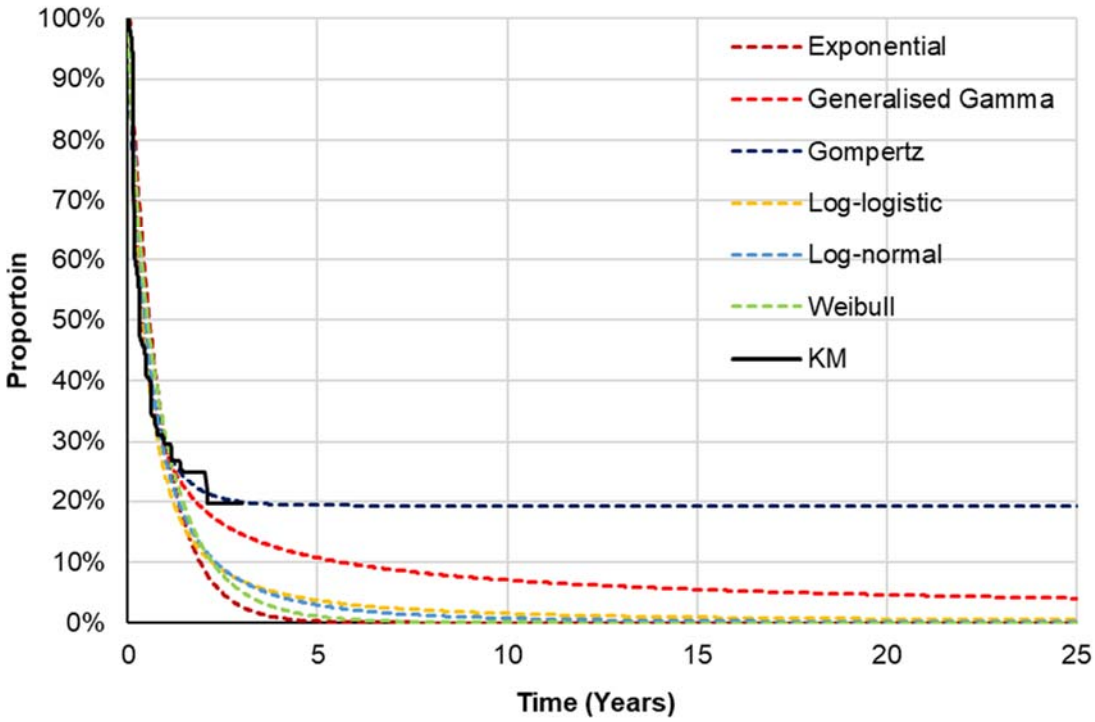
models outperformed the generalised gamma based on both metrics with both progression criteria.

A 3-knot spline-based model was consistently preferred, though the 'best' functional form varied depending on the treatment arm and progression definition. Based on the statistical goodness-of-fit scores, 3-knot splines were considered to likely be the most suitable to inform the base-case analysis.

B.3.3.3.2.4 Plausibility of fitted models after the end of follow-up in JAVELIN Bladder 100

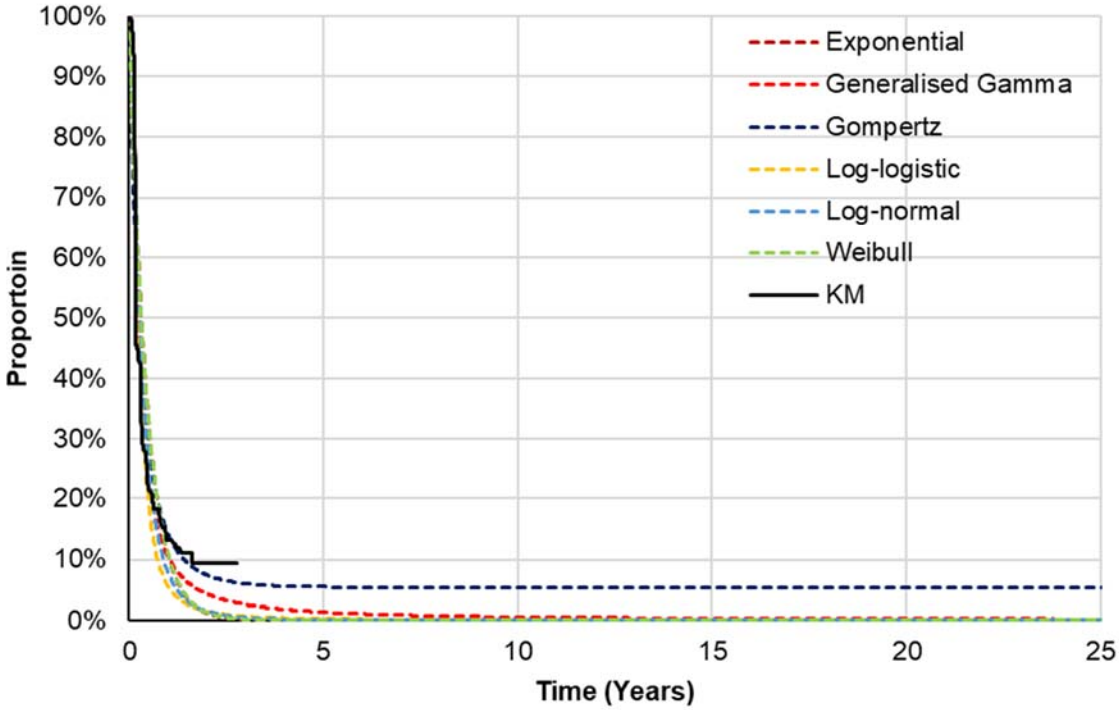
Figure B.3.14 presents the PFS parametric survival curves fit to the avelumab arm in JAVELIN Bladder 100 over the model time horizon of 25 years. Figure B.3.15 presents the equivalent model fits for the watchful waiting arm.

Figure B.3.14. Parametric survival model extrapolations for PFS (avelumab)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

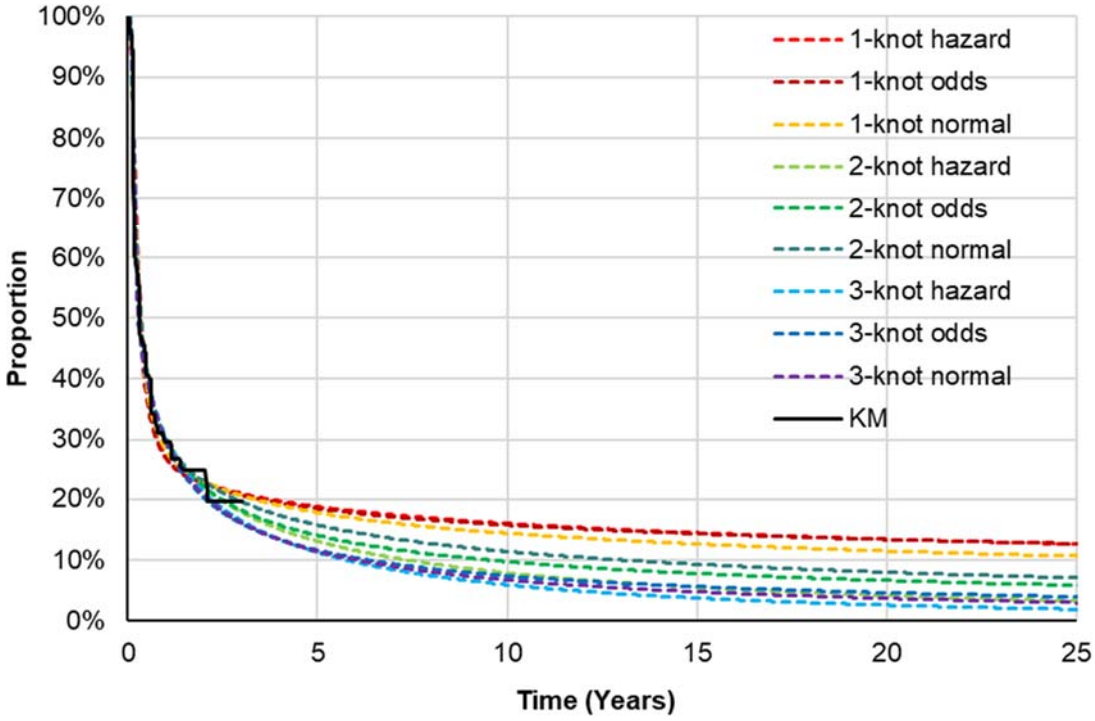
Figure B.3.15. Parametric survival model extrapolations for PFS (watchful waiting)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

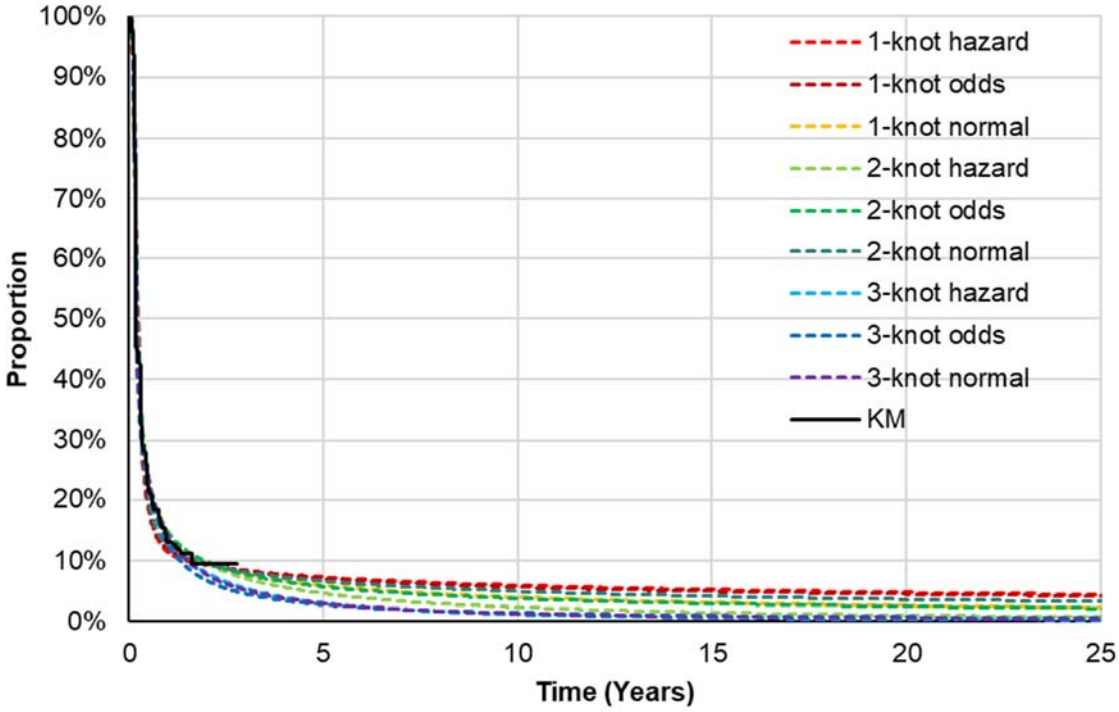
The Gompertz models fitted to each arm exhibit long-term hazards of a PFS event that trend to zero, which is not clinically plausible. Of the standard parametric modes, the generalised gamma model is the only model that does not appear to substantially under-estimate PFS for both arms (notwithstanding the aforementioned issues with the goodness-of-fit for this model, and the other standard parametric models). The corresponding projections for the spline-based models are provided in Figure B.3.16 (avelumab) and Figure B.3.17 (watchful waiting).

Figure B.3.16. Spline-based parametric survival model extrapolations for PFS (avelumab)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

Figure B.3.17. Spline-based parametric survival model extrapolations for PFS (watchful waiting)



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

For the avelumab arm, 10-year PFS was estimated to be in the range of 5–20% by UK consultant oncologists. This broad range is indicative of the fact that long-term PFS may be difficult to estimate. Ten-year PFS for the watchful waiting arm was estimated to be up to 4%, with the majority of estimates provided in the range of 0–2%.

The 3-knot splines fitted to the avelumab arm provided a 10-year PFS estimates of 5.90–7.36%, which were considered reasonable (yet potentially conservative) by UK consultant oncologists. Spline-based models with 1- or 2- knots provided estimates of 10-year PFS that were slightly higher, up to approximately 15.96% (1-knot odds spline model). With the exception of the Gompertz model (which yielded unrealistic long-term extrapolations), and the generalised gamma model (which estimated 10-year PFS at 7.01%), the remaining 'standard' parametric models each estimated 10-year PFS to be in the region of 0.00–1.52%.

For the watchful waiting arm, the 3-knot splines provided estimates of 10-year PFS between 1.10% and 1.34%. However, with the exception of the Gompertz model (which, as per the avelumab arm, also yielded an unrealistic extrapolation), the remaining 'standard' models estimated 10-year OS to be between 0.00% and 0.53%.

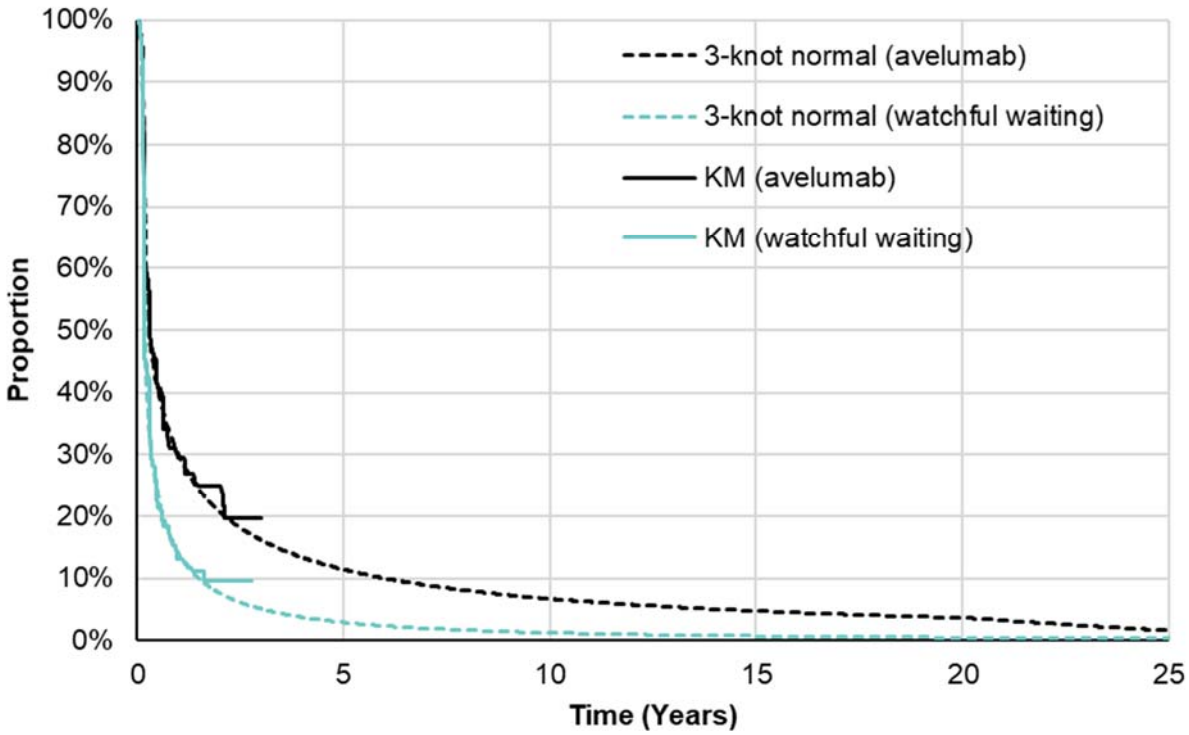
B.3.3.3.2.5 Requirement for any adjustments to be made

In order to ensure the selection of independent OS and PFS curves did not lead to the estimation of patients that were simultaneously progression-free and alive, but also dead (i.e. crossing of the OS and PFS curves), the occupancy of the progression-free state was capped by the OS curve. To do this, the proportion of patients estimated to reside in the progression-free state was assumed to be the minimum of the proportion estimated by the PFS curve or the OS curve. This also includes any adjustments made to the OS curve, described further in Section B.3.3.3.1.

B.3.3.3.2.6 Summary of base-case model(s)

Figure B.3.18 provides a summary of base case extrapolations for PFS applied within the model.

Figure B.3.18. Base-case extrapolations for PFS (avelumab and watchful waiting)



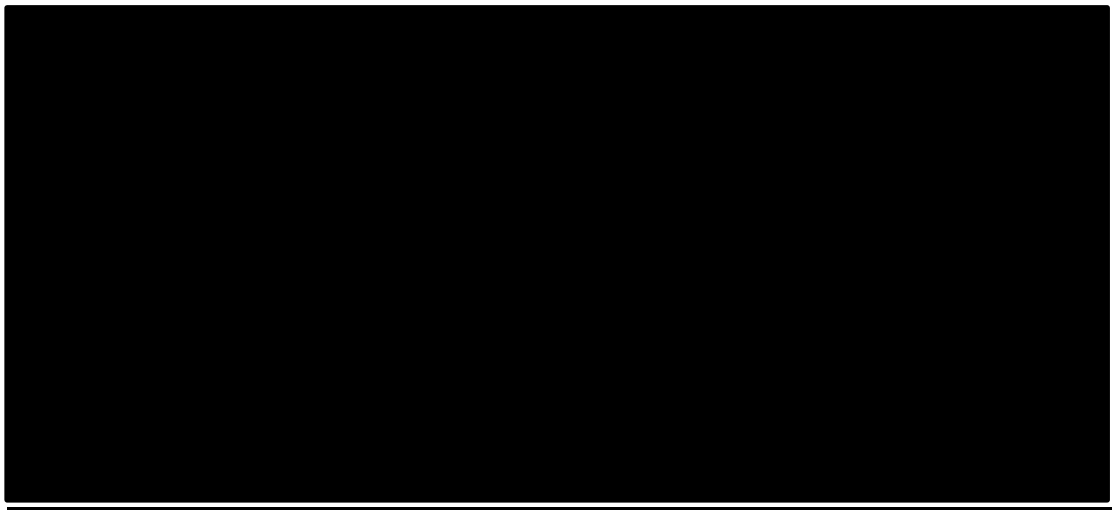
Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

The base-case analysis includes the specification of a 3-knot normal spline-based model for both the avelumab and watchful waiting arms. This model was deemed to provide a suitable fit to the Kaplan-Meier curve for both treatment arms, good statistical goodness-of-fit scores, and reasonable long-term extrapolations (including adjustment based on the OS curve selected). Alternative parametric curves were explored in scenario analysis to test the structural uncertainty within the model.

B.3.3.3.3 Time to treatment discontinuation

As with OS and PFS, survival modelling was also required to inform the estimation of treatment duration within the economic model. However, as only the avelumab arm is associated with active treatment costs upon model entry, the model requires only the specification of parametric models for the outcome of TTD for the avelumab arm. Parametric model fits are provided in Figure B.3.19.

Figure B.3.19. Parametric survival model fits for TTD (avelumab)



Abbreviations: KM = Kaplan-Meier; TTD = time to treatment discontinuation

Based on an inspection of the fitted models, the Gompertz and generalised gamma models provide the best fits to the Kaplan-Meier curve (especially towards the tail end of the curve, though this part of the curve is uncertain due to the small number of patients still at risk). The log-normal and log-logistic models each provide reasonable fits to the Kaplan-Meier curve. The Weibull and exponential models provide a poor fit to the earliest portions of the curve in particular.

B.3.3.3.3.1 Inspection of statistical goodness-of-fit scores for fitted models

Statistical goodness-of-fit scores for the TTD models are provided in Table B.3.6.

Table B.3.6. Statistical goodness-of-fit scores (TTD)

Model	Avelumab	
	AIC	BIC
Exponential	1,050.86	1,054.70
Generalised gamma	**997.73**	**1,009.26**
Gompertz	1,051.63	1,059.31
Log-logistic	1,004.54	1,012.22
Log-normal	1,012.27	1,019.95
Weibull	1,033.63	1,041.31

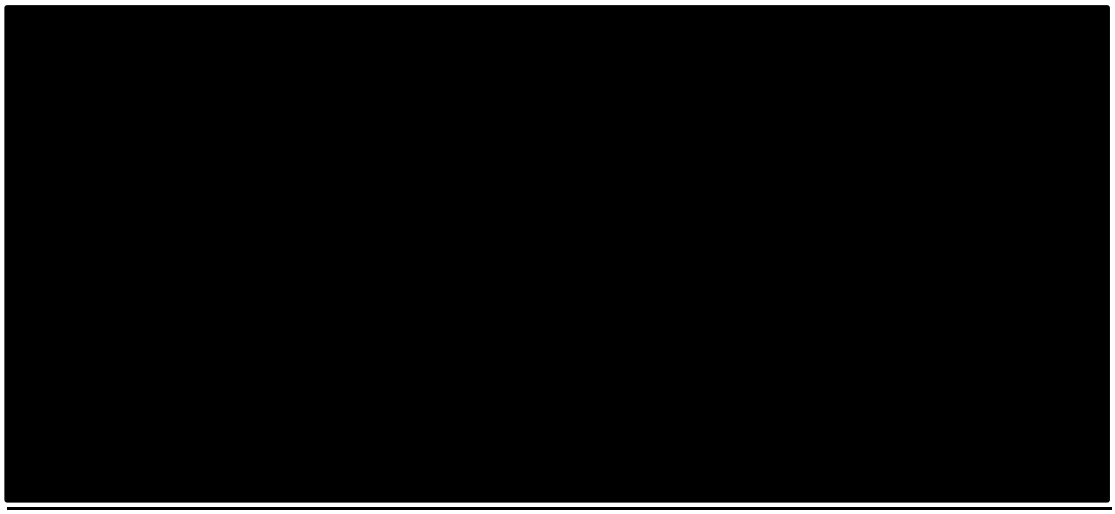
Abbreviations: AIC = Akaike's information criteria; BIC = Bayesian information criteria; TTD = time to treatment discontinuation
Notes: values shown in bold represent the lower scores (i.e. statistically best-fitting models).

Based on the statistical goodness-of-fit scores (Table B.3.6), the generalised gamma and log-normal models provide the best statistical goodness-of-fit scores, with all other models providing scores <10 points from the statistically best-fitting model (generalised gamma).

B.3.3.3.3.2 Plausibility of fitted models after the end of follow-up in JAVELIN Bladder 100

Figure B.3.20 presents the TTD parametric survival curves fit to the avelumab arm in JAVELIN Bladder 100 over the model time horizon of 25 years.

Figure B.3.20. Extrapolations for TTD (avelumab)



Abbreviations: KM = Kaplan-Meier; TTD = time to treatment discontinuation

With the exception of the Weibull and exponential models, each of the models project at least 5% of patients to continue treatment after 5 years. UK consultant oncologists considered it highly unlikely that patients would continue treatment beyond 5 years. Therefore, in terms of longer-term plausibility, the Weibull and exponential models may be considered the most reasonable estimates, though it should be noted that their fits to the Kaplan-Meier curve (and statistical fit scores) were poor versus the other models considered.

B.3.3.3.3.3 Requirement for any adjustments to be made

To ensure that patients do not continue treatment with avelumab longer than is deemed clinically plausible, the model base-case analysis assumes all patients will have discontinued treatment by 5 years.

UK consultant oncologists indicated that after 2 years, some patients may discontinue treatment with avelumab. The timepoint of 2 years has been considered in a number of previous NICE appraisals in other clinical indications for patients receiving anti-PD-1/PD-L1 therapies. With respect to UC specifically, the recommendation for TA519 (pembrolizumab) and TA525 (atezolizumab) is that treatment is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, for patients with locally advanced or metastatic UC after platinum-based chemotherapy.[81,84]

Within the context of avelumab maintenance in JAVELIN Bladder 100, no formal stopping rule was mandated, and continued treatment was at the discretion of the investigator. However, in clinical practice, it is anticipated that treatment for the majority of patients will have been discontinued by this time. This expectation was echoed in clinical advice provided to NICE as part of its previous assessment of avelumab in MCC, wherein clinical advisers explained that for many immunotherapies used in other diseases, when there is a durable response and patients remain well, treatment tends to be stopped by 2 years for the majority of patients.[133]

It is acknowledged that no parametric model is capable of reflecting a proportion of patients that discontinue treatment at approximately 2 years. Therefore, the base-case analysis assumes that by 2 years, 95% of patients will have discontinued treatment. The remaining 5% of patients are then assumed to follow the pattern of discontinuation per the selected

parametric model, before discontinuing at a maximum of 5 years. This approach is expected to more closely resemble clinical practice with avelumab, and a number of alternative scenarios relating to treatment discontinuation are explored within sensitivity analysis.

B.3.3.3.3.4 Summary of base-case model(s)

Figure B.3.21 provides a summary of base case extrapolations for TTD applied within the model.

Figure B.3.21. Base-case extrapolations for TTD (avelumab)

Abbreviations: KM = Kaplan-Meier; TTD = time to treatment discontinuation

In the base-case analysis, a log-normal model is applied until 2 years, after which 95% of patients are assumed to have discontinued (leaving a total of 5% continuing thereafter). The remaining 5% then follow the log-normal model extrapolation until 5 years, at which point all patients estimated to still remain on treatment are assumed to immediately discontinue. This method was considered to represent a reasonable trade-off between visual fit to the Kaplan-Meier curve, and long-term extrapolation, as other models did not exhibit clear face validity:

- The Weibull and exponential models exhibited reasonable longer-term extrapolations (0.9% and 0.6% at 5 years, respectively), but did not fit the Kaplan-Meier curve well compared to the other models
- The generalised gamma, Gompertz, and log-logistic models fit the Kaplan-Meier curve well, but predicted a relatively large proportion patients to remain on treatment at 5 years (7.5%, 9.1%, and 4.8%, respectively)
- The log-normal model exhibited a good visual and statistical fit to the Kaplan-Meier curve (second-best AIC and BIC score), while predicting 4.0% of patients to continue treatment at 5 years (i.e. the lowest proportion of the models exhibiting a reasonable visual and statistical fit to the Kaplan-Meier curve, although still higher than expected [i.e. 0%])

Additionally, the log-normal model predicts a relatively low number of patients still receiving avelumab treatment at 2 years (compared with some of the other parametric models, without adjustments). This is consistent with an emerging acceptance that few patients will continue immunotherapy treatment beyond this time point, though without explicit adjustment to

account for patients discontinuing at 2 years, only the exponential and Weibull estimated nearly 95% of patients to have discontinued by 2 years).

Alternative TTD extrapolations were explored in scenario analysis to test the structural uncertainty within the model.

B.3.3.3.3.5 Summary of clinical parameters and variables applied in model

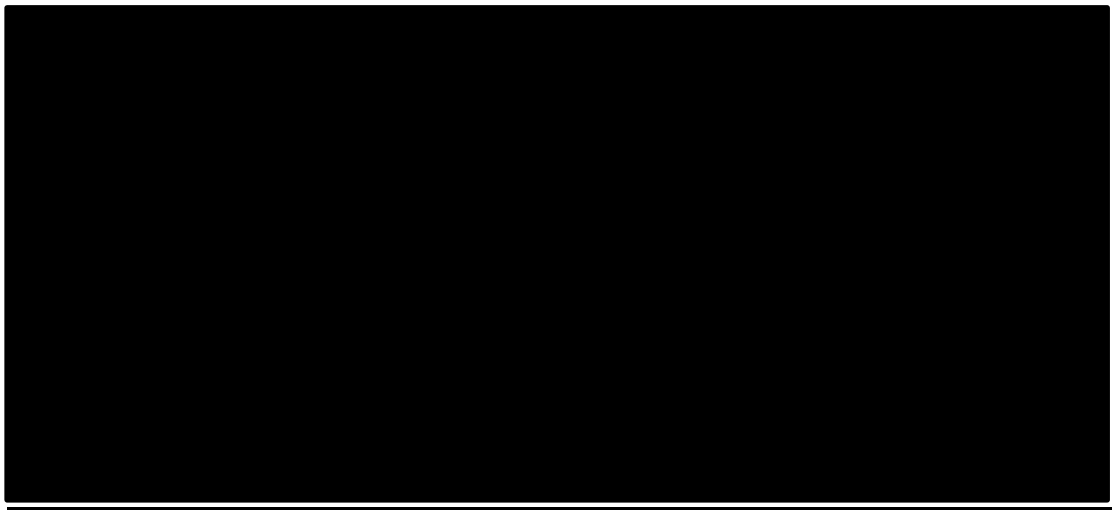
A summary of the main clinical parameters and variables applied in the economic model is provided in Table B.3.7. The base-case survival models used to inform the cost-effectiveness analyses are provided in Figure B.3.22 (over a shorter 10-year period, in order to compare the fitted models to the corresponding Kaplan-Meier curves).

Table B.3.7. Summary of clinical model parameters and variables

Parameter	Value	Rationale	Section
Baseline characteristics	As presented in Table B.3.2	Reflective of JAVELIN Bladder 100 patient population	B.3.3.1
AEs included	Most common Grade ≥3 TEAEs or TRAEs occurring in ≥1% of patients in either arm, plus all Grade ≥3 irAEs occurring in ≥1% of patients in either arm	Considered to reflect the main AEs experienced by patients.	B.3.3.2
OS models	Generalised gamma models fitted to each treatment arm	Good visual fit to KM, best statistical goodness-of-fit scores, reasonable extrapolation of longer-term OS	B.3.3.3.1
PFS models	3-knot normal spline-based models fitted to each treatment arm	Spline model provided improved fit versus standard models. 3-knot normal splines provided good visual and statistical fit, with reasonable extrapolation of longer-term PFS	B.3.3.3.2
TTD models	Log-normal model, with 95% of patients assumed to have discontinued by 2 years, and all patients assumed to discontinue by 5 years	Trade-off between visual fit to the Kaplan-Meier curve and plausibility of long-term extrapolation, accounting for discontinuation of most/all patients after 2/5 years based on clinical expert opinion	B.3.3.3.3

Abbreviations: AE = adverse event; irAE = immune-related adverse event; OS = overall survival; PFS = progression-free survival; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; TTD = time to treatment discontinuation

Figure B.3.22. Summary of survival models applied within the base-case analysis



Abbreviations: KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life studies

An SLR was conducted to identify evidence on the humanistic outcomes of avelumab and relevant comparators for the treatment of locally advanced or metastatic UC (see Appendix H). Of the eleven identified studies (six based on RCT populations and two retrospective post-hoc trial analyses), none were conducted in the UK.

B.3.4.2 Health-related quality-of-life data from clinical trials

In JAVELIN Bladder 100, patients self-reported HRQoL using the EQ-5D-5L questionnaire at each treatment cycle of 28 days, at the end of treatment, and at 30-, 60-, and 90-day follow-up visits after discontinuation of study drug.[110] The EQ-5D encapsulates five domains of HRQoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and the 5L version has five levels for each domain: no problems, slight problems, moderate problems, severe problems and extreme problems or inability.

The use of EQ-5D as a generic, preference-based HRQoL measure aligns with the NICE reference case requirements.[136] However, the -5L version of the EQ-5D is not aligned with the NICE reference case requirements, and so EQ-5D-5L responses were ‘crosswalked’ to produce equivalent EQ-5D-3L values.

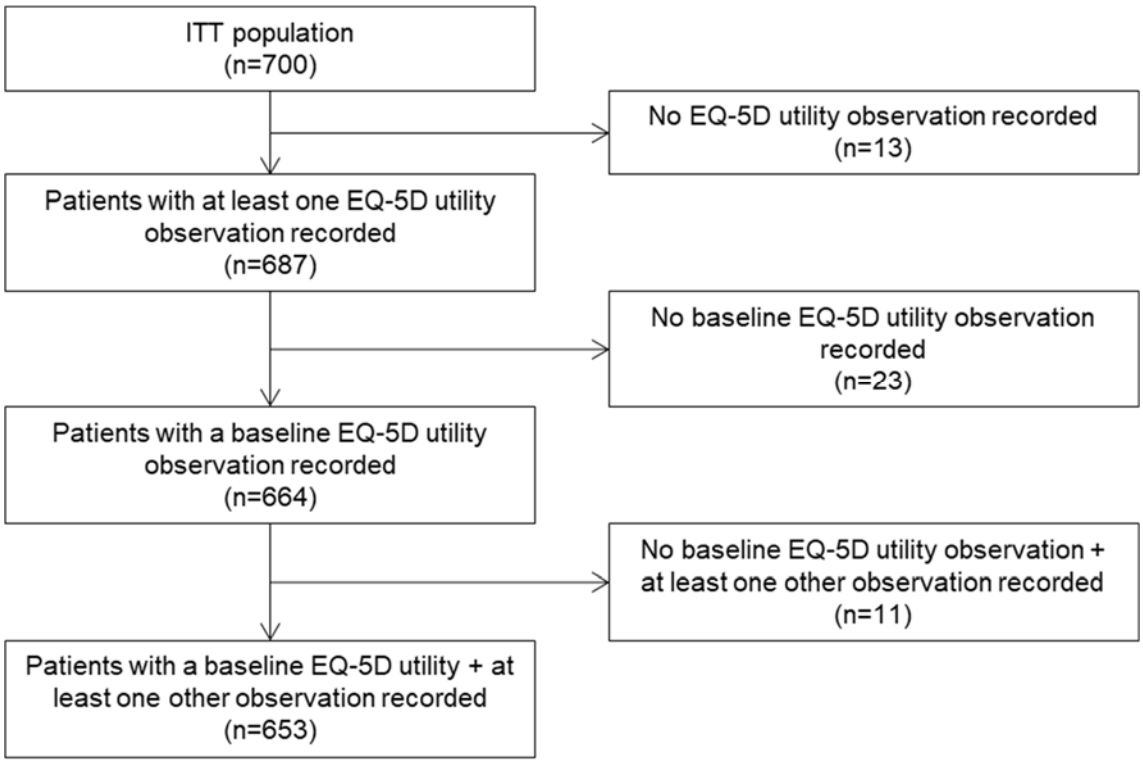
Patients were included within the analysis set for consideration in the cost-effectiveness analysis based on the following criteria:

- Available baseline EQ-5D utility
    - Patients were excluded if a baseline utility value was not reported, as analyses were adjusted for baseline utility (centred at the mean value of the eligible population) as a (continuous) fixed effect, to consider between patient differences in utilities at baseline
- At least one follow-up EQ-5D utility (i.e., after the baseline assessment)

- As baseline utility was used to adjust for between patient differences, patients with no further observations could not be included within utility analysis and were therefore excluded from consideration

The number of patients with missing observations (precluding them from inclusion within the utility analysis) is provided in Figure B.3.23.

Figure B.3.23. Availability of patient data from JAVELIN Bladder 100 for consideration in utility analysis



Abbreviations: EQ-5D = EuroQoL-Five Dimensions; ITT = intention-to-treat

Table B.3.8 presents a summary of the EQ-5D data available from JAVELIN Bladder 100 ultimately used to inform the utility analysis to inform the cost-effectiveness analysis.

Table B.3.8. EQ-5D questionnaire completion in JAVELIN Bladder 100

Assessment	Patients with recorded utility values, n		
	Avelumab (N=333)	Watchful waiting (N=320)	Overall (N=653)
Cycle 1 (baseline)	[redacted]	[redacted]	[redacted]
Cycle 2 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 3 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 4 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 5 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 6 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 7 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 8 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 9 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 10 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 11 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 12 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 13 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 14 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 15 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 16 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 17 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 18 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 19 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 20 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 21 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 22 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 23 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 24 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 25 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 26 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 27 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 28 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 29 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 30 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 31 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 32 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 33 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 34 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 35 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 36 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 37 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 38 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 39 (day 1)	[redacted]	[redacted]	[redacted]
Cycle 40 (day 1)	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]
Follow-up (day 30)	[redacted]	[redacted]	[redacted]
Follow-up (day 60)	[redacted]	[redacted]	[redacted]
Follow-up (day 90)	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D = EuroQoL-Five Dimensions; N = number of patients evaluable; n = number of patients in the category
Note: % expressed based on the total number of patients with a baseline utility recorded
Source: Pfizer Inc., 2020;[110] Powles et al., 2020[47]

A description of the statistical methods used to analyse the EQ-5D data is provided in Section B.3.4.5. In the base-case analysis, utility values are lower after disease progression

but there is no utility benefit applied specifically to patients treated with avelumab versus watchful waiting within a given health state.

B.3.4.3 Mapping

Health state utilities were estimated using EQ-5D data from JAVELIN Bladder 100. As described in Section B.3.4.2, utilities were obtained using a crosswalk algorithm by van Hout et al. (2012) for mapping EQ-5D-5L responses to EQ-5D-3L responses, along with the value set for EQ-5D-3L-derived weights for England from Dolan et al. (1997).[137,138] This approach is currently recommended by NICE.[139] However, no specific mapping was performed to obtain EQ-5D estimates from a different measure of HRQoL (as EQ-5D data were collected in JAVELIN Bladder 100).

B.3.4.4 Adverse reactions

The frequency of AEs for avelumab and watchful waiting were obtained from JAVELIN Bladder 100, with the costs incurred for associated treatment of AEs incorporated into the economic model (see Section B.3.5.4). A summary of AEs included within the model are summarised in Table B.3.3 (Section B.3.3.2).

The disutilities for AEs and assumed durations over which they are applied within the model are summarised in Table B.3.9

Table B.3.9. AE-related disutilities and durations

Adverse event	Disutility		Duration of disutility (days)	
	Value	Reference	Value	Reference
Fatigue	-0.073	Nafees et al., 2008[140]	108	TA581[141]
Vomiting	-0.048	Nafees et al., 2008[140]	19	TA581[141]
Urinary tract infection	-0.009	Sullivan et al., 2006 (ICD-9 599)[142]	14	Assumption
Anaemia	-0.090	Beusterien et al. 2010[143]	28	TA581[141]
Lipase increased	-0.090	Assumed equivalent to anaemia	28	Assumed equivalent to anaemia
Amylase increased	-0.090	Assumed equivalent to anaemia	28	Assumed equivalent to anaemia
Back pain	-0.046	Sullivan et al., 2006 (ICD-9 724)[142]	17	TA378 same as abdominal pain taken from TA306[144]
Immune-mediated hepatitis	-0.057	Sullivan et al., 2006 (ICD-9 573) [142]	33	Gauci et al., 2018[145]
Immune-mediated rash	-0.032	Nafees et al., 2008[140]	84	TA581[141]
Asthenia	-0.073	Assumed equivalent to fatigue	108	Assumed equivalent to fatigue
Haematuria	-0.009	Assumed equivalent to urinary tract infection	14	Assumed equivalent to urinary tract infection

Abbreviations: AE = adverse event; ICD-9 = International Classification of Diseases, 9th revision

Due to the infrequent occurrence of Grade ≥3 AEs in either treatment arm, the overall impact on QALYs is small (-0.0012 QALYs applied to the avelumab arm, compared with -0.0006 QALYs applied to the watchful waiting arm).[145]

AEs related to subsequent therapies were not considered within the analysis. This simplifying assumption (i.e. that AEs related to subsequent therapies have a negligible impact on HRQoL) is likely biased against avelumab, owing to the increased use of subsequent therapies for patients managed with watchful waiting following first-line chemotherapy.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

When considering HRQoL data from JAVELIN Bladder 100, it is important to acknowledge that all patients achieved either stable disease (27.9%) or a PR/CR (72.1%) following first-line chemotherapy, and thus were eligible to receive avelumab maintenance (though may have been randomised to either treatment arm). This patient population may therefore be considered to be in a relatively better health state compared with those who did not respond to chemotherapy (i.e. did not achieve stable disease, PR or CR).

The assessment of HRQoL at the beginning of avelumab maintenance is notably distinct from assessing HRQoL for patients initiating a new line of treatment following progression on a previous treatment, which is often the case in other economic evaluations of late-stage cancer treatments. Patients initiating avelumab maintenance (or being managed with watchful waiting) therefore have not recently experienced disease progression, and the role of treatment is to maintain their health status following first-line chemotherapy.

Following an assessment of the options available to analyse EQ-5D data from JAVELIN Bladder 100, utilities were analysed by progression status to inform the cost-effectiveness analysis. The methodological approach used to inform the base-case analysis is described in Section B.3.4.5.1. Adjustments made to utilities to account for age-related effects are described in Section B.3.4.5.2. Alternative values used in scenario analysis are described in Section B.3.4.5.3.

B.3.4.5.1 Progression status approach (base-case analysis)

A mixed-effects linear regression model with two covariates (baseline utility and progression status) was fitted to the crosswalked utility data. The fitted model (Equation 1) expresses mean utility (left-hand side of the equation) as a sum of factors (right-hand side of the equation) including an intercept (representing the reference state as progression-free for patients of average baseline utility) and two other factors related to the effect of each covariate (progression and baseline utility).

Equation 1 Linear regression model for utilities by progression status

$$\begin{aligned}\text{Mean EQ} - \text{5D utility} \\ = 0.772 + {'Progressed'} \times (-0.075) + {'utility\ at\ baseline} \\ - average\ utility\ at\ baseline' \times 0.698\end{aligned}$$

Where:

- 'Progressed' takes a value of 1 for a patient who has experienced disease progression, and 0 for a patient who is progression-free at the time utility was recorded
- 'Utility at baseline – average utility at baseline' refers to a 'centred baseline utility', which takes a value of zero for a patient with an average utility at baseline
- 0.772 is the mean utility when all other factors in the equation are zero (i.e. 0.772 is the mean utility for patients who are progression-free and have average utility at baseline)

For the purpose of informing the economic model, the baseline utility term takes a value of zero, and so Equation 1 may be simplified to Equation 2.

Equation 2 Simplified model for estimating utilities to inform the model

$$\text{Utility} = 0.772 + {'Progressed'} \times (-0.075)$$

Utilities by progression status are shown in Table B.3.10.

Table B.3.10. Utility values by progression status

Health state	Utility value
Progression-free	0.772
Post-progression	0.698

In the base-case analysis, progression state utilities with adjustment for age- and sex-related disutility are used (see Section B.3.4.5.2 for age adjustment). This approach makes use of the 'gold-standard' of EQ-5D data taken directly from JAVELIN Bladder 100, and adjusts the produced values to account for the effects of aging over the course of the model time horizon. Alternative values are explored within scenario analysis.

B.3.4.5.2 Age-related disutility

Within the model, age adjustment was applied in the base case to account for the deterioration in well-being as patients age. Age-related disutility was based on a formula from Ara and Brazier (Equation 3 and Table B.3.11).[146] This was applied within the model by use of the baseline age (67.5 years) and proportion of males (77.3%).

Equation 3 Age-related disutility

$$\text{General population utility} = \beta_0 + \beta_1 \text{male} + \beta_2 \text{age} + \beta_3 \text{age}^2$$

Table B.3.11. Age utility adjustment

Coefficient	Value
Male (β_1)	0.021213
Age (β_2)	-0.000259
Age2 (β_3)	-0.000033
Constant (β_0)	0.950857

Source: Ara and Brazier, 2010[146]

B.3.4.5.3 Alternative values

Alternative utility values were considered in scenario analysis to inform the model. These were from NICE TA519 (pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-based chemotherapy) where the committee preferred the use of progression-based utility values that were pooled across treatment arms.[84] The equivalent utility values were 0.731 for progression-free patients and 0.641 for progressed patients.

The values from TA519 are similar to, but slightly lower than, the values obtained based on analysis of JAVELIN Bladder 100 data.[84] This is expected given that TA519 is concerned with a patient population treated with pembrolizumab after progression following first-line chemotherapy; whereas this appraisal is concerned with the use of avelumab after response to first-line chemotherapy, but before progression. In spite of this limitation, these values were considered to represent a potential lower bound of the expected health state utility values relevant to the economic model in this appraisal.

A summary of the utility values explored within scenario analyses is provided in Table B.3.12, compared with the utility values used in the base-case analysis.

Table B.3.12. Utility values explored in scenario analyses

State	JAVELIN Bladder 100 (base-case)	TA519 (scenario)
Progression-free	0.772	0.731
Post-progression	0.698	0.641

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Resource identification, measurement and valuation studies

An SLR was conducted to identify and summarise the available cost and resource use studies relevant to the decision problem. Full details of the SLR are included in Appendix I.

B.3.5.2 Intervention and comparator costs and resource use

B.3.5.2.1 Avelumab costs

Avelumab is available as a 200 mg vial and is administered as an IV infusion once Q2W at a flat dose of 800 mg. The list price is £768 per vial (BNF), equating to £3,072 per dose (4 x 200 mg vials).[147] The flat dose of 800 mg aligns with the anticipated licenced dose for avelumab for the treatment of locally advanced and metastatic UC (and the current licenced avelumab dose for aRCC and MCC).[46]

Although a weight-based dose of 10 mg/kg was used in JAVELIN Bladder 100, efficacy outcomes are expected to be the same with a flat dose of 800 mg and hence there was no adjustment to efficacy to account for the difference in dose. A flat dose of 800 mg also falls firmly in the middle of the mean dose administered in JAVELIN Bladder 100 ([redacted]) and the required volume of avelumab when accounting for wastage ([redacted]).[110]

When considering the use of avelumab in clinical practice, it is important to note that some patients may have delayed or reduced doses. Previous appraisals have used estimates of the relative dose intensity (RDI) to account for the proportion of doses planned versus those received. However, as the weight-based dose of 10mg/kg was used in JAVELIN Bladder 100, estimates of dose adjustments from the trial may not reflect the anticipated dose reductions in practice (given the anticipated use of a flat dose of 800 mg). Therefore, for the purpose of informing the economic model, an alternative, pragmatic approach was taken to account for the anticipated use of avelumab:

- The mean duration of treatment with avelumab in JAVELIN Bladder 100 was [redacted], and the mean number of avelumab infusions was [redacted]. Given that avelumab administrations are anticipated to be 2 weeks apart, an estimated ratio of the mean number of infusions per treatment cycle may be estimated as [redacted]. This ratio is then applied within the cost-effectiveness analysis to account for missed or delayed doses per treatment cycle. This approach may overestimate the true average cost of avelumab per cycle, as it does not account for any dose reductions.

A summary of dosing information for avelumab is provided in Table B.3.13.

Table B.3.13. Dosing information for avelumab

Component	Value
Dose	800 mg
Vial size	200 mg
Cost per vial	£768.00
Cost per mg	£3.84
Cost per treatment (list price, unadjusted)	£3,072.00
Administration information	IV infusion once every 2 weeks
Mean duration of treatment in JAVELIN Bladder 100	[redacted]
Mean number of infusions in JAVELIN Bladder 100	[redacted]
Estimate of planned doses per cycle	[redacted]
Cost per treatment (list price, adjusted)	[redacted]

Abbreviations: RDI = relative dose intensity; IV = intravenous
Source: Pfizer Inc., 2020[110]

The administration cost for avelumab treatment is shown in Table B.3.14. As avelumab is administered on day 1 of each 14-day cycle over 60 minutes, a single administration cost of £183.54 is applied (given that no subsequent elements of the treatment cycle are required).

Table B.3.14. Administration costs for avelumab

Component	Cost	Source
Deliver simple parenteral chemotherapy at first attendance in an outpatient setting	£183.54	National cost collection for the NHS 2018/19, SB12Z, OP

Abbreviations: OP = outpatient
Source: NHS England[148]

B.3.5.2.2 Patient Access Scheme

A Patient Access Scheme (PAS) has been applied, comprising a simple discount of [redacted] from the list price of avelumab. The economic evaluation presented in this submission applies the PAS in the base case analysis (Table B.3.15).

Table B.3.15. Acquisition cost of avelumab following application of PAS

Cost approach	Cost per 200mg vial	Cost per treatment cycle (2 weeks)*
No PAS	£768.00	[redacted]
PAS	[redacted]	[redacted]

Abbreviations: OP = outpatient
*This cost accounts for the adjustment made to account for missed or delayed doses

B.3.5.2.3 Supportive care costs

BSC was administered in JAVELIN Bladder 100 according to local practice, and based on patient needs and clinical judgment (e.g., antibiotics, nutritional support, hydration and pain management). Other systemic anti-tumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable.[110,111] The nature of BSC administered within JAVELIN Bladder 100 is expected to broadly reflect current UK NHS practice.

The provision of BSC in both treatment arms (i.e., avelumab + BSC [avelumab] and BSC alone [watchful waiting]) means that active treatment costs are not applied to the watchful waiting arm. Instead, costs related to BSC are captured as part of the health-state resource use associated with the management of locally advanced or metastatic UC patients (see Section B.3.5.3).

B.3.5.3 Health-state unit costs and resource use

B.3.5.3.1 Health-state resource use

As published data on the resource use associated with patients with locally advanced or metastatic UC is limited, medical resource use was informed by previous NICE submissions for urothelial cancers (TA492, TA522 and TA272).[79,80,82] In the base-case analysis, resource use frequencies were informed via clinical expert opinion, with a sensitivity analysis conducted using values reported in TA272.

Resource use estimates are assumed to not differ between avelumab and watchful waiting; however, patients with progressive disease are expected to require greater medical resource use than progression-free patients (based on these patients having a relatively greater burden of disease). Table B.3.16 reports the resource use for monitoring and disease management in the progression-free and post-progression health states.

Table B.3.16. Resource use frequencies for patients in by progression status (per month)

Resource	Progression-free	Progressed
Consultant-led oncologist follow-up visit	0.88	0.93
Clinical nurse specialist	0.62	1.00
Dietician	0.06	0.16
GP home consultation	0.26	0.72
Urologist	0.07	0.04
District nurse	0.27	0.96

Abbreviations: GP = general practitioner

As a scenario analysis, the resource use frequencies specified in TA272 were also considered to inform the model.[82] These frequencies are presented in Table B.3.17. The resource use categories in TA272 are similar, with the following main differences:

- Clinical advice indicated that patients would continue to see a consultant after progression (as opposed to non-consultant-led outpatient visits)
- Nurse specialist visits are not expected to be required every month
- A small proportion of patients are expected to require outpatient urologist consultations, which were not captured in TA272

Table B.3.17. Scenario analysis resource use frequencies (per month)

Resource	Progression-free	Progressed
Consultant led oncologist follow-up visit	1.00	-
Non-consultant led oncologist follow-up visit	-	1.00
Health home visitor	1.00	1.00
Community nurse specialist visit	4.00	4.00
Dietician	1.00	1.00

Abbreviations: GP = general practitioner

The above resource use costs do not include end-of-life (palliative) care. Costs relating to palliative care are described in Section B.3.5.3.4

B.3.5.3.2 Resource use and monitoring costs

Resource use and monitoring costs were taken from the Personal and Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (2019), and NHS reference costs (2018–19).[148,149]The cost of resources applied in the model are outlined in Table B.3.18.

Table B.3.18. Resource use unit costs

Item	Cost	Information	Code	Reference
Consultant led oncologist follow-up visit	£194.17	Consultant led: Medical Oncology, Non-Admitted Face-to-Face, Follow-up.	WF01A	National cost collection for the NHS 2018/19[148]
Non-consultant led oncologist follow-up visit	£147.38	Non-consultant led: Medical Oncology, Non-Admitted Face-to-Face, Follow-up.	WF01A	
Urologist	£104.92	Consultant led: Urology, Non-Admitted Face-to-Face, Follow-up	WF01A	
Health home visitor	£28	Home care worker – Face-to-face per hour per weekday	-	PSSRU - Unit Costs of Health and Social Care 2019[149]
Community nurse specialist visit	£84	Community nurse - Band 6; Cost per working hour of patient-related work	-	
Dietician	£35	Dietitian per working hour; band 5	-	
GP home consultation	£156	General practitioner — unit costs per hour of GMS activity	-	
District nurse	£84	District nurse - Band 6; Cost per working hour of patient-related work	-	
Clinical nurse specialist	£84	Assumed same cost as community nurse specialist visit	-	

Abbreviations: GP = general practitioner; MRI = magnetic resonance imaging; NHS = National Health Service; PET = positron emission tomography; PSSRU = Personal and Social Services Research Unit.

B.3.5.3.3 Resource use and monitoring costs per model cycle

To calculate a cost per model cycle, resource use frequency (Table B.3.16) per week was multiplied by the proportion of patients receiving the resource, and subsequently multiplied by

the corresponding resource use unit cost (Table B.3.18). The resulting resource use costs are presented in Table B.3.19.

Table B.3.19. Resource use costs per model cycle for patients by progression status

Total cost	Progression-free	Progressed
Cost per model cycle	£67.76	£108.03

B.3.5.3.4 Terminal care cost

A one-off terminal care cost was applied within the model which was assumed to cover costs of supporting patients in a palliative stage before death. The same flat cost was applied to both treatment arms based on the proportion of patients who die in each cycle.

The unit cost applied was based on data reported in Round et al. (2015), which was a modelling study estimating the cost of caring for people with cancer at the end of their life.[150] The mean value health care cost was taken from this study (£4,254.00) and uplifted to current values using the PSSRU NHSCII indices.[149] This produced a total cost of £4,506.69, which was applied within the cost-effectiveness analysis.

B.3.5.4 Adverse reaction unit costs and resource use

AE costs were identified from NHS reference costs 2018–19 (Table B.3.20).[148]

Table B.3.20. Adverse event costs (per event)

AE	Cost	Code*	Information
Anaemia	£1,477.37[148]	SA01G-K	Aligned with TA522 - Other Red Blood Cell Disorders; weighted average of day case and non-elective short-stay and non-electric short-stay
Amylase increased	£194.17[148]	370	Non-Admitted Face-to-Face Attendance, Follow-up; Medical Oncology
Asthenia	£3,518.70[148]	-	Assumed equivalent to fatigue
Back pain	£377.42[148]	HC32H-K	Low Back Pain without Interventions; Non-elective short-stay
Fatigue	£3,518.70[148]	WH52A	Aligned with TA522 - Follow-up Examination for Malignant Neoplasm, with Interventions; Assumed one non-elective long-stay hospital admission
Haematuria	£1,454.75[148]	-	Assumed equivalent to urinary tract infection.
Immune-mediated hepatitis	£499.01[148]	GC17A-K	Non-Malignant, Hepatobiliary or Pancreatic Disorders, with or without (single or multiple) interventions; non-elective short-stay
Immune-mediated rash	£404.26[148]	JD07A-K	Skin Disorders; non-elective short-stay
Lipase increased	£194.17[148]	370	Non-Admitted Face-to-Face Attendance, Follow-up; Medical Oncology
Urinary tract infection	£1,454.75[148]	LA04N-S	Aligned with TA522 - Kidney or Urinary Tract Infections; weighted average of day case and non-elective short-stay and non-electric short-stay
Vomiting	£176.99[148]	WF01B	Gastroenterology - Consultant Led First Visit

Abbreviations: AE = adverse event; TA = technology appraisal

AE	Cost	Code*	Information

* Codes based on reference from national cost collection for the NHS 2018/19. If a range is presented, the weighted average by activity was calculated to produce a single unit cost to inform the model

The cost of treating AEs was calculated based on the frequency that each AE was incurred (as reported in JAVELIN Bladder 100 and Section B.3.3.2) multiplied by the corresponding cost of each event. A total cost per treatment arm was obtained and applied as a one-off cost within the first cycle of the model. This approach was considered appropriate as most patients in JAVELIN Bladder 100 discontinued treatment during follow-up, and it is therefore expected that the majority of AEs will have occurred.

The resulting total costs for AE resolution, which were applied in full during the first model cycle, were £234.41 for avelumab, and £174.11 for watchful waiting.

B.3.5.5 Subsequent treatment costs

The costs of subsequent treatment following disease progression and cessation of allocated treatment in JAVELIN Bladder 100 were included within the model to reflect both JAVELIN Bladder 100 data and clinical practice, where patients are expected to receive treatment following disease progression either after avelumab maintenance or after a watchful waiting strategy.

The cost of subsequent therapies is modelled as a weighted distribution of treatments and accounts for expected time on treatment. The total expected cost of subsequent therapies is applied at the estimated time of progression based on the proportion of patients receiving subsequent active treatment (which was defined for avelumab and watchful waiting separately and were based on observations from JAVELIN Bladder 100). Using this data, it is assumed that [redacted] ([redacted]) of patients who progress after avelumab receive subsequent active treatments, while [redacted] ([redacted]) who progress after watchful waiting receive subsequent treatments.[110]

Subsequent active treatments were modelled separately for avelumab and watchful waiting based on JAVELIN Bladder 100. Of the patients who were allocated to watchful waiting and received treatment after disease progression, 71.3% received a second-line, non-avelumab anti-PD-1/PD-L1 treatment. The majority of those on subsequent treatments following avelumab received a second-line chemotherapy (as opposed to another anti-PD-1/PD-L1 treatment). Those who received active subsequent treatments incurred drug acquisition costs (Table B.3.24) and administration costs (

Table B.3.25).

Although patients in JAVELIN Bladder 100 received subsequent nivolumab, pembrolizumab and durvalumab (as second-line anti-PD-1/PD-L1 treatments), these treatments are not considered standard of care nor part of routine commissioning in England or Wales as second-line therapy. Therefore, a simplifying assumption was made, costing these patients as receiving atezolizumab (an anti-PD-L1 treatment) instead, which is recommended by NICE (TA525).[81]

While the differential efficacy of alternative anti-PD-1/PD-L1 treatments administered beyond progression cannot be robustly tested in the model structure (based on data from JAVELIN Bladder 100), a scenario analysis is provided which costs the proportions true to those treatments received in JAVELIN Bladder 100. A summary of the redistribution is provided in Table B.3.21, and is applied in the base-case analysis.

Table B.3.21. Subsequent anti-PD-1/PD-L1 treatments (base-case and scenario analysis)

Treatment	Base case		Scenario analysis (JAVELIN Bladder 100)	
	Avelumab	Watchful waiting	Avelumab	Watchful waiting
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	-	-	[redacted]	[redacted]
Pembrolizumab	-	-	[redacted]	[redacted]
Durvalumab	-	-	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse Abbreviations: PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1; TA = technology appraisal

Table B.3.22 also provides subsequent treatments that include chemotherapies (referred to as standard of care). For the purpose of the UK market, the following treatments were considered:

- Cisplatin
- Carboplatin
- Gemcitabine
- Docetaxel
- Paclitaxel
- Pemetrexed

To avoid the underestimation of subsequent therapy costs, treatments that were received in JAVELIN Bladder 100 outside of the list outlined above were redistributed.

Table B.3.22. Subsequent standard of care treatments (JAVELIN Bladder 100 and base case).

SoC treatments	Observed in JAVELIN Bladder 100		Base case (with alternative treatments redistributed)	
	Avelumab	Watchful waiting	Avelumab	Watchful waiting
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC = standard of care

The dosing regimens for each drug were obtained from the relevant summary of product characteristics (SmPC) and RCTs involving patients with advanced or metastatic UC. Where information for advanced or metastatic UC was not available, dosing regimens for non-small cell lung cancer (NSCLC) were used. NSCLC was used as a proxy to identify regimens given in a similar cancer where other anti-PD-1/PD-L1 therapies and chemotherapies are used, acknowledging that the variation of subsequent therapies received as part of JAVELIN Bladder 100 are (in part) reflective of the trial being an international, multicentre study.

The majority of subsequent therapies are dosed according to body surface area (BSA); therefore, the method of moments approach was used in order to provide an accurate estimate of the average number of vials required per administration, and consequently the average cost of treatment per patient. The method of moments approach accounts for wastage by considering all patients who would require a given number of vials and applying the cost of that particular quantity in full. This method is preferred and literature has shown that the alternative (use of mean weight or BSA) underestimates drug costs.[151] Furthermore, the approach has also been widely utilised in previous submissions to NICE.[133,152-154]

Distributions of patient BSA were obtained from JAVELIN Bladder 100. A normal distribution was fitted to patient BSA data, and the proportion of patients requiring each number of vials based upon this distribution was obtained. The weighted average of all possible quantities of vials according to the proportions of patients that would receive them was then used to derive an estimate of the total number of vials required per administration. The average dose required per administration was then calculated by multiplying the average number of vials by the vial size in milligrams. This was then multiplied by the cost per milligram to obtain a cost for each treatment.

Two treatments required alternative approaches to be taken in order to accurately estimate the cost per administration for inclusion within the model:

- Atezolizumab: In NICE TA525, the anticipated dose of atezolizumab was used to inform the economic model, with atezolizumab assumed to be administered as a flat dose (as per IMvigor210 [1,200 mg every 3 weeks]). Since the publication of TA525, the SmPC for atezolizumab states that it may be administered at a dose of 840 mg Q2W, or 1,680 mg every four weeks.[78] For the purpose of informing the economic model, a dose of 840 mg

Q2W was applied, given that atezolizumab is available in an 840 mg vial in the UK and the majority of other anti-PD-1/PD-L1 therapies used in UC are administered once every 2 or 3 weeks

- Carboplatin: The dosing regimen for carboplatin is based on eGFR levels. In order to inform the model, the mean value was taken from the trial and applied

Dosing information relating to subsequent therapies is provided in Table B.3.23.

Table B.3.23. Dosing regimens and assumptions for subsequent treatments

Treatment	Used in base case?	Dose per administration	Administrations per cycle	Cycle length (weeks)	Reference
Atezolizumab	✓	840 mg	1	2	SmPC[78]
Nivolumab	X Scenario only	480 mg	1	2	SmPC[76]
Pembrolizumab	X Scenario only	200 mg	1	3	SmPC[77]
Durvalumab	X Scenario only	10 mg/kg	1	2	SmPC[155]
Cisplatin*	✓	70 mg/m^2	1	4	SmPC[156]
Carboplatin	✓	470 mg†	1	4	SmPC[157]
Gemcitabine	✓	1,000 mg/m^2	3	4	SmPC[158]
Docetaxel	✓	75 mg/m^2	1	3	SmPC[159]
Paclitaxel	✓	175 mg/m^2	3	3	SmPC[160]
Pemetrexed	✓	500 mg/m^2	1	3	SmPC[161]
Vinflunine‡	X Not used	-	-	-	

* Dose of 50 to 120mg/m2 recommended every week so assumption made; † Dose of =5*(eGFR+25) – as a dose of 4-6 mg/ml.min was outlined in the previously treated setting in the SmPC; ‡ Patients on vinflunine were proportionally distributed to each of the other chemotherapy drugs because vinflunine is not recommended by NICE.

The administration costs for subsequent immunotherapy and chemotherapy were based on the delivery of simple parenteral chemotherapy (HRG: SB12Z), with the exception of cisplatin which was considered as the delivery of complex chemotherapy, including prolonged infusional treatment (HRG: SB14Z) due to the extended infusion time.[148]

The costs associated with treatment acquisition and administration for each subsequent therapy are summarised in Table B.3.24 and

Table B.3.25, respectively.

Table B.3.24. Product costs for subsequent treatments

Treatment	Form	Strength	Package size	Package price	Reference
Atezolizumab	Solution for infusion	60 mg/mL	14 mL	£2,665.38	BNF[162]
Cisplatin	Solution for infusion	1 mg/mL	50 mL	£4.12	eMIT[163]
Carboplatin	Solution for infusion	10 mg/mL	45 mL	£27.90	eMIT[163]
			5 mL	£3.75	eMIT[163]
Gemcitabine	Powder for solution	1 g	1 g	£17.85	eMIT[163]
Docetaxel	Solution for infusion	20 mg/mL	4 mL	£12.50	eMIT[163]
Paclitaxel	Solution for infusion	6 mg/mL	25 mL	£18.89	eMIT[163]
Pemetrexed	Powder for solution	100 mg	100 mg	£150.00	BNF[164]

Abbreviations: BNF = British National Formulary; eMIT = electronic market information tool

Table B.3.25. Administration costs for subsequent treatments

Treatment	Cost per admin	HRG*	Per cycle			Reference
			Admins	Length	Cost	
Atezolizumab	£183.54	SB12Z, OP	1	3	£61.18	SmPC[78]
Cisplatin	£317.73	SB14Z, OP	1	4	£79.43	Bellmunt et al.,2012[18]
Carboplatin	£183.54	SB12Z, OP	1	4	£45.89	De Santis et al., 2012[87]
Gemcitabine	£183.54	SB12Z, OP	3	4	£137.66	Bellmunt et al., 2012[18]
Docetaxel	£183.54	SB12Z, OP	1	3	£61.18	SmPC†[159]
Paclitaxel	£183.54	SB12Z, OP	3	3	£61.18	SmPC†[160]
Pemetrexed	£183.54	SB12Z, OP	1	3	£61.18	SmPC†[161]

Abbreviations: admin = administration; HRG = Healthcare resource group; SmPC = summary of product characteristics
* National cost collection for the NHS 2018/19; b regimen for NSCLC used as a proxy for UC

Table B.3.26 provides a summary of the subsequent therapy costs applied within the base-case analysis. Duration of therapy for each drug class (immunotherapy and chemotherapy) is taken from JAVELIN Bladder 100. The resulting subsequent therapy cost of avelumab is £4,533 applied to 68.5% of the patients who progress in each cycle. The resulting subsequent therapy cost for watchful waiting patients is £23,540 applied to 86.1% of the patients who progress in each cycle. This is aligned to clinical expectation in that fewer patients in the avelumab arm would be expected to receive later lines of therapy and subsequently incur fewer subsequent treatment costs.

Table B.3.26. Summary of subsequent treatment costs

Input	Avelumab	Watchful waiting
Progressed patients receiving subsequent treatment(s)	[redacted]	[redacted]
Time on subsequent immunotherapy (weeks)	[redacted]	[redacted]
Time on subsequent chemotherapy (weeks)	[redacted]	[redacted]
Total costs for subsequent immunotherapy*	£3,531	£25,510
Total costs for subsequent chemotherapy*	£3,085	£1,844
Total subsequent therapy cost by treatment arm	**£6,616**	**£27,354**
Total subsequent therapy costs applied in the model⁺	**£4,533**	**£23,540**

* Subsequent treatment costs based on a weighted average of therapies in Table B.3.21. ⁺ accounting for proportion of patients receiving subsequent treatment.
Source: Pfizer Inc., 2020;[110]

Using the same duration assumptions as those in Table B.3.26, the scenario analysis using the JAVELIN Bladder full anti-PD-1/PD-L1 subsequent therapy distributions (as provided in Table B.3.21) result in subsequent therapy costs of £6,616 and £27,354 for avelumab and watchful waiting respectively.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

In line with the NICE reference case, analyses were conducted from the NHS and PSS perspective, with discounted costs and QALYs (3.5% discount rate). Results are presented over a lifetime (25 years) time horizon. Table B.3.27 summarises how the base-case inputs and variables were explored in sensitivity and scenario analyses. A full list of parameter inputs and the associated distributions are presented in Appendix L.

Table B.3.27. Summary of variables applied in the economic model

Component	Parameter bundle	Tested in:		
		OWSA?	PSA?	Scenario analysis?
Model settings	Time horizon			✓
	Cycle length			
Patient characteristics	Patient age	✓	✓	
	Patient body surface area	✓	✓	
	Patient glomerular filtration rate	✓	✓	
	Proportion male	✓	✓	
Avelumab treatment	Drug costs			
	Administration	✓	✓	
	Relative dose intensity	✓	✓	
	Treatment discontinuation			✓
Survival curve extrapolations	Overall survival		✓	✓
	Progression-free survival		✓	✓
	Time to treatment discontinuation		✓	✓
Utilities	Progression-free		✓	✓
	Progressed disease		✓	✓
Resource use	Costs	✓	✓	
	Frequencies	✓	✓	
	Terminal care	✓	✓	
Subsequent treatment	Drug costs	✓	✓	
	Proportions			✓
	Administration	✓	✓	
	Durations	✓	✓	
Adverse events	Frequencies	✓	✓	
	Durations	✓	✓	
	Costs	✓	✓	
	Utility decrements	✓	✓	

Abbreviations: OWSA = one-way sensitivity analysis; PSA = probabilistic sensitivity analysis

B.3.6.2 Key model assumptions

The base case analysis was subject to several key assumptions, summarised in Table B.3.28. This table also provides a summary of the sensitivity and scenario analyses conducted.

Table B.3.28. Summary to key model assumptions

Assumption	Justification	Section
Model cycle length of 1 week is appropriate	A weekly cycle length is assumed to be sufficiently short enough to represent the frequency of clinical events and interventions, and is aligned with the administration of avelumab (every 2 weeks) as well as subsequent treatments.	B.3.2.5
A lifetime time horizon of 25 years is appropriate	The economic model runs for 25 years to reflect the extrapolated life expectancy of the avelumab cohort. The impact of varying time horizon on the results was tested in sensitivity analysis.	B.3.2.5
Patients' baseline characteristics used in the model (based on patients in JAVELIN Bladder 100) are representative of the UK patient population	These patients are considered representative of the types of patients treated in UK clinical practice. Sensitivity analyses (probabilistic and deterministic) have been conducted to assess the impact of variability in these parameters.	B.3.3.1
Identification of the most appropriate survival curves describing OS, PFS and TTD	Extensive analyses have been undertaken to identify appropriate and conservative survival curves describing avelumab efficacy, with reference to the guidance from the NICE DSU. The approach and identified survival extrapolations have been validated by clinical and health economic experts. However, to address the uncertainty around this parameter, scenario analyses have been conducted by applying alternative assumptions around extrapolations.	B.3.3.3
Only a small proportion of patients on avelumab will continue treatment beyond 2 years	Based on clinical expert opinion, it was deemed reasonable to expect that relatively few patients are expected to be on treatment at 2 years or continue treatment beyond this time point. A two-year timepoint at which discontinuation may occur in practice has strong support from the clinical community, and there is precedence in other cancer types where immuno-oncology therapies are given.	B.3.3.3.3
There is a maximum treatment duration for all patients	Based on clinical expert opinion, it is reasonable to expect that no patient will remain on treatment beyond 5 years; therefore, treatment is capped in the model at this time point.	B.3.3.3.3
Terminal care costs from Round et al. are applicable to this population[150]	This approach has been used in multiple previous NICE TA appraisals, and palliative care is expected to be similar to the four cancer types considered by Round et al. (breast, prostate, lung, and colorectal cancer).[150]	B.3.5.3.4
Subsequent treatment regimens reflect UK clinical practice, and the efficacy of subsequent anti-PD-1/PD-L1 therapies assumed equivalent to atezolizumab	Subsequent use of anti-PD-1/PD-L1 therapy was noted primarily in the watchful waiting arm of JAVELIN Bladder 100, yet at the time of developing the model only atezolizumab was recommended by NICE.[81] Clinical advice provided for this appraisal suggested that different PD-1/PD-L1 therapies are generally associated with similar efficacy and safety profiles, and that for the purpose of informing the model, it is acceptable to consider all subsequent anti-PD-1/PD-L1 treatment would be with atezolizumab (based on the NICE reference case and position statement concerning treatment recommended via the CDF).	B.3.5.5

Abbreviations: CDF = Cancer Drugs Fund; DSU = Decision Support Unit; OS = overall survival; PD 1 = programmed death 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; TTD = time to treatment discontinuation; EQ-5D = EuroQoL Five Dimensions.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Discounted results for avelumab versus watchful waiting are presented in Table B.3.29, with undiscounted results presented in Table B.3.30. Compared with watchful waiting, avelumab is associated with [redacted] LYs gained, [redacted] QALYs, and incremental costs of £[redacted] per patient. The ICER is £29,245 per additional QALY gained.

Table B.3.29. Base-case results (discounted)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,245

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table B.3.30. Base-case results (undiscounted)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,969

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

B.3.7.2 Clinical outcomes from the model

As part of the validation process, results from the model were compared with outcomes in the JAVELIN Bladder 100 trial. A summary of this comparison in terms of median and mean OS and PFS is presented in Table B.3.31. The comparison of model results with clinical data demonstrate similar values between the model and available trial data.

Table B.3.31. Summary of model results compared with JAVELIN Bladder 100 clinical data

Outcomes		Watchful waiting		Avelumab	
		Trial	Model	Trial	Model
PFS	Median (months)	1.9	2.1	3.7	3.2
	6 months	[redacted]	23.5%	[redacted]	40.4%
	12 months	[redacted]	14.0%	[redacted]	30.0%
	18 months	[redacted]	10.0%	[redacted]	24.4%
	Mean (months)	NR	9.6	NR	27.1
OS	Median (months)	14.3	15.9	21.4	22.8
	6 months	[redacted]	81.3%	[redacted]	88.5%
	12 months	[redacted]	59.7%	[redacted]	71.1%
	18 months	[redacted]	45.9%	[redacted]	58.1%
	24 months	[redacted]	36.7%	[redacted]	48.5%
	30 months	[redacted]	30.3%	[redacted]	41.2%
	36 months	[redacted]	25.5%	[redacted]	35.6%
	Mean (months)	NR	35.4	NR	47.4

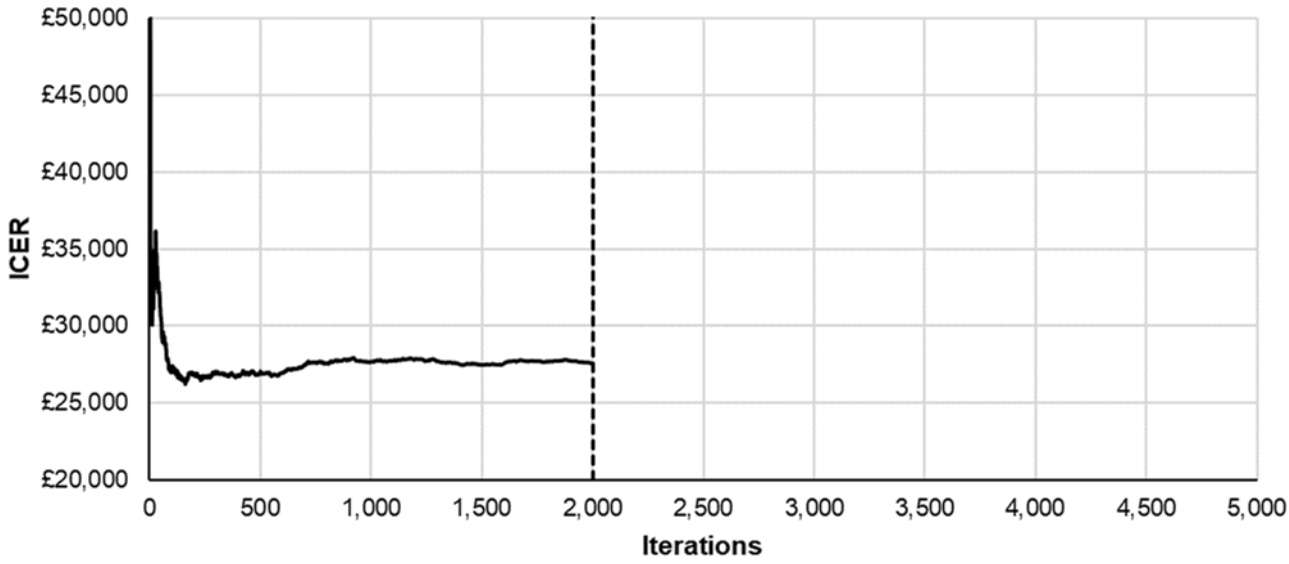
Abbreviations: NR = not reported; OS = overall survival; PFS = progression-free survival
Source: Pfizer Inc., 2020[110]

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to establish the impact of model parameter uncertainty when all parameters were varied simultaneously (parameters and respective distributions are detailed in Appendix L). Model parameters were sampled within their respective bounds of uncertainty for 2,000 iterations, with the results recorded for each iteration. A total of 2,000 iterations was chosen as the mean ICER was shown to be suitably stable at this point (Figure B.3.24).

Figure B.3.24. Convergence of mean ICER by number of PSA iterations



Abbreviations: ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis

The mean of these results was recorded, and the results from individual iterations were utilised to inform a PSA scatterplot and a cost-effectiveness acceptability curve. Mean probabilistic model results are presented in comparison to the deterministic results Table B.3.32. The results for both analyses are broadly consistent, though due to the magnitude of the incremental QALY gain, small changes in QALYs can lead to relatively large changes in the ICER.

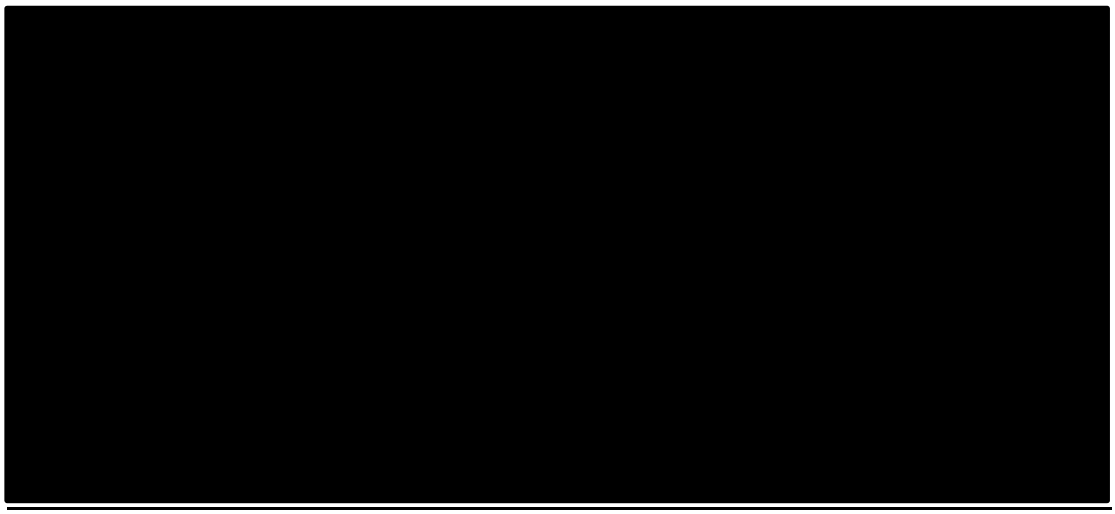
Table B.3.32. Deterministic versus probabilistic base-case model results

Results	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Deterministic	[redacted]	[redacted]	[redacted]	£29,245
Probabilistic	[redacted]	[redacted]	[redacted]	£27,506

Abbreviations: LY = life years; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio

The PSA scatter plot is presented in Figure B.3.25. This shows a relatively large spread of uncertainty in the model results, driven predominantly by the fact that OS curves are sampled independently of each other, and therefore there is a large spread in the incremental QALYs estimated for each iteration.

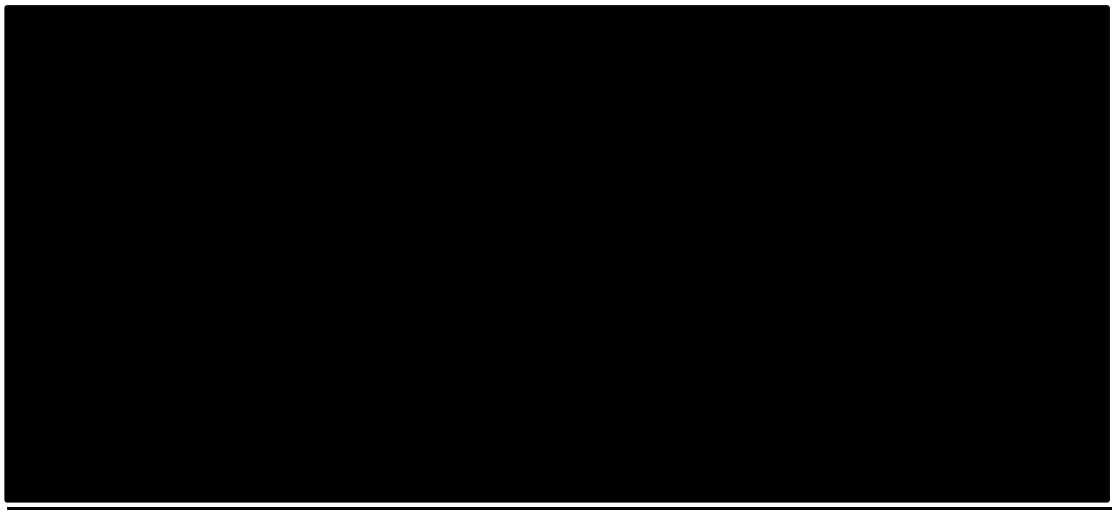
Figure B.3.25. PSA scatter plot



Abbreviations: PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

The cost-effectiveness acceptability curve (CEAC) is presented in Figure B.3.26. The probability of avelumab being the most cost-effective treatment at a willingness-to-pay threshold of £50,000 per QALY gained is 76.6% compared with watchful waiting.

Figure B.3.26. Cost-effectiveness acceptability curve

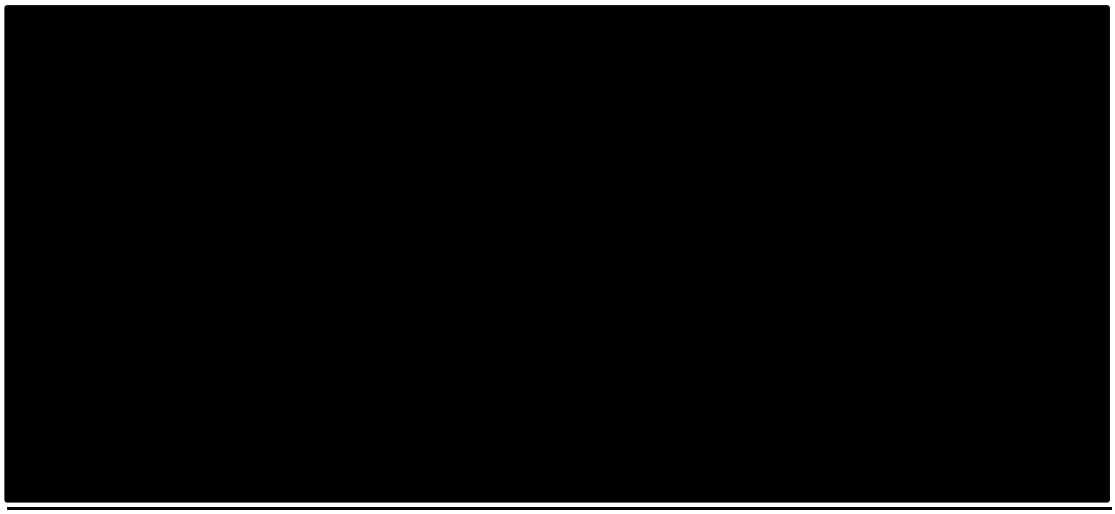


B.3.8.2 Deterministic sensitivity analysis

B.3.8.2.1 One-way sensitivity analysis

Deterministic one-way sensitivity analysis (OWSA) was conducted to explore the sensitivity in the deterministic base-case model results when one parameter is varied at a time. Each parameter was set to its lower and upper bound and model results were recorded. Parameters associated with direct correlation (e.g. curve fit parameters) and areas of structural uncertainty (e.g. choice of distribution) were not considered in this analysis, and are instead explored within the PSA (Section B.3.8) and scenario analyses (Section B.3.8.2.2). The top ten most influential parameters on the ICER are presented as a tornado diagram in Figure B.3.27.

Figure B.3.27. One-way sensitivity analysis tornado diagram



Abbreviations: Admin = administration, ICER = incremental cost-effectiveness ratio; IO = immuno-oncology; PFS = progression-free survival; PP = post-progression; RU = resource use; Subs = subsequent; tx= treatment; WW = watchful waiting.

The results of the OWSA demonstrate that the most influential model parameters on cost-effectiveness results were adjustments to account for missed or delayed doses of avelumab, and parameters related to subsequent treatment for patients not given avelumab maintenance. Subsequent treatment as a driver of results is to be expected, given that use of avelumab maintenance is expected to displace some subsequent use of anti-PD-1/PD-L1 treatment currently provided to patients following progression. Other parameters explored within OWSA had a small impact on cost-effectiveness results.

B.3.8.2.2 Scenario analysis

Scenario analyses were performed to further assess the robustness of the economic analysis results. Base-case model settings were changed and the impact of these changes on results were assessed. Scenarios explored included selecting varying time horizons, survival assumptions, treatment duration assumptions, utility values and costs. The full list of scenarios considered are presented in Table B.3.33.

Table B.3.33. Results of scenario analysis

#	Topic	Sub-topic	Scenario	ICER
Base-case analysis				**£29,245**
1	Model settings	Time horizon	10 years	£35,971
2			20 years	£29,961
3		Discount rates	0%	£24,969
4	Time-to-event outcomes	OS – both arms	Log-logistic	£32,185
5			Log-normal	£30,629
6		PFS – both arms	Generalised gamma	£27,991
7			3-knot odds	£28,750
8			3-knot hazard	£29,677
9		PFS approach	PFS-INV	£27,069
10		TTD	Log-normal with no drop but stop at 5 years	£38,657
11			Generalised gamma with drop at 2 years to 5% and stop at 5 years	£30,317
12			Log-normal extrapolated curve with no adjustment	£45,745
13	Utilities	PFS/PPS	TA519	£30,558
14		Age-adjustment	No age-adjustment applied	£28,144
15		Wastage	No wastage (cost per mg for all treatments)	£29,221
16		Resource use	Based on TA272	£37,747
17		Subsequent IOs	IOs not redistributed to atezolizumab	£24,032
18		Dose adjustment	No dose adjustment applied	£32,166

Abbreviations: ICER = incremental cost-effectiveness ratio; IOs = immuno-oncology agents; OS = overall survival; PFS = progression-free survival; PFS-INV = PFS investigator assessed; PPS = post-progression survival

B.3.8.3 Summary of sensitivity analyses results

Sensitivity analyses were undertaken to explore key areas of uncertainty associated with the cost-effectiveness analysis. Parameter uncertainty was explored through probabilistic and deterministic OWSA, with structural uncertainty and key assumptions explored through scenario analyses.

Probabilistic sensitivity analysis results demonstrated that parameter uncertainty in the cost-effectiveness results were most sensitive to inputs related to the estimation of QALYs (for which the selection of independent models for the outcome of OS in particular may artificially over-estimate the uncertainty in model results). OWSA showed the key parameters of influence on cost-effectiveness results were related to subsequent use of anti-PD-1/PD-L1 therapies. Scenario analyses highlighted key areas of uncertainty around survival models, utility values, and key cost components (including subsequent treatments and medical resource use).

B.3.9 Subgroup analysis

No subgroup analyses were conducted.

B.3.10 Validation

A number of complementary validation approaches were undertaken to ensure the outputs of the cost-effectiveness analysis were robust and suitable to inform decision making.

At an advisory board held in July 2020 and during additional one-to-one discussions held in August 2020, eight practicing UK oncologists were consulted to discuss key aspects of the cost-effectiveness analysis that required clinical input.[108] These included the expected longer-term outcomes beyond the follow-up period in the JAVELIN Bladder 100 trial for patients on either treatment arm for both OS and PFS, the expected pattern of health care resource use, the face validity of utility values derived based on progression status, and the anticipated duration of treatment with avelumab maintenance specifically.

The cost-effectiveness analysis was subject to an internal quality control check prior to submission. The model was reviewed by a health economist not involved in the development of the submission, with any calculation errors or suggestions for improvements to labelling/formatting incorporated into the model prior to submission.

B.3.11 Interpretation and conclusions of economic evidence

The economic evaluation presented in this submission is, to the best of our knowledge, the first to compare avelumab as maintenance treatment to watchful waiting for patients with locally advanced or metastatic UC after platinum-based chemotherapy. In the base-case analysis, avelumab was shown to be a cost-effective use of NHS resources, based on a willingness-to-pay threshold of £50,000 per QALY gained (accounting for the simple PAS discount of [redacted] applied to the list price of avelumab).

One of the key strengths of the submitted cost-effectiveness analysis is that the majority of the model parameters were informed by data from JAVELIN Bladder 100, a high-quality, pivotal, Phase 3 RCT that randomised 700 patients (1:1) to receive either avelumab maintenance or watchful waiting (BSC). This comparison is aligned fully with the scope of this appraisal, meaning that a robust comparison of outcomes between the alternative strategies can be obtained without the need to rely on indirect comparisons.

The economic analysis adopts a PartSA model structure, which allows for an intuitive implementation of the primary endpoint of JAVELIN Bladder 100 (OS), as well as relevant secondary endpoints (PFS and safety outcomes) and other supporting information (e.g., TTD and HRQoL). This model structure has been used to inform a number of previous appraisals conducted by NICE, and allows for a thorough exploration of alternative settings and assumptions to understand their influence on cost-effectiveness results.

A range of model inputs, assumptions and settings were explored in sensitivity analysis; including the key drivers of model results (survival, HRQoL, and TTD). These analyses showed the results were largely unchanged when various settings and assumptions were changed, illustrating the robustness of the base-case analysis results and the overall conclusion of the analysis presented.

The cost-effectiveness analysis presented within this submission is not without limitations. As is often the case with clinical trials conducted in cancer populations, survival data are incomplete, and so for the purpose of informing an economic analysis considering a lifetime horizon, extrapolation of outcomes was necessary. To inform the cost-effectiveness analysis,

a range of parametric modelling approaches were considered, with alternative models explored within sensitivity analyses. Models were explored separately by treatment arm, allowing for the consideration of a broad range of possible extrapolations.

While the precise magnitude of survival benefit attributable to avelumab as maintenance is uncertain, data from JAVELIN Bladder 100 demonstrate a substantial improvement compared with patients managed with watchful waiting. Average current life expectancy is considerably shorter than 24 months (median of 14.3 months for watchful waiting patients in JAVELIN Bladder 100), and avelumab provides a survival benefit of at least three months (median improvement of 7.1 months in JAVELIN Bladder 100).[110] Therefore, avelumab meets NICE's end-of-life criteria (see Table B.2.25), offering a median improvement close to an additional 50% of baseline survival.

In current NHS practice, no active treatment is offered to patients following first-line chemotherapy until disease progression. As such, there remains uncertainty with regards to how long patients may continue treatment with avelumab as maintenance in clinical practice. However, as is the case with several other cancer immunotherapies, treatment is not expected to continue indefinitely, and so the base-case analysis assumes only a small proportion of patients on avelumab will continue treatment beyond 2 years, and all patients will have discontinued by 5 years (with alternative options explored within sensitivity analysis).

In conclusion, the economic evaluation presented within this submission demonstrates that the use of avelumab as maintenance offers both a clinically- and cost-effective treatment option for patients who respond to first-line platinum-based chemotherapy. Given the significant number of patients ineligible for second-line treatment,[108] the sequential administration of induction chemotherapy followed by avelumab maintenance enables patients with locally advanced or metastatic UC to benefit from the mechanistic advantages of receiving an immunotherapy after chemotherapy,[122-125] extending the benefit of first-line therapy in a patient group likely to derive the most benefit from treatment before disease progression, after which the capacity for patients to respond to cancer immunotherapy may be compromised. Avelumab therefore represents a step-change in the management of UC.

B.4. References

1. Boustead GB, Fowler S, Swamy R, Kocklebergh R, Hounsome L. Stage, grade and pathological characteristics of bladder cancer in the UK: British Association of Urological Surgeons (BAUS) urological tumour registry. BJU Int. 2014;113(6):924-30.
2. Knott C, Health Data Insight CIC. Observational cohorts of patients with advanced or metastatic cancer in England (MS100070-0027). 2019.
3. Office for National Statistics. Deaths registered in England and Wales (2018). 2019.
4. Queen's University Belfast. Cancer incidence, prevalence and survival statistics for Northern Ireland: 1993-2017. Bladder cancer (C67). 2019.
5. Office for National Statistics. Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018. 2019.
6. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016. Bethesda, MD: National Cancer Institute; 2019.
7. Yu XQ, Baade PD, O'Connell DL. Conditional survival of cancer patients: an Australian perspective. BMC Cancer. 2012;12:460.
8. Fung C, Pandya C, Noyes K, et al. Impact of bladder cancer (BC) on health-related quality of life (HRQL) in 1,476 older Americans. J Clin Oncol. 2013;31(Suppl 15):9549.
9. Roychowdhury DF, Hayden A, Liepa AM. Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol. 2003;21(4):673-8.
10. Smith AB, Jaeger B, Pinheiro LC, et al. Impact of bladder cancer on health-related quality of life. BJU international. 2018;121(4):549-57.
11. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management 2015 [Available from: https://www.nice.org.uk/guidance/ng2.
12. Oudard S, Culine S, Vano Y, et al. Multicentre randomised phase II trial of gemcitabine+platinum, with or without trastuzumab, in advanced or metastatic urothelial carcinoma overexpressing Her2. Eur J Cancer. 2015;51(1):45-54.
13. Dogliotti L, Carteni G, Siena S, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol. 2007;52(1):134-41.
14. Bamias A, Dafni U, Karadimou A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol. 2013;24(4):1011-7.
15. Krege S, Rexer H, vom Dorp F, et al. Prospective randomized double-blind multicentre phase II study comparing gemcitabine and cisplatin plus sorafenib chemotherapy with gemcitabine and cisplatin plus placebo in locally advanced and/or metastasized urothelial cancer: SUSE (AUO-AB 31/05). BJU Int. 2014;113(3):429-36.
16. Hussain M, Daignault S, Agarwal N, et al. A randomized phase 2 trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial carcinoma. Cancer. 2014;120(17):2684-93.
17. Lorusso V, Crucitta E, Silvestris N, et al. Randomised, open-label, phase II trial of paclitaxel, gemcitabine and cisplatin versus gemcitabine and cisplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium. Oncol Rep. 2005;13(2):283-7.
18. 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.
19. Culine S, Flechon A, Gravis G, et al. Results of the GETUG-AFU 19 trial: A randomized phase II study of dose dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) with or without anti-epidermal growth factor receptor (EGF-R) monoclonal antibody

panitumumab (PANI) in advanced transitional cell carcinoma (ATCC). J Clin Oncol. 2017;35(Suppl 6):307.
20. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001;19(10):2638-46.
21. Dreicer R, Manola J, Roth BJ, et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. Cancer. 2004;100(8):1639-45.
22. Siefker-Radtke AO, Millikan RE, Tu SM, et al. Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. J Clin Oncol. 2002;20(5):1361-7.
23. Baitar A, De Vos M, Vandebroek A, Schrijvers D. Carboplatin and gemcitabine in patients with advanced and/or metastatic urothelial cancers: A phase II study. J Geriatric Oncol. 2011;2(1):31-5.
24. De Santis M, Wiechno PJ, Bellmunt J, et al. Vinflunine-gemcitabine versus vinflunine-carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: results of an international randomized phase II trial (JASINT1). Ann Oncol. 2016;27(3):449-54.
25. Khaled H, Emara ME, Gaafar RM, et al. Primary chemotherapy with low-dose prolonged infusion gemcitabine and cisplatin in patients with bladder cancer: a Phase II trial. Urol Oncol. 2008;26(2):133-6.
26. Hsieh MC, Chiang PH, Rau KM, et al. The comparison of oncologic outcomes between metastatic upper tract urothelial carcinoma and urothelial carcinoma of the bladder after cisplatin-based chemotherapy. Urol Oncol. 2015;33(11):495 e9- e14.
27. Locke JA, Pond GR, Sonpavde G, et al. Cisplatin- Versus Non-Cisplatin-based First-Line Chemotherapy for Advanced Urothelial Carcinoma Previously Treated With Perioperative Cisplatin. Clin Genitourin Cancer. 2016;14(4):331-40.
28. Morales-Barrera R, Bellmunt J, Suarez C, et al. Cisplatin and gemcitabine administered every two weeks in patients with locally advanced or metastatic urothelial carcinoma and impaired renal function. Eur J Cancer. 2012;48(12):1816-21.
29. Stadler WM, Hayden A, von der Maase H, et al. Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. Urol Oncol. 2002;7(4):153-7.
30. Nogue-Aliguer M, Carles J, Arrivi A, et al. Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. Cancer. 2003;97(9):2180-6.
31. Bamias A, Lainakis G, Kastritis E, et al. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. Oncology. 2007;73(5-6):290-7.
32. Bamias A, Aravantinos G, Deliveliotis C, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol. 2004;22(2):220-8.
33. Adamo V, Magno C, Spitaleri G, et al. Phase II study of gemcitabine and cisplatin in patients with advanced or metastatic bladder cancer: long-term follow-up of a 3-week regimen. Oncology. 2005;69(5):391-8.
34. Jones RJ, Crabb SJ, Chester JD, et al. TOUCAN: A randomised phase II trial of carboplatin and gemcitabine +/- vandetanib in first line treatment of advanced urothelial cell cancer in patients who are not suitable to receive cisplatin. J Clin Oncol. 2016.
35. Bamias A, Moulopoulos LA, Koutras A, et al. The combination of gemcitabine and carboplatin as first-line treatment in patients with advanced urothelial carcinoma. A Phase II study of the Hellenic Cooperative Oncology Group. Cancer. 2006;106(2):297-303.

36. 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.
37. 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.
38. Narayanan S, Harshman LC, Srinivas S. Second-line therapies in metastatic urothelial carcinoma. Hematol Oncol Clin North Am. 2015;29(2):341-59.
39. American Society of Clinical Oncology. Understanding Maintenance Therapy 2019 [Available from: https://www.cancer.net/navigating-cancer-care/how-cancer-treated/understanding-maintenance-therapy.
40. Lympoma Action. Maintenance therapy (including rituximab maintenance) [Available from: https://lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma/maintenance-therapy-including-rituximab-maintenance.
41. Yuan M, Huang LL, Chen JH, Wu J, Xu Q. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther. 2019;4:61.
42. National Institute for Health Research. Olaparib (Lynparza) for metastatic breast cancer with germline BRCA mutation – second line 2016 [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/migrated/Olaparib-Jan16.pdf.
43. Argiris A, Harrington KJ, Tahara M, et al. Evidence-Based Treatment Options in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck. Front Oncol. 2017;7:72.
44. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.
45. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379(26):2495-505.
46. Merck Europe BV. Bavencio (avelumab) summary of product characteristics 2020 [Available from: https://www.medicines.org.uk/emc/product/8453.
47. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218-30.
48. Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2020.
49. Boyerinas B, Jochems C, Fantini M, et al. Antibody-Dependent Cellular Cytotoxicity Activity of a Novel Anti-PD-L1 Antibody Avelumab (MSB0010718C) on Human Tumor Cells. Cancer Immunol Res. 2015;3(10):1148-57.
50. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. Cancer Control. 2014;21(3):231-7.
51. Dahan R, Sega E, Engelhardt J, et al. FcgammaRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. Cancer Cell. 2015;28(4):543.
52. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. Expert Opin Biol Ther. 2017;17(4):515-23.
53. Kohrt HE, Houot R, Marabelle A, et al. Combination strategies to enhance antitumor ADCC. Immunotherapy. 2012;4(5):511-27.
54. Merck Healthcare KGaA. Periodic Benefit Risk Evaluation Report for avelumab/Bavencio (23 September 2019 to 22 March 2020). 2020.
55. American Cancer Society. What is Bladder Cancer? 2019 [Available from: https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html.
56. World Health Organization. World Cancer Report 2014. 2014.
57. Zhao M, He XL, Teng XD. Understanding the molecular pathogenesis and prognostics of bladder cancer: an overview. Chin J Cancer Res. 2016;28(1):92-8.

58. European Association of Urology. Non-muscle-invasive Bladder Cancer (TaT1 and CIS) 2018 [Available from: https://uroweb.org/wp-content/uploads/EAU-Guidelines-Non-muscle-invasive-Bladder-Cancer-TaT1-CIS-2018.pdf.
59. European Association of Urology. Muscle-invasive and Metastatic Bladder Cancer 2018 [Available from: https://uroweb.org/wp-content/uploads/EAU-MIBC-Guidelines-2018V2.pdf.
60. Bellmunt J, Orsola A, Leow JJ, et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii40-8.
61. Smolensky D, Rathore K, Cekanova M. Molecular targets in urothelial cancer: detection, treatment, and animal models of bladder cancer. Drug Des Devel Ther. 2016;10:3305-22.
62. Cancer Research UK. Bladder cancer incidence statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence.
63. National Cancer Registration and Analysis Service. TNM stage group by CCG by tumour type for 10+3 tumour types, 2012-2017. 2019.
64. Park JC, Citrin DE, Agarwal PK, Apolo AB. Multimodal management of muscle-invasive bladder cancer. Curr Probl Cancer. 2014;38(3):80-108.
65. Milowsky MI, Rumble RB, Booth CM, et al. Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol. 2016;34(16):1945-52.
66. Yaxley JP. Urinary tract cancers: an overview for general practice. J Family Med Prim Care. 2016;5(3):533-8.
67. National Comprehensive Cancer Network (NCCN). Bladder Cancer version 4.2019 2019 [
68. Cancer Research UK. Bladder cancer mortality statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/mortality.
69. Leal J, Luengo-Fernandez R, Sullivan R, Witjes JA. Economic burden of bladder cancer across the European Union. Eur Urol. 2016;69(3):438-47.
70. Mason SJ, Downing A, Wright P, et al. Health-related quality of life after treatment for bladder cancer in England. Br J Cancer. 2018;118(11):1518-28.
71. Månsson Å, Davidsson T, Hunt S, Månsson W. The quality of life in men after radical cystectomy with a continent cutaneous diversion or orthotopic bladder substitution: is there a difference? BJU Int. 2002;90(4):386-90.
72. Caffo O, Fellin G, Graffer U, Luciani L. Assessment of quality of life after cystectomy or conservative therapy for patients with infiltrating bladder carcinoma: A survey by a self-administered questionnaire. Cancer. 1996;78(5):1089-97.
73. Matsuda T, Aptel I, Exbrayat C, Grosclaude P. Determinants of quality of life of bladder cancer survivors five years after treatment in France. Int J Urol. 2003;10(8):423-9.
74. Allareddy V, Kennedy J, West MM, Konety BR. Quality of life in long-term survivors of bladder cancer. Cancer. 2006;106(11):2355-62.
75. Cox E, Saramago P, Kelly J, et al. Effects of Bladder Cancer on UK Healthcare Costs and Patient Health-Related Quality of Life: Evidence From the BOXIT Trial. Clin Genitourin Cancer. 2019.
76. Bristol-Myers Squibb Pharmaceuticals Ltd. Opdivo (nivolumab) summary of product characteristics 2019 [Available from: https://www.medicines.org.uk/emc/product/6888.
77. Merck Sharp & Dohme Ltd. Keytruda (pembrolizumab) summary of product characteristics 2019 [Available from: https://www.medicines.org.uk/emc/product/2498/smpc.
78. Roche Registration GmbH. Tecentriq (atezolizumab) summary of product characteristics 2020 [Available from: https://www.medicines.org.uk/emc/product/8442/smpc.
79. National Institute for Health and Care Excellence. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable 2018 [Available from: https://www.nice.org.uk/guidance/ta492.

80. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable 2018 [Available from: https://www.nice.org.uk/guidance/ta522.
81. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy 2018 [Available from: https://www.nice.org.uk/guidance/ta525.
82. National Institute for Health and Care Excellence. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract 2013 [Available from: https://www.nice.org.uk/guidance/ta272.
83. National Institute for Health and Care Excellence. Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy 2018 [Available from: https://www.nice.org.uk/guidance/ta530.
84. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy 2018 [Available from: https://www.nice.org.uk/guidance/ta519.
85. Pfizer Data on File. B9991037 Non-interventional study protocol. 2019.
86. Pfizer Data on File. B9991037 Cohort II table shells. 2020.
87. 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.
88. Sternberg CN, Skoneczna IA, Castellano D, et al. Larotaxel with Cisplatin in the first-line treatment of locally advanced/metastatic urothelial tract or bladder cancer: a randomized, active-controlled, phase III trial (CILAB). Oncology. 2013;85(4):208-15.
89. Galsky MD, Krege S, Lin CC, et al. Relationship between 6- and 9-month progression-free survival and overall survival in patients with metastatic urothelial cancer treated with first-line cisplatin-based chemotherapy. Cancer. 2013;119(16):3020-6.
90. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389(10064):67-76.
91. ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (MK-3475-052/KEYNOTE-052) 2020 [Available from: https://clinicaltrials.gov/ct2/show/results/NCT02335424.
92. Vuky J, Balar AV, Castellano DE, et al. Updated efficacy and safety of KEYNOTE-052: A single-arm phase 2 study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol. 2018;36(15_suppl):4524.
93. Galsky MD, Arija JAA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10236):1547-57.
94. Merck & Company Inc. Merck Provides Update on Phase 3 KEYNOTE-361 Trial Evaluating KEYTRUDA® (pembrolizumab) as Monotherapy and in Combination with Chemotherapy in Patients with Advanced or Metastatic Urothelial Carcinoma 2020 [Available from: https://investors.merck.com/news/press-release-details/2020/Merck-Provides-Update-on-Phase-3-KEYNOTE-361-Trial-Evaluating-KEYTRUDA-pembrolizumab-as-Monotherapy-and-in-Combination-with-Chemotherapy-in-Patients-with-Advanced-or-Metastatic-Urothelial-Carcinoma/default.aspx.
95. Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol. 2012;30(5):507-12.
96. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909-20.

97. Powles T, Duran I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391(10122):748-57.
98. Han KS, Joung JY, Kim TS, et al. Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy. Br J Cancer. 2008;98(1):86-90.
99. Kouno T, Ando M, Yonemori K, et al. Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. Eur Urol. 2007;52(4):1115-22.
100. Necchi A. Three-year follow-up from the phase 3 KEYNOTE-045 trial: pembrolizumab (pembro) versus investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC). Ann Oncol. 2019;30(Suppl_5):v356-v402.
101. Matsumoto R, Abe T, Ishizaki J, et al. Outcome and prognostic factors in metastatic urothelial carcinoma patients receiving second-line chemotherapy: an analysis of real-world clinical practice data in Japan. Jpn J Clin Oncol. 2018;48(8):771-6.
102. Johnson KR, Ringland C, Stokes BJ, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol. 2006;7(9):741-6.
103. Buyse M, Thirion P, Carlson RW, et al. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Meta-Analysis Group in Cancer. Lancet. 2000;356(9227):373-8.
104. Cremolini C, Loupakis F, Antoniotti C, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. Ann Oncol. 2015;26(6):1188-94.
105. McCoach CE, Blumenthal GM, Zhang L, et al. Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small-cell lung cancer treated with a targeted therapy or immunotherapy. Ann Oncol. 2017;28(11):2707-14.
106. Morgensztern D, Ko A, O'Brien M, et al. Association between depth of response and survival in patients with advanced-stage non-small cell lung cancer treated with first-line chemotherapy. Cancer. 2019;125(14):2394-9.
107. Guancial EA, Roussel B, Bergsma DP, et al. Bladder cancer in the elderly patient: challenges and solutions. Clin Interv Aging. 2015;10:939-49.
108. Merck–Pfizer Data on File. Merck–Pfizer Alliance urothelial cancer virtual UK advisory board (2 July 2020): Meeting report. 2020.
109. Powles T, Kopyltsov E, Su P-J, et al., editors. Patient-reported outcomes from JAVELIN Bladder 100: avelumab first-line maintenance + best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma. ESMO; 2020.
110. Pfizer Data on File. JAVELIN Bladder 100 (Study B9991001): Interim Clinical Study Report. 2020.
111. Powles T, Park SH, Voog E, et al. Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis. J Clin Oncol. 2020;38(18_suppl):LBA1.
112. Pfizer Inc. JAVELIN Bladder 100 (Study B9991001): Clinical Protocol. 2015.
113. Pfizer Data on File. JAVELIN Bladder 100 (Study B9991001): Statistical Analysis Plan. 2019.
114. Pfizer Data on File. JAVELIN Bladder 100 (Study B9991001): Table P-1. Subgroup analysis of overall survival - full analysis set. 2020.
115. National Institute for Health and Care Excellence. Avelumab for maintenance treatment of advanced urothelial cancer after platinum-based chemotherapy. Final scope 2020.

116. Grivas P, Park SH, Voog E, et al., editors. Avelumab 1L maintenance + best supportive care (BSC) vs BSC alone with 1L chemotherapy for advanced urothelial carcinoma: subgroup analyses from JAVELIN Bladder 100. ESMO; 2020.
117. Merck KGaA. Clinical Study Report Urothelial Carcinoma Cohorts JAVELIN Solid Tumor. 2017.
118. Pfizer Data on File. JAVELIN Bladder 100 (Study B9991001): Table 14.3.3.3.1.1.10. Summary of treatment given for irAEs - overall and by cluster - safety analysis set. 2020.
119. Committee for Medicinal Products for Human Use. Summary of opinion (post authorisation) - Keytruda (pembrolizumab). European Medicines Agency; 2017.
120. Committee for Medicinal Products for Human Use. Summary of opinion (initial authorisation) - Tecentriq. European Medicines Agency; 2017.
121. European Medicines Agency. EMA restricts use of Keytruda and Tecentriq in bladder cancer. 2018.
122. de Biasi AR, Villena-Vargas J, Adusumilli PS. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. Clin Cancer Res. 2014;20(21):5384-91.
123. Shevchenko I, Karakhanova S, Soltek S, et al. Low-dose gemcitabine depletes regulatory T cells and improves survival in the orthotopic Panc02 model of pancreatic cancer. Int J Cancer. 2013;133(1):98-107.
124. Rassy E, Assi T, Kattan J. Is there a role for maintenance therapy after platinum chemotherapy in bladder cancer in the era of immune therapy? Future Oncol. 2019;15(34):3877-9.
125. Luskin MR, Murakami MA, Manalis SR, Weinstock DM. Targeting minimal residual disease: a path to cure? Nat Rev Cancer. 2018;18(4):255-63.
126. Bellmunt J, Eigl BJ, Senkus E, et al. Borealis-1: a randomized, first-line, placebo-controlled, phase II study evaluating apatorsen and chemotherapy for patients with advanced urothelial cancer. Ann Oncol. 2017;28(10):2481-8.
127. National Institute for Health and Care Excellence. Avelumab with axitinib for untreated advanced renal cell carcinoma. 2020 2020.
128. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.
129. Stata. STATA package streg manual. 2019.
130. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. Sociological Methods & Research. 2004;33(2):261-304.
131. Raftery AE. Bayesian Model Selection in Social Research. Sociological Methodology. 1995;25:111-63.
132. Office for National Statistics. National life tables: UK. 2020.
133. National Institute for Health and Care Excellence. Avelumab for treating metastatic Merkel cell carcinoma. 2018.
134. Lambert P. STPM2: Stata module to estimate flexible parametric survival models: Boston College Department of Economics; [Available from: https://ideas.repec.org/c/boc/bocode/s457128.html.
135. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Statistics in Medicine. 2002;21(15):2175-97.
136. Brazier JE, Longworth L. NICE DSU Technical Support Document 8: An introduction to the measurement and valuation of health for NICE submissions. 2011.
137. van Hout B, Janssen MF, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
138. Dolan P. Aggregating Health State Valuations. Journal of Health Services Research & Policy. 1997.
139. Longworth L, Rowen D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011.

140. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes. 2008;6:84.
141. National Institute for Health and Care Excellence. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. 2019.
142. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. Medical decision making : an international journal of the Society for Medical Decision Making. 2006;26(4):410-20.
143. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health and Quality of Life Outcomes. 2010;8:50.
144. National Institute for Health and Care Excellence. TA378: Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy. 2016.
145. Gauci M-L, Baroudjian B, Zeboulon C, et al. Immune-related hepatitis with immunotherapy: Are corticosteroids always needed? Journal of Hepatology. 2018;69(2):548-50.
146. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
147. National Institute for Health and Care Excellence. BNF: British National Formulary - NICE. 2020.
148. NHS England. National Schedule of Reference Costs 2018/2019.; 2020.
149. Curtis L, Burns A. Unit Costs of Health and Social Care 2019. 2020.
150. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliative Medicine. 2015;29(10):899-907.
151. Hatswell AJ, Porter J, Lee D, Hertel N, Latimer NR. The cost of costing treatments incorrectly: errors in the application of drug prices in economic evaluation due to failing to account for the distribution of patient weight. Value Health. 2016;19(8):1055-8.
152. National Institute for Health and Care Excellence. Nivolumab for previously treated advanced renal cell carcinoma. 2016.
153. National Institute for Health and Care Excellence. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. 2017.
154. National Institute for Health and Care Excellence. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies. 2019.
155. AstraZeneca AB. Durvalumab (Imfinzi®) summary of product characteristics 2020 [updated 2018/09/21/.
156. Hospira UK Ltd. Cisplatin 1 mg/ml sterile concentrate summary of product characteristics 2020 [Available from: https://www.medicines.org.uk/emc/medicine/623/smpc.
157. Hospira UK Ltd. Carboplatin 10 mg/ml intravenous infusion summary of product characteristics 2020 [Available from: https://www.medicines.org.uk/emc/product/3787/smpc.
158. Sun Pharmaceutical Industries Europe BV. Gemcitabine 10 mg/ml, solution for infusion summary of product characteristics 2019 [Available from: https://www.medicines.org.uk/emc/product/7298/smpc.
159. Seacross Pharmaceuticals Ltd. Docetaxel 20 mg/ml concentrate for solution for infusion summary of product characteristics 2018 [Available from: https://www.medicines.org.uk/emc/product/7206/smpc.
160. Accord Healthcare Ltd. Paclitaxel 6 mg/ml concentrate for solution for infusion summary of product characteristics 2020 [Available from: https://www.medicines.org.uk/emc/product/6076/smpc.
161. Eli Lilly Nederland BV. Pemetrexed (Alimta) summary of product characteristics 2020 [Available from: https://www.medicines.org.uk/emc/product/3862/smpc.
162. National Institute for Health and Care Excellence. BNF: British National Formulary - NICE: atezolizumab 2020 [Available from: https://bnf.nice.org.uk/medicinal-forms/atezolizumab.html.

163. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2020.
164. National Institute for Health and Care Excellence. BNF: British National Formulary - NICE: pemetrexed 2020 [Available from: https://bnf.nice.org.uk/medicinal-forms/pemetrexed.html.

B.5. Appendices

Appendix C. Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D. Identification, selection and synthesis of clinical evidence

Appendix E. Subgroup analysis

Appendix F. Adverse reactions

Appendix G. Published cost-effectiveness studies

Appendix H. Health-related quality-of-life studies

Appendix I. Cost and healthcare resource identification, measurement and valuation

Appendix J. Clinical outcomes and disaggregated results from the model

Appendix K. Checklist of confidential information

Appendix L. Economic model parameters

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
ID3735 Avelumab Clarification letter response 12Nov20 ACIC.asd	FINAL	Yes	12th November 2020

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

Identification and selection of relevant studies

A1. Document B, Section B2.1, page 23, and Appendix D.1.1, pages 32-69.

Please clarify the purpose of including the randomised controlled trials (RCTs), single-arm trials (SATs) and real-world evidence studies (RWEs) in the systematic literature review (SLR). The company submission states that 113 records for RCTs and SATs, and 120 records for RWEs, were included in the SLR (Appendix D1.1.2, Figures B.5.1 and B.5.2, pages 49-50); however, there is no further mention of these studies in the submission. Please clarify.

In line with NICE requirements, the company conducted extensive SLRs of all available evidence which were presented in the Company Submission. However, as there was no need for an indirect treatment comparison none of the studies were included in Section D.1.1.3. The company are able to provide the SLR report if required.

A2. Appendix D1.1, Section D.1.1.2; Figure B.5.1 and Figure B.5.2, pages 49-50 and Section D.1.1.2.1, page 51.

Please clarify the numbers of studies excluded from the SLR of RCTs and SATs and the SLR of RWE. Figure B.5.1 shows that 299 records were excluded from the SLR of RCTs and SATs at full-text screening and Figure B.5.2 shows that 374 records were excluded from the SLR of SATs. However, the embedded Excel file "Avelumab_UC_Excluded Studies_02Oct2" lists 291 studies and 366 studies, respectively, as excluded from the two reviews. Please clarify.

The embedded Excel file ("Avelumab_UC_Excluded Studies_02Oct2") lists the identified SLRs separately from the other studies whereas the PRISMA diagrams (Figures B.5.1 and B.5.2) list these as excluded during full-text screening. For the clinical SLR, there were 291 excluded full-text articles + 8 excluded published SLRs = 299 in total; and for the RWE SLR, there were 366 excluded full-text articles + 8 excluded published SLRs = 374 in total.

Methods used to assess the main clinical effectiveness evidence

A3. Document B, section B.2.5, page 35 and Appendix D.1.3, page 70.

These sections of the company submission refer to the quality assessment of the JAVELIN Bladder 100 study. Please clarify: (i) the methodological tool/checklist used for assessing the risk of bias; (ii) how many reviewers carried out the risk of bias assessment; and (iii) whether the reviewers worked independently.

Critical appraisal of the JAVELIN Bladder 100 Study was conducted using the minimum criteria listed in the NICE template section 2.5.2, based on CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). The appraisal was undertaken by two reviewers and then validated independently.

Company reference pack

A4. Reference package.

Please provide the Interim Clinical Study Report (reference 110 in Document B: Pfizer Data on File. JAVELIN Bladder 100 (Study B9991001): Interim Clinical Study Report. 2020), as the PDF file in the company reference package appears to be damaged and not readable.

The JAVELIN Bladder 100 (Study B9991001): Interim Clinical Study Report have been included in in the reference pack provided alongside this response. Please note that the information included in the Clinical Study Reports (CSRs) are confidential, unless presented unmarked elsewhere in the submission.

JAVELIN Bladder 100 trial – primary and secondary outcomes

A5. PRIORITY. Document B.

Please supply the time to event data for overall survival (Figure B.2.2, page 37), progression free survival (Figure B.2.3, page 39) and time to treatment discontinuation (Figure B.3.19, page 83)

The life tables from the Kaplan-Meier analyses are presented in a PDF file and provided as separate HTML files in the reference pack. The Kaplan-Meier life tables have been provided for the following:

- Time to death from any cause, stratified by treatment arm, from the 21 October 2019 data cut-off.
- Time to disease progression to death based on blinded independent central review (BICR), stratified by treatment arm, from the 21 October 2019 data cut-off
- Time to disease progression to death based on investigator assessment, stratified by treatment arm, from the 21 October 2019 data cut-off (as per Clarification Question A6).

Please note that the information included in these files is confidential.

- Time to treatment discontinuation, stratified by treatment arm, from the 21 October 2019 data cut-off

A6. <u>PRIORITY.</u> Document B.

Please replicate progression free survival (PFS) data from the submission (Table B.2.10, page 38; Figure B.2.3, page 39 and Table B.2.11, page 40) using the investigator-assessed (INV) definition of progression. Please also provide the time to event data for PFS, using the INV definition of progression.

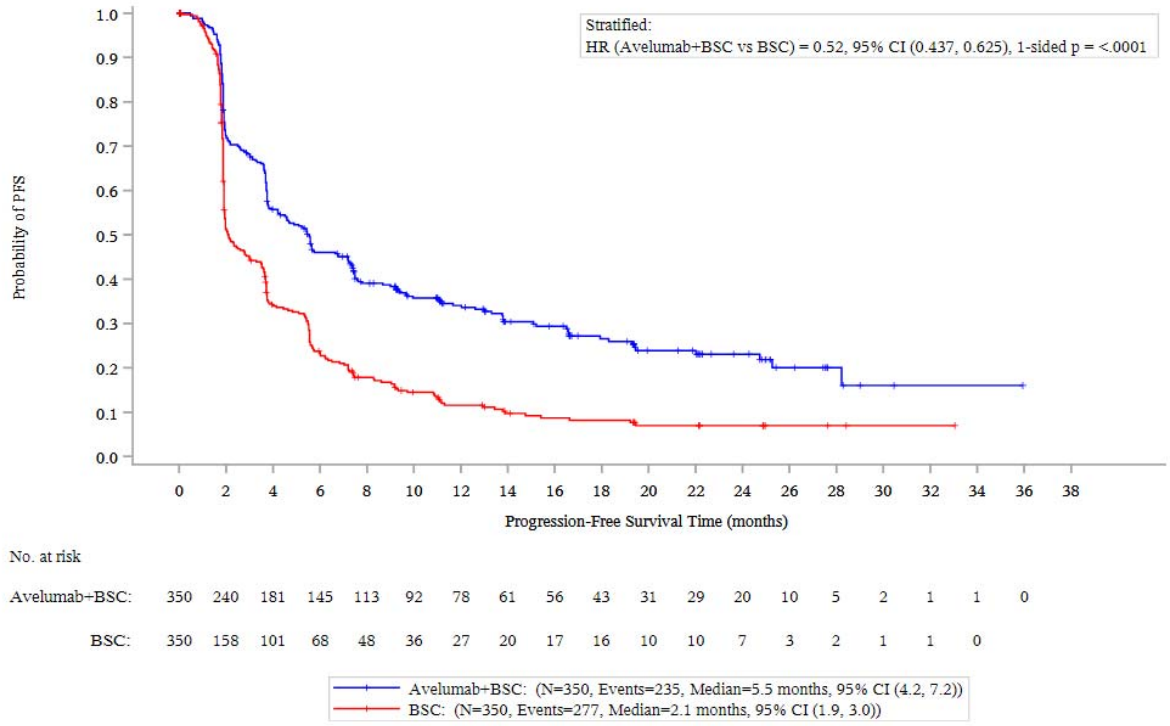
A summary of PFS (based on Investigator assessment) in all randomised patients is presented in Table 1 and the Kaplan-Meier curves are shown in Figure 1. At the time of the IA, patients assigned to avelumab + BSC (FAS) had an improvement in PFS, with a 48% reduction of the risk of progression or death compared with patients assigned to BSC alone (HR: 0.52; 95% CI: 0.437, 0.625; two-sided p<0.0001). The median PFS for avelumab + BSC was 5.5 months (95% CI: 4.2, 7.2) and for BSC alone was 2.1 months (95% CI: 1.9, 3.0) (1, 2).

Table 1: Summary of PFS (based on investigator assessment) in all randomised patients (FAS; secondary endpoint)

Endpoint	**All patients (N=700)**	
	Avelumab + BSC (N=350)	**BSC (N=350)**
Events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumour assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Median PFS (95% CI), months	5.5 (4.2, 7.2)	2.1 (1.9, 3.0)
HR (95% CI)	0.52 (0.437, 0.625)	
Two-sided p-value	<0.0001	
Probability (95% CI) of being event-free at:		
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
15 months	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; PFS = progression-free survival
Source: Pfizer Inc., 2020 (1); Powles et al., 2020 (2)

Figure 1: Kaplan-Meier plot of PFS (based on investigator assessment) in all randomised patients (FAS; secondary endpoint)



Abbreviations: BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; PFS = progression-free survival; vs = versus
Source: Pfizer Inc., 2020 (1); Powles et al., 2020 (2)

The results of the analysis of Best Overall Response (BOR) and Overall Response (OR) (measured from randomisation) based on investigator assessment according to RECIST v1.1 in all randomised patients are summarised in Table 2. The Objective Response Rate (ORR) for avelumab + BSC was [redacted], compared with [redacted] for BSC alone (odds ratio: [redacted]) (2,3). At the time of the IA the median duration of response (DOR) for patients who responded was [redacted] for the avelumab + BSC arm and [redacted] for BSC alone.[110]

Table 2: Summary of response (based on investigator assessment) in all randomised patients (FAS; secondary endpoint)

Endpoint	All patients (N=700)	
	Avelumab + BSC (N=350)	**BSC (N=350)**
Confirmed BOR, n (%)		
CR	22 (6.3)	5 (1.4)
PR	21 (6.0)	7 (2.0)
Stable disease	78 (22.3)	52 (14.9)
Non-CR/Non-PD	57 (16.3)	55 (15.7)
PD	102 (29.1)	168 (48.0)
NE	70 (20.0)	63 (18.0)
OR, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
DC, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median DOR (95% CI), months	[redacted]	[redacted]

Abbreviations: BOR = best overall response; BSC = best supportive care; CI = confidence interval; CR = complete response; DC = disease control (CR, PR, stable disease, and non-CR/non-PD); FAS = full analysis set; N = number of patients evaluable; NR = not reached; OR = objective response (CR and PR); PD = progressive disease; PR = partial response
Source: Pfizer Inc., 2020 (1); Powles et al., 2020 (2, 4)

A7. **Document B. Table B.2.9 page 37.**

The analyses presented in the company submission are interim analyses, as the JAVELIN Bladder 100 is still ongoing and planned to be completed in 2022. Please explain how the overall survival data should be interpreted considering that more than half of the participants are still alive and are therefore contributing censored overall survival times.

The JAVELIN Bladder 100 trial achieved the primary objectives of the study at the interim analysis and therefore this also forms the final analysis though patients are still being followed up. The maturity of the OS data was determined by the information fraction (IF, percentage of observed deaths out of the target number of deaths), rather than the percentage of participants who have died. An interim analysis was planned after 74% (IF) and 66.7% (IF) of the target events (deaths) were estimated to have occurred in the overall population and the PD-L1–positive population, respectively. Following review of the 21st October 2019 data cut-off by the External Data Monitoring Committee, it was reported that the efficacy boundaries

for overall survival in the overall population and the PD-L1–positive population (P<0.0053 and P<0.0014, respectively) had been crossed (2). As efficacy boundaries were crossed, data from the interim analysis also forms the final analysis of this study and the primary objectives of the study have been achieved

A clinically meaningful and statistically significant improvement in OS was demonstrated for all patients assigned to avelumab + BSC (FAS), with a 31% reduction in the risk of death compared with patients assigned to BSC alone (HR: 0.69; 95% CI: 0.556, 0.863; two-sided p=0.001). Treatment with avelumab led to a median 7.1-month improvement in OS – the median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab + BSC arm, and 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm (measured from randomisation) (1, 2). This benefit in OS was observed despite a high proportion of patients in the control group receiving subsequent anticancer therapies including second line immunotherapy agents.

The KM plot of OS (Figure B.2.2 of the Company Submission) shows that the curves do not cross, indicating a consistent and continued benefit for avelumab throughout the follow-up period. In addition, Table B.2.9 in the Company Submission shows that the improvement in probability of being event free (OS) is consistent across the reported time points (6,12,18,24 and 30 months), providing further evidence that this benefit is likely to continue.

As part of the cost-effectiveness analysis it was necessary to extrapolate outcomes, and this was conducted following best practice guidance set out in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 (5). The generalised gamma model was selected as the most suitable extrapolation for both treatment arms and this was validated by UK consultant oncologists. Therefore, the OS benefit for avelumab versus watchful waiting seen in the JAVELIN Bladder 100 trial is likely to persist, with the parametric modelling presented in the Company Submission providing the most suitable method of extrapolation.

A8. Document B. Table B.2.4 page 30 and Table B.2.10 page 38.

Please clarify if there is any discrepancy between the numbers shown in these tables. In Table B.2.4, there are 265 and 324 participants, who had

discontinued treatment leaving 85 and 26, respectively receiving treatment. Though, Table B.2.10 shows that 84 and 27 have not progressed and are still ongoing in the trial.

Table B.2.4 in the Company Submission summarizes the reasons reported on the Case Report Form (CRF) by the Investigators/sites for discontinuing study treatment for each individual patient, whereas the PFS summary presented in Table B.2.10 is based on BICR tumour assessments during the on-treatment and follow-up study periods. Consequently, these are different analyses which cannot be directly compared since patients who continue in the treatment phase of the study (Table B.2.4) may include some who BICR has assessed as having had disease progression, and those who are listed as “ongoing without an event” in Table B.2.10 may include patients who are in any phase of the study (including follow-up).

A9. Document B. Table B.2.4 page 30 and Table B.2.10 page 38.

Table B.2.4 states that 189 and 263 participants, respectively, stopped treatment due to progressive disease and 5 and 14 stopped treatment due to death. Please explain how these numbers relate to Table B.2.10, which shows 216 and 251 participants progressing and 9 deaths in both the avelumab and BSC arms.

As per Clarification Question A8, Table B.2.4 of the Company Submission summarizes the reasons reported on the CRF by the Investigators/sites for discontinuing study treatment for each individual patient, whereas the PFS summary presented in Table B.2.10 is based on BICR tumour assessments during the on-treatment and follow-up study periods.

The appearance of a discrepancy in the number of disease progression events between Tables B.2.4 and B.2.10 may be due to a number of reasons, including: differences in the tumour assessments performed by Investigators and BICR, such as different target and nontarget lesion selection; objective non-radiographic disease progression that may be informative for Investigators, such as new tumour lesions identified by routine cystoscopy; and that Table B.2.10 includes tumour progression events assessed by BICR during the treatment and study follow-up periods, whereas

Table B.2.4 only covers the study treatment period and the cause for treatment discontinuation as reported by the study Investigators.

The appearance of a discrepancy in the number of deaths is similarly due to the different sources of information in these tables: the Investigators (Table B.2.4) may record “death” as the reason for treatment discontinuation for patients who died during the on-treatment period (including deaths due to disease progression), whereas BICR (Table B.2.10) may have assessed disease progression prior to the date of death; and Table B.2.10 may include deaths that occur during study follow-up without a prior BICR assessed disease progression event.

Section B: Clarification on cost-effectiveness data

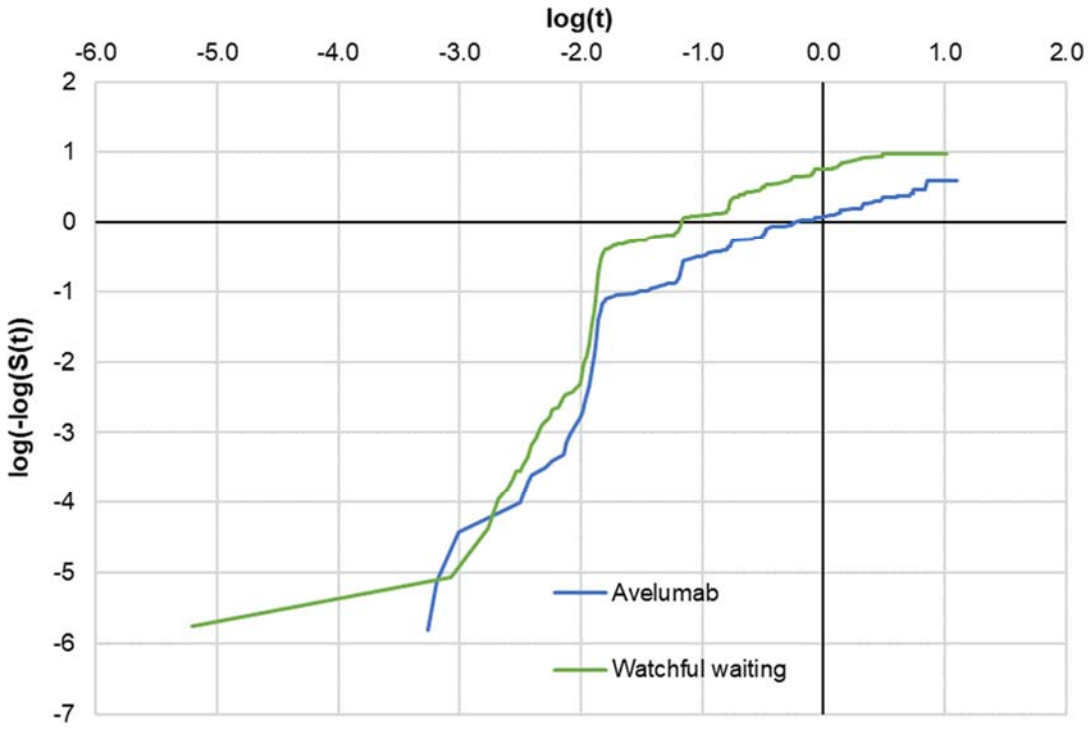
Progression free survival

B1. Document B, section B.3.3.3.2.

Please provide full details of progression free survival using the INV definition of progression. Please include log-cumulative hazard plots, graphical illustration of parametric survival model fits, and extrapolations for both the avelumab and watchful waiting arms.

Please see below the requested information concerning investigator-assessed (INV) progression for the outcome of progression-free survival (PFS). The ability to select parametric models for INV-based PFS is included within the model file previously submitted. A log-cumulative hazard plot for INV-based PFS is presented in Figure 2.

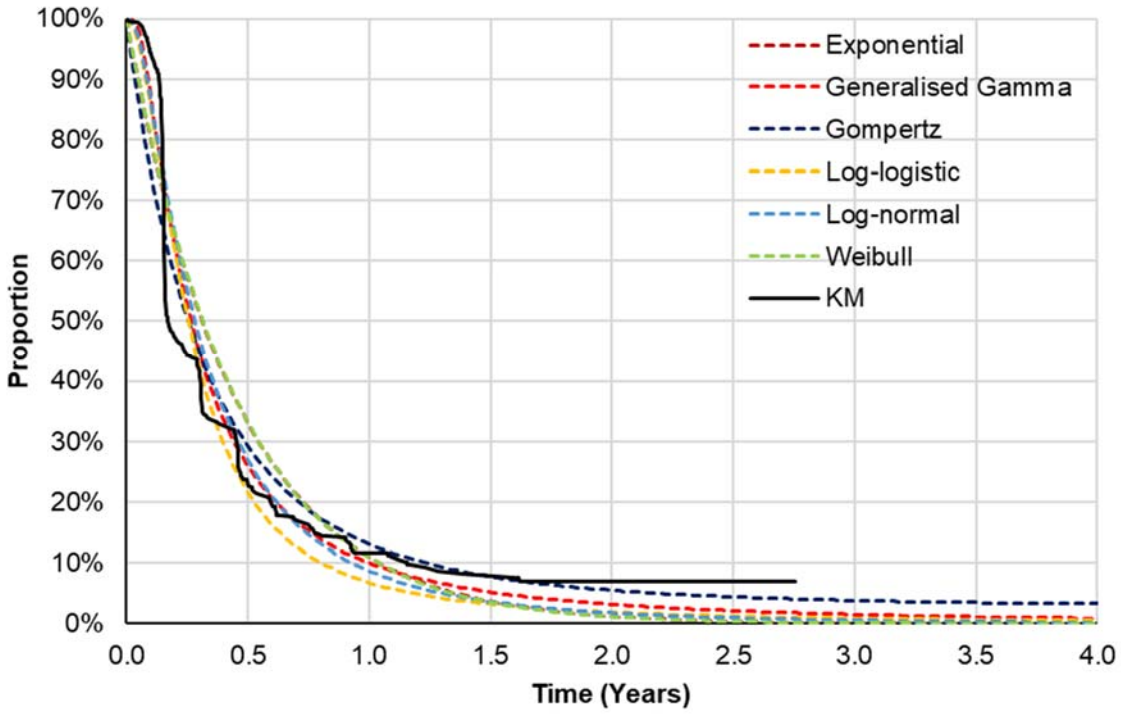
Figure 2: Log-cumulative hazard plot for INV-based PFS



Abbreviations: INV = investigator-assessed; PFS = progression-free survival; S(t) = Survival at time t

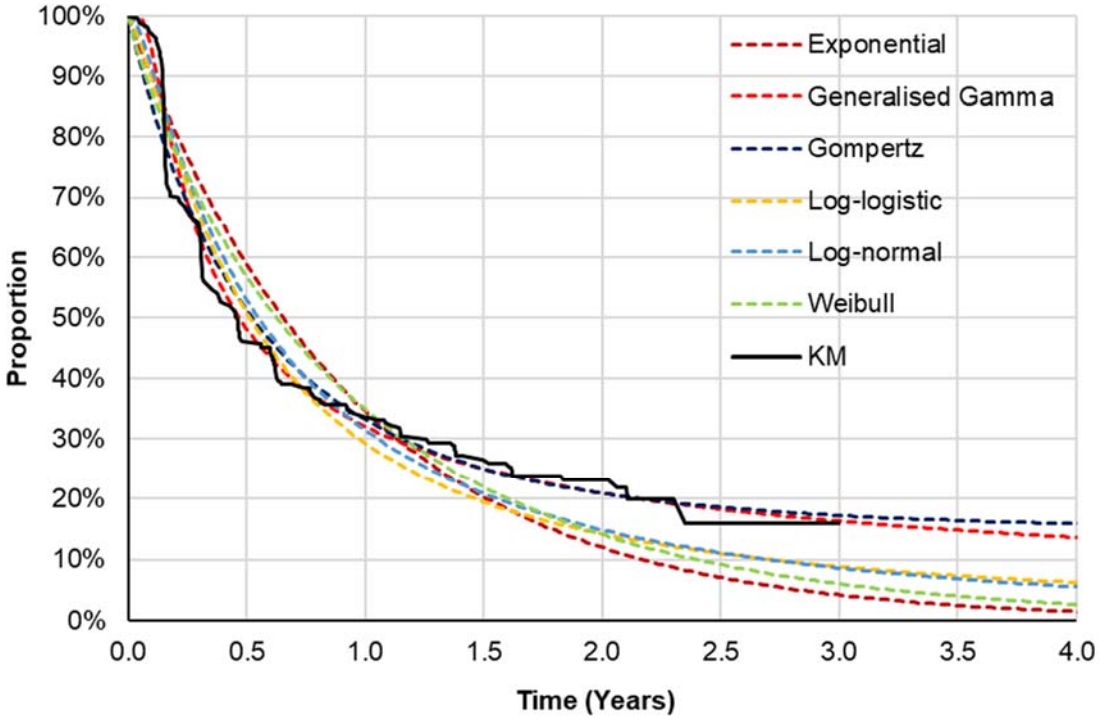
Fits for the parametric survival models are provided in Figure 3 and Figure 4:

Parametric survival model fits for INV-based PFS (watchful waiting)



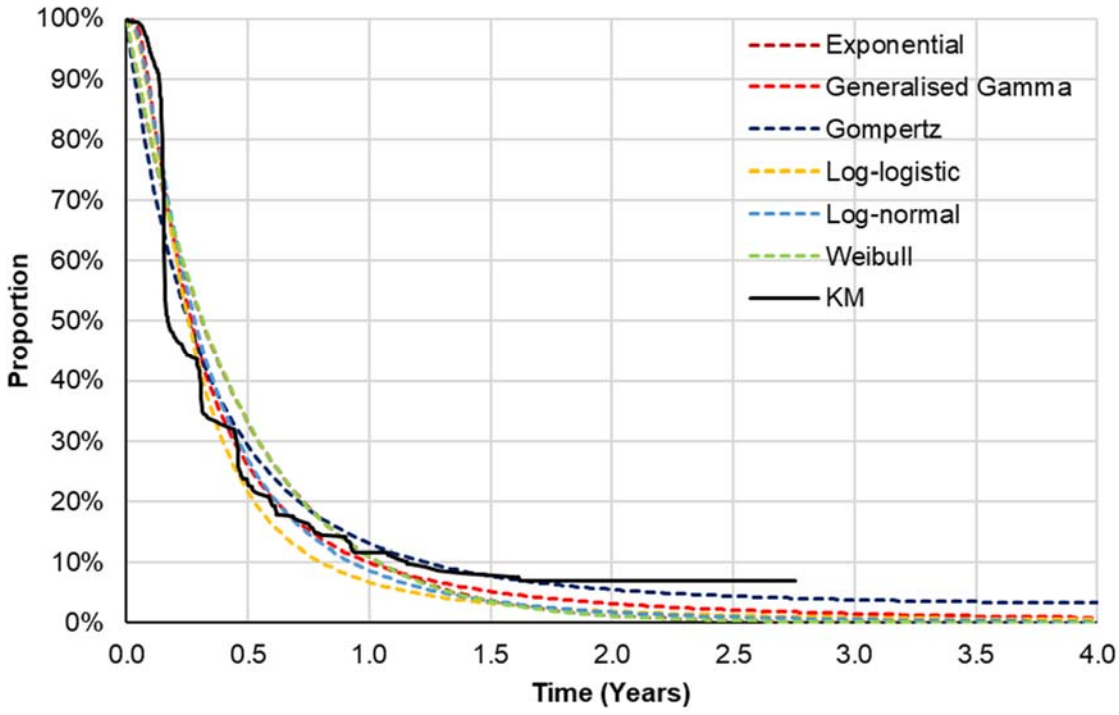
for avelumab and watchful waiting (WW), respectively.

Figure 3: Parametric survival model fits for INV-based PFS (avelumab)



Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

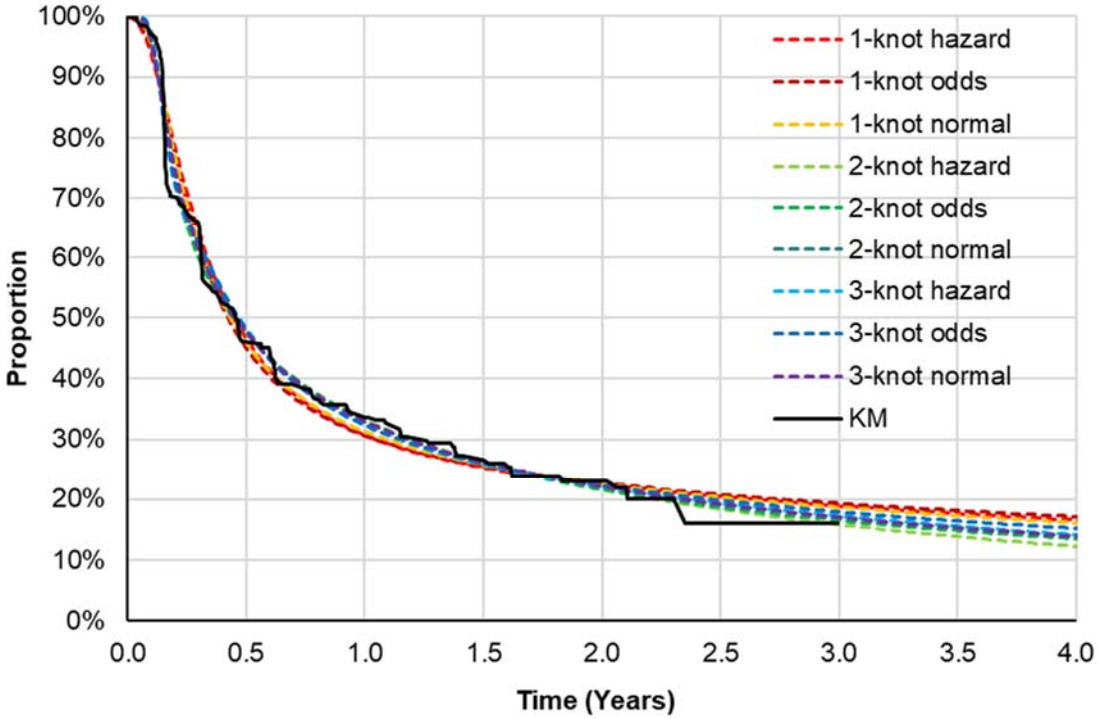
Figure 4: Parametric survival model fits for INV-based PFS (watchful waiting)



Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

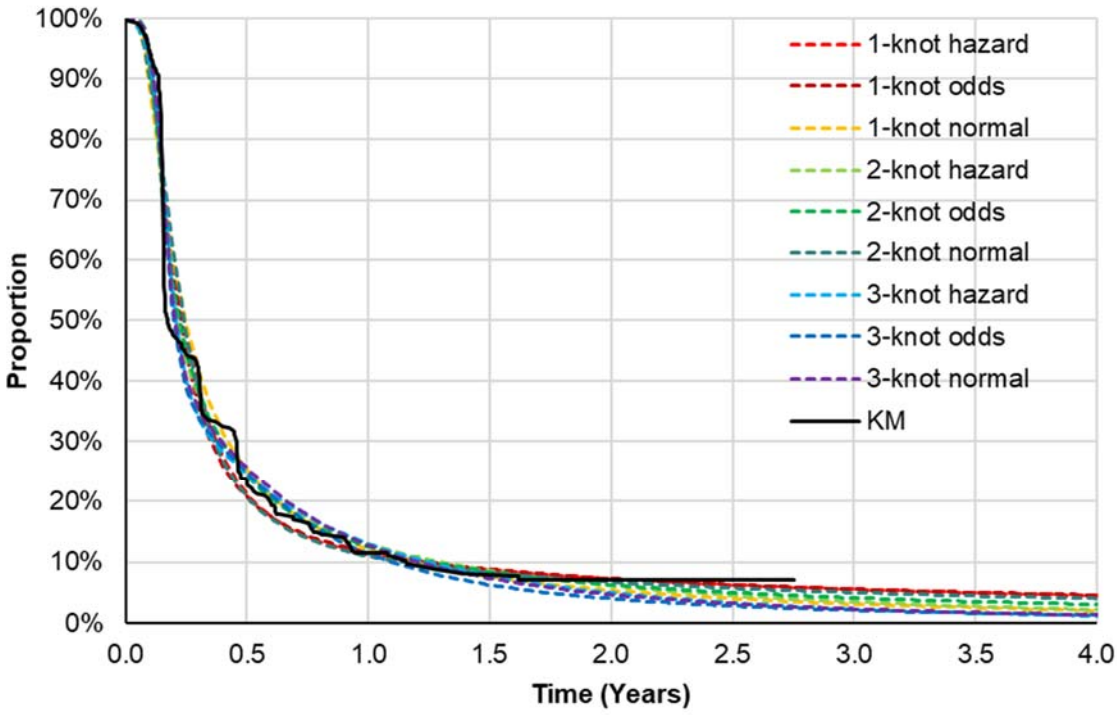
Fits for the spline-based parametric survival models are provided in Figure 5 and Figure 6 for avelumab and WW, respectively.

Figure 5: Spline-based parametric survival model fits for INV-based PFS (avelumab)



Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

Figure 6: Spline-based parametric survival model fits for INV-based PFS (watchful waiting)

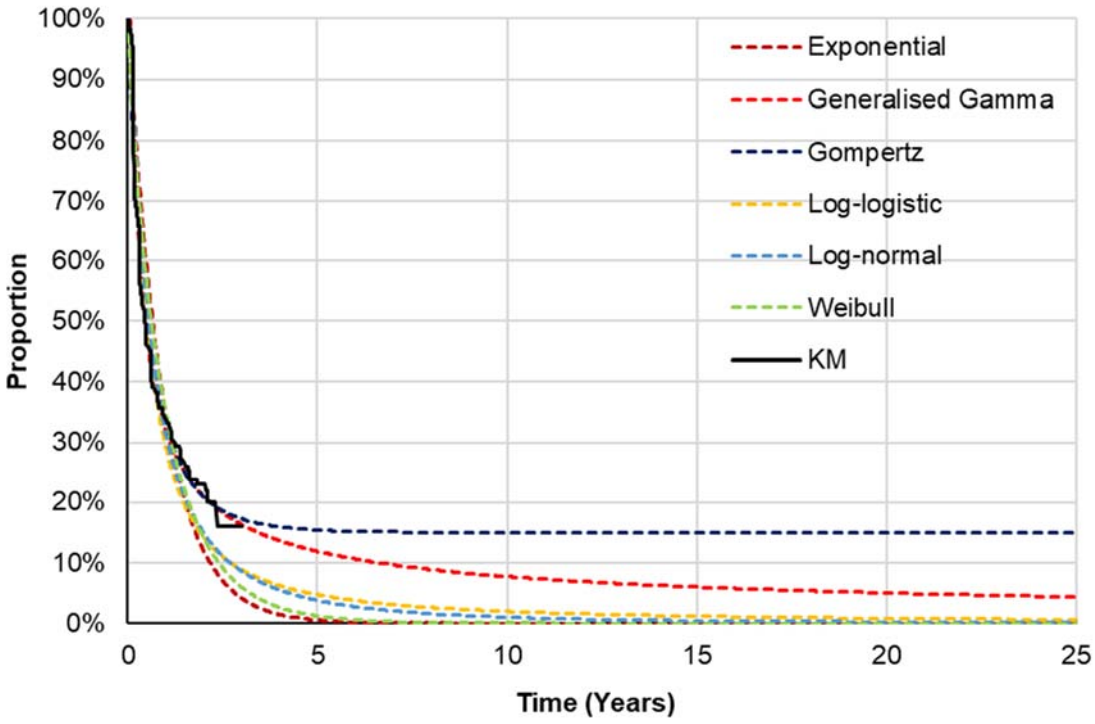


Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

Equivalent plots considering a longer extrapolation period (aligned with the model time horizon of up to 25 years) are provided in Figure 7 to Figure 10. These

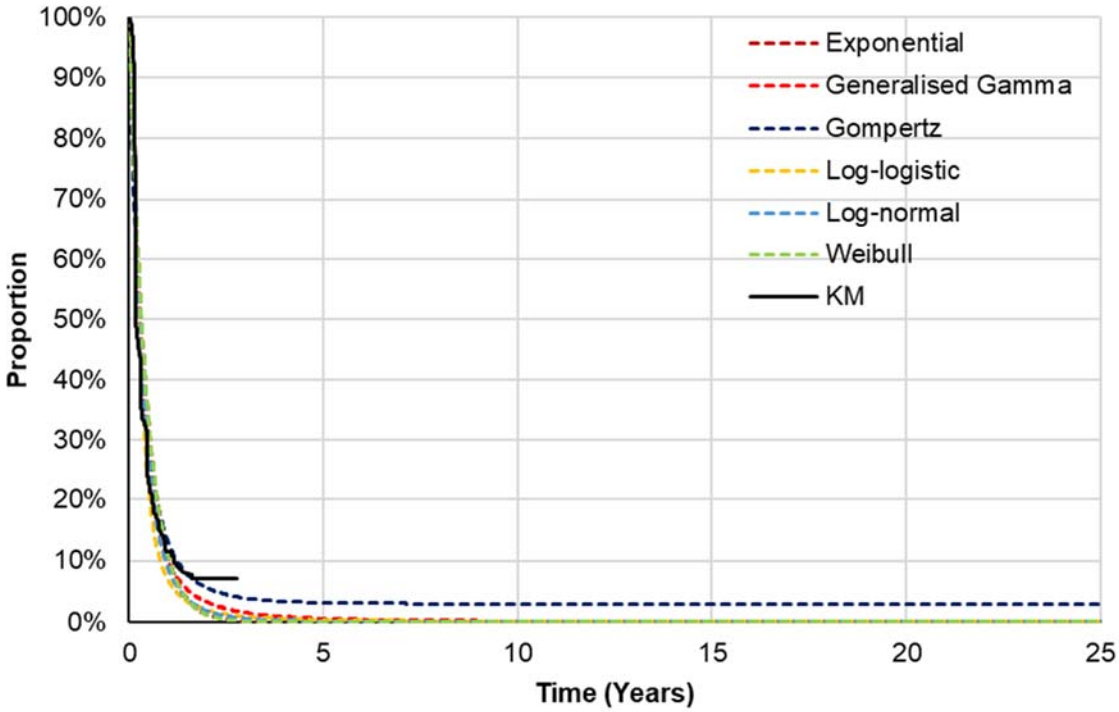
extrapolations are presented without adjustment. As detailed within the CS (Section B.3.3.3.2.5), the occupancy of the progression-free state was capped by the overall survival (OS) curve. To do this, the proportion of patients estimated to reside in the progression-free state was assumed to be the minimum of the proportion estimated by the PFS curve or the OS curve.

Figure 7: Parametric survival model fits for INV-based PFS (avelumab) – 25-year time horizon



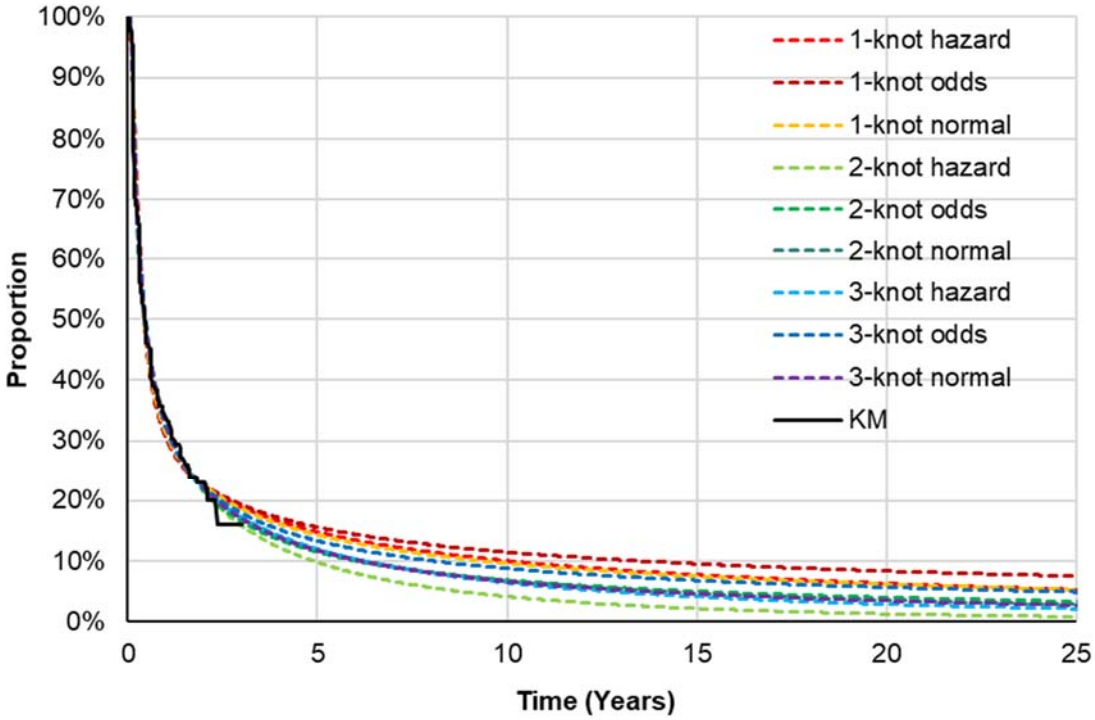
Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

Figure 8: Parametric survival model fits for INV-based PFS (watchful waiting) – 25-year time horizon



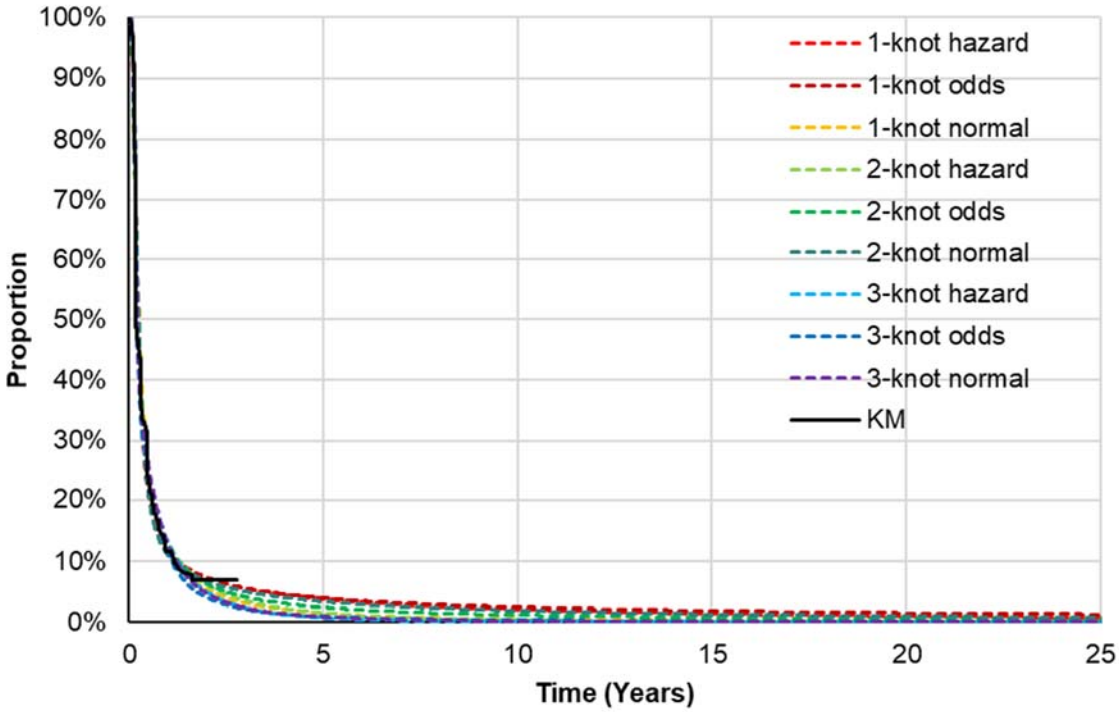
Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

Figure 9: Spline-based parametric survival model fits for INV-based PFS (avelumab) – 25-year time horizon



Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

Figure 10: Spline-based parametric survival model fits for INV-based PFS (watchful waiting) – 25-year time horizon



Abbreviations: INV = investigator-assessed; KM = Kaplan-Meier; PFS = progression-free survival

The model fits for the outcome of INV-based PFS versus IRC-based PFS lead to generally similar conclusions concerning the models most likely to provide the best fit. More specifically, none of the standard parametric models provide a particularly good fit to the KM curve for either arm, most likely due to the protocol-driven bumps in the KM curve. Of the standard models, the generalised gamma (avelumab only) and Gompertz (both arms) models provided the best fits, but the spline-based models were seen to provide overall an improved fit to the KM curves, with similar extrapolations to the generalised gamma for the avelumab arm.

Statistical goodness-of-fit scores are provided in CS Table B.3.5, which show generally similar recommendations (i.e. the selection of a 3-knot spline-based model), though the preferred functional form for INV-assessed progression is shown to be based on the log-cumulative odds of an event, versus based on the log-cumulative hazard of an event for IRC-based progression.

Subsequent treatments

B2. <u>PRIORITY.</u> Document B, section B.2.6.1.6 states that the proportion of patients, receiving subsequent anti-cancer therapies, is considerably lower in UK clinical practice than observed in the JAVELIN Bladder 100 trial (41.9% versus 70.8%). Please clarify the potential impact on the cost-effectiveness results of fewer patients receiving subsequent treatments in clinical practice. Please also provide sensitivity analyses to explore this uncertainty further and to reflect the likely proportion of patients receiving subsequent treatments in clinical practice.

The company would like to note that 70.8% is a typo, and instead should be 71.3% (154/216 [71.3%] patients rather than 154/216 [70.8%]) – this is already implemented within the cost-effectiveness model but is a typo within the submission dossier. This figure represents the proportion of patients who received immunotherapy out of all patients who received a second-line therapy in the JAVELIN Bladder 100 trial (see CS Section B.2.6.1.6).

The 41.9% figure highlighted above has been derived from the Systematic Anti-Cancer Therapy (SACT) dataset not JAVELIN Bladder 100 trial data, and is an estimate of the proportion of patients in UK clinical practice that receive a second-line therapy following a first-line platinum-based chemotherapy (also CS Section B.2.6.1.6). These two values should therefore not be compared directly, as they are reflecting different metrics. It is important to acknowledge that the proportion of patients in UK practice that receive a second-line anti-cancer drug therapy highlighted above is based on all patients who receive a first-line platinum-based chemotherapy regimen. Conversely, in the JAVELIN Bladder 100 trial, this estimate is based on only patients who achieved at least stable disease to the platinum-based chemotherapy (as patients who had progressive disease were not randomised in the JAVELIN Bladder 100 trial). The difference in patient population between the two data sets could explain why we are seeing a discrepancy in the proportion of patients who receive subsequent therapy. Patients who respond to initial platinum-based chemotherapy are likely to be in a better health state than those who did not respond to chemotherapy and thus would be more likely to be eligible for subsequent therapy.

Consequently, the data from the trial provides a more reliable estimate for the proportion of patients receiving subsequent treatments in clinical practice.

Reducing the proportion of avelumab maintenance and watchful waiting patients who receive subsequent therapy will have a varying impact on the ICER dependent on the assumptions made. The impact on the ICER is explored in the following additional analyses:

- Analysis 1 - Setting the proportion of patients who receive subsequent therapy after progression to 100% on both arms.
- Analysis 2 - Setting the proportion of patients who receive subsequent therapy after progression in each arm as an average of the proportion observed in the JAVELIN Bladder 100 trial (68.52% for avelumab and 86.06% for watchful waiting) and the 41.9% from the SACT dataset (resulting in [redacted] and [redacted] for avelumab and watchful waiting respectively).
- A threshold analysis concerning the volume of subsequent therapy cost savings versus the ICER is also presented.

For comparison, the company's original base case analysis is presented in Table 3, with Analyses 1 and 2 presented subsequently.

Table 3: Base-case analysis (applying values of 68.52% and 86.06% for avelumab and watchful waiting respectively)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,245

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 4: Analysis 1 (applying values of 100% and 100% for avelumab and watchful waiting respectively)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,330

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 5: Analysis 2 (applying values of 55.21% and 63.98% for avelumab and watchful waiting respectively)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab							
Watchful waiting							

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

The results of this analysis show that an increase in the proportion of patients expected to require subsequent therapy causes an increase in the total costs for a given treatment arm. Depending on the assumptions imposed for each treatment arm, the directional effect on the ICER may change – i.e. if only the costs for avelumab are increased, the ICER increases; whereas when both assumptions were set to 100%, the ICER decreased (as a higher proportion of patients receiving subsequent treatment on the watchful waiting arm received immunotherapy drugs). It is important to note that these scenario analyses do not consider the impact that the subsequent treatments have on overall survival and should be interpreted with caution. This assumption is explored further in Clarification Question B5.

Threshold analysis

In the threshold analysis, the total incremental costs not related to subsequent therapies were left unchanged, and the total incremental costs related to subsequent therapies were manually set outside the context of the model calculations. Following this, the revised total costs were obtained by summing these values, and then used to determine the ICER (based on the same total QALYs per the base-case analysis). This allows for an exploration of the impact of subsequent therapy cost savings on the ICER, but importantly should be interpreted with caution as all other input parameters are assumed not to be affected.

The results of the threshold analysis are presented below in **Error! Reference source not found.**. Centred on the base-case analysis ICER of £29,245, the total cost savings related to subsequent therapies are estimated at [redacted]. In order

for the ICER to increase to £50,000, assuming all other model parameters are unchanged, the cost savings related to subsequent therapies would need to be reduced from [redacted] to [redacted]. (i.e. approximately [redacted] of the base-case estimate).

[redacted]

Abbreviations: ICER = incremental cost-effectiveness ratio

B3. Document B, section B.3.5.5. Please explain why a smaller proportion of patients who progressed after avelumab received subsequent active treatments compared with those who progressed after watchful waiting ([redacted] and [redacted] respectively). Does this reflect the timing of progression due to maintenance avelumab delaying progression in the model?

The percentage of patients receiving subsequent active treatments after they have progressed (68.52% [148/216] for avelumab + BSC and 86.06% (216/251) for BSC watchful waiting) was calculated as the number of subjects with at least one follow-up anti-cancer drug therapy divided by the number with progressive disease. This is in part due to moving IO treatment (avelumab) further up the pathway as a maintenance treatment and a bigger proportion of patients in the watchful waiting arm going on to receive a PD-1/PD-L1 inhibitor.

The company has presented scenario and threshold analyses investigating the impact the proportion of patients receiving subsequent active treatments has on the ICER in the responses to Clarification Questions B2 and B5.

B4. PRIORITY. Document B, section B.3.5.5. Please explain why a proportion of patients ([redacted]) in the JAVELIN Bladder 100 trial, who progressed after avelumab maintenance treatment, received another PD-L1 treatment (atezolizumab). The feedback received from the ERG's clinical expert suggests that in practice patients will not receive subsequent anti PD-1/PD-L1 treatments following avelumab.

The company agrees with the ERG's clinical expert and does not expect patients to receive subsequent anti PD-1/PD-L1 treatments following avelumab in clinical practice.

The JAVELIN Bladder 100 trial is an international RCT conducted from 2016 to 2019 in 29 countries, with no restrictions imposed on the type of subsequent therapies that patients were allowed to receive following end of treatment (EOT) on either the avelumab maintenance treatment arm or the best supportive care arm. The case report forms were not designed to collect the reason for the selection of subsequent therapies or lack of subsequent treatment administered after EOT visit, which remained at the discretion of the treating physician. After study drug discontinuation, the treating physician evaluated the patient, and if appropriate, selected the subsequent treatment based on the patient's overall condition, prior response to chemotherapy, and country-specific reimbursement and availability of drugs, including PD-1/PD-L1 inhibitors.

The company have provided a scenario analysis exploring the impact of no subsequent treatment with an IO for avelumab in question B5.

B5. PRIORITY. Document B, section B.3.5.5. Please provide a sensitivity analysis that assumes all patients who progress after avelumab maintenance receive subsequent standard of care treatments (as per table B.3.22).

Table 7 provides the results of the analysis when it is assumed patients in the avelumab arm do not receive subsequent immunotherapy treatments. The total proportion assumed to receive subsequent treatment remains the same with

redistribution to other standard of care regimens. The original distributions and revised distributions are provided in Table 6. All components of the watchful waiting arm remained the same.

Table 6: Subsequent therapy avelumab – redistributed immunotherapy treatments to standard of care

Class of treatment	Treatment regimen	% receiving Subs tx – model base case	% receiving Subs tx – reweighted scenario
Immunotherapy	Atezolizumab	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]
	Pembrolizumab	[redacted]	[redacted]
	Durvalumab	[redacted]	[redacted]
SoC	Cisplatin	[redacted]	[redacted]
	Carboplatin	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]
	Pemetrexed	[redacted]	[redacted]
Total received from IO and SoC list		[redacted]	[redacted]

Abbreviations: IO = immunotherapy; SoC = standard of care; tx = treatment;

The results in Table 7 show a decrease of £3,423 in the estimated ICER when immunotherapies are excluded from the avelumab arm and instead the [redacted] is redistributed to alternative SoC regimens.

Table 7: Revised results - subsequent therapy for avelumab is standard of care only

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,822**

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Avelumab costs

B6. Document B, section B.3.5.2.1 states that dose adjustments from the trial may not reflect dose reductions in practice due to the flat licensed dose of 800mg and, therefore, an alternative pragmatic approach was taken resulting in a relative dose intensity (RDI) of 95.05% being applied in the model. Please provide further clarification on this and provide a comparison of RDI based on

the trial with the RDI using the alternative pragmatic approach applied in the economic model to show how the two approaches differ.

As noted within the CS, the dose of avelumab administered in JAVELIN Bladder 100 is similar to, but not the same as, the dose specified within the SmPC (which will be used if avelumab is recommended). In JAVELIN Bladder 100, patients were administered a dose of 10mg per kg of body weight, whereas the licensed dose is a flat dose of 800mg irrespective of body weight.

The mean and median relative dose intensity (RDI) estimates for avelumab in the JAVELIN Bladder 100 trial were 84.6% and 88.2%, respectively (CS, Table B.2.13 – values reported in the CSR). RDI is calculated as the quotient of actual dose intensity and planned dose intensity. Dose intensity is calculated as the overall cumulative dose received by patients over a specified time period divided by the intended duration of avelumab treatment. For the purpose of reporting in the CSR, a time period of 4 weeks was used to calculate dose intensity. The mean dose intensity in the JAVELIN Bladder 100 trial was 16.9 mg/kg/4 weeks, leading to an estimate of the mean RDI of 84.6% (= 16.9/20.0, where 20.0 is the anticipated dose per 4 weeks (i.e. 10mg/kg every 2 weeks).

RDI therefore provides a summary of the proportion of planned treatment received by patients. However, it does not differentiate between dose delays, dose reductions, missed doses etc., all of which may contribute to the overall actual dose intensity for patients. The anticipated use of avelumab in practice is based on the 800mg flat dose, and the SmPC (Appendix C, CS) states that dose escalation or reduction is not recommended. In addition, RDI does not take into account the difference in costs attributable to wastage (i.e. it is a measure of the dose planned to the dose received, irrespective of product wastage). The flat dose ensures all patients receive a full 4 vials of avelumab, eliminating wastage, and therefore RDI is not anticipated to be as low as the 84.6% observed in the trial.

In consideration of the above, the following approach was taken in favour of using the JAVELIN Bladder 100 RDI to estimate the proportion of avelumab assumed to be administered to patients at each treatment cycle:

- The mean duration of treatment with avelumab in the JAVELIN Bladder 100 trial was [redacted] weeks, and the mean number of infusions was [redacted] (irrespective of the dose received).

- Per the trial protocol (and the anticipated use of avelumab in practice), avelumab is expected to be administered once every 2 weeks (excluding any dose delays or missed doses).

- If the mean number of infusions reflected no dose delays or missed doses, the corresponding mean duration of treatment would theoretically be calculated as [redacted] x 2 = [redacted] weeks. This estimate is shorter than the true value of 38.7 weeks, reflecting the fact that some patients had dose delays or missed doses.

- Therefore, the ratio of the mean duration of treatment and the mean number of infusions was calculated to obtain an estimate of the volume of avelumab used on average per administration, accounting for delays or missed doses. This is estimated as a simple ratio of [redacted] / ([redacted] / 2) = [redacted].

It should be noted that the value of [redacted] is not a true measure of RDI; rather, it is a measure of the anticipated proportion of avelumab used per administration when accounting for dose delays or missed doses. The true value of RDI (84.6%) is lower because this measure also accounts for dose reductions and is determined on a per-mg basis (i.e. does not account for product wastage).

For completeness, the following scenarios were conducted to explore the impact of this setting on the cost-effectiveness results:

- **Base-case analysis:** Using value of [redacted]

- **Dosing scenario 1:** Sensitivity analysis using mean RDI value of [redacted]

- **Dosing scenario 2:** Sensitivity analysis using median RDI value of [redacted]

The results of these additional scenario analyses are provided in Table 8 to Table 10.

Table 8: Base-case analysis using value of 95.05%

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,245

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 9: Dosing scenario 1: Sensitivity analysis using mean RDI value of 84.6%

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,002

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 10: Dosing scenario 2: Sensitivity analysis using median RDI value of 88.2%

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,144

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Quality of life

B7. Document B, section B.3.4.2 and table B.3.10. Please provide the EQ-5D data sample size used to estimate progression-free and post-progression utility values in the model. Please provide this information separately by treatment arm and by health state.

The number of patients and records by treatment arm and health state used for the base-case EQ-5D model (including progression but not proximity to death) are presented in Table 11.

Table 11: Sample sizes used to estimate progression-free and post-progression utility values

	Number of patients	Number of observations
Progressed – Avelumab + BSC	196	722
Progressed - BSC	234	504
Progression-free – Avelumab + BSC	311	2273

Progression-free - BSC	282	1258

Scenario analyses

B8. Document B, section B.3.8.2.2, Table B.3.33. Please provide a revised Table of scenario analyses that also includes costs per arm, QALYs per arm, incremental costs and incremental QALYs as well as the ICERs already reported.

The table of scenario analyses provided within the CS (Table B.3.33) presents the results for the scenarios detailed below in Table 12. The corresponding breakdown of results (including costs per arm, QALYs per arm, incremental costs and incremental QALYs as well as the ICERs already reported) are provided in Table 13, by the scenario number shown in Table 12.

Table 12: Scenario analyses presented in CS

#	Topic	Sub-topic	Scenario
Base-case analysis			
1	Model settings	Time horizon	10 years
2			20 years
3		Discount rates	0%
4	Time-to-event outcomes	OS – both arms	Log-logistic
5			Log-normal
6		PFS – both arms	Generalised gamma
7			3-knot odds
8			3-knot hazard
9		PFS approach	PFS-INV
10		TTD	Log-normal with no drop but stop at 5 years
11			Generalised gamma with drop at 2 years to 5% and stop at 5 years
12			Log-normal extrapolated curve with no adjustment
13	Utilities	PFS/PPS	TA519
14		Age-adjustment	No age-adjustment applied
15	Costs	Wastage	No wastage (cost per mg for all treatments)
16		Resource use	Based on TA272
17		Subsequent IOs	IOs not redistributed to atezolizumab
18		Dose adjustment	No dose adjustment applied

Abbreviations: IOs = immuno-oncology agents; OS = overall survival; PFS = progression-free survival; PFS-INV = PFS investigator assessed; PPS = post-progression survival

Table 13: Scenario analyses results breakdown

#	Avelumab total			WW total			Incremental			
	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
1	[redacted]									£35,971
2										£29,961
3										£24,969
4										£32,185
5										£30,629
6										£27,991
7										£28,750
8										£29,677
9										£27,069
10										£38,657
11										£30,317
12										£45,745
13										£30,558
14										£28,144
15										£29,221
16										£37,747
17										£24,032
18										£32,166

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life year; WW = watchful waiting

References

1. Pfizer Data on File. JAVELIN Bladder 100 (Study B9991001): Interim Clinical Study Report. 2020.

2. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218-30.

3. Grivas P, Park SH, Voog E, et al., editors. Avelumab 1L maintenance + best supportive care (BSC) vs BSC alone with 1L chemotherapy for advanced urothelial carcinoma: subgroup analyses from JAVELIN Bladder 100. ESMO; 2020.

4. Powles T, Park SH, Voog E, et al. Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis. J Clin Oncol. 2020;38(18_suppl):LBA1.

5. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

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.

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- 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 donations, legacies, fundraising events and by corporate donations. Our corporate donors are bound by our corporate statement as follows: *CORPORATE STATEMENT Action Bladder Cancer UK is a charity working to support those with bladder cancer and to improve outcomes for patients. We are committed to working in ethical collaboration with commercial and corporate partners in the interest of people affected by bladder cancer. We will accept funding from appropriate corporate and industry supporters. Neither our work, our campaigning nor our information materials will be influenced by accepting any corporate donations or sponsorship. We feel it is important to work with companies that manufacture drugs, treatments or devices which will treat or support bladder cancer patients. We will work in a transparent partnership with appropriate pharmaceutical companies and the medical device industry where these relationships will help promote and improve the interests of bladder cancer patients and fit within the objectives of our charity. We would not accept support from any pharmaceutical or medical industry company for work that we consider to that lie outside the agreed objectives of our charity. We are happy to accept funding, or support in kind, from appropriate corporate supporters outside the health or pharmaceutical sectors. Each corporate collaboration will be assessed and agreed on an individual basis by the charity executive. We are grateful for the support shown by our existing corporate supporters which help us in our work.*
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	A number of pharmaceutical companies have offered to provide our charity funding during the coronavirus epidemic. This is in recognition that many charities such as ours are experiencing a shortfall in income, as fundraising activities by supporters are curtailed. We expect to receive a donation not exceeding £10,000 from Merck Serono Ltd, to support the general activities of the charity.

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 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?	All our Trustees and staff work closely with patients, both directly and via our network of support groups. In addition, four of our trustees and many of our volunteers and fundraisers are patients or carers. It is absolutely fundamental to our work that we have a deep and current understanding of our patients, their hopes and fears and their treatment options, current and future.
Living with the condition	
6. What is it like to live with the condition? What do carers	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. The particular

experience when caring for someone with the condition?	condition for this consultation is the advanced case where platinum chemotherapy has already been given and where survival rates are known to be poor. Carers find themselves in a situation where they can feel helpless, and with very little understanding of what can happen next or how they might help. Thus both patient and carer struggle with the situation. This new drug represents an innovative treatment and potential lifeline for patients.
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 is by platinum based chemotherapy and/or palliative care. These are readily available but response rates and quality of life are poor. Many patients with metastatic bladder cancer are not suitable for cisplatin and so there is an urgent need for alternatives
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. Many are unable to tolerate the current standard of cisplatin chemotherapy. Side effects of cisplatin are severe, even when combined with other drugs, leading to a poor quality of life. 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.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	In its simplest form the treatment represents hope to many for whom other treatment options have been exhausted. Therefore the main benefits include: • complete response • prolonging life • improved quality of life for patient, carers and family.

	Trials have shown that the treatment does prolong life and for about 20% of patients the positive effects are long lasting. Side effects for the majority of patients are minor and tolerable. The treatment is relatively easy to administer. If the treatment is licensed and similar outcomes to those observed in trials are experienced here, there may be scope to use the treatment at other stages of the disease or as a primary treatment.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None. The treatment is widely regarded as an innovative, breakthrough treatment and ABC UK is not aware of any disadvantages perceived by patients or carers.
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.	The mechanism for this treatment is not known precisely, although there is some improvement in patients that express higher levels of PD1/PDL1. It may be possible to develop biomarkers that could more accurately predict which patients would respond best (or even which may not respond or experience a serious adverse event), leading to a precision medicine. Currently about 5,000 patients die each year in the UK from metastatic bladder cancer. All of these could potentially benefit and approximately 20% could be expected to show an enduring and high quality of life benefit. By stimulating the body's own immune system, the treatment has also shown great benefit in the group of patients who are not suitable for cisplatin, leading to a first line application for the treatment. It is our hope at ABC UK that the treatment may prove effective earlier in the treatment pathway, for instance instead of BCG to treat HR NMIBC (High Risk Non Muscle Invasive Bladder Cancer). This could avoid the need for

	cystectomies in a significant minority of patients which are expensive and can cause substantial erosion in the quality of life.
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 has had relatively little research or new treatment developments in recent decades. Despite it being the 4th most prevalent cancer in men and 7th overall, and very expensive for the NHS to treat, mortality rates of c50% have shown NO improvement in the past 30 years. The mechanism of this new drug is different from anything available to treat bladder cancer today; hence the treatment is highly innovative. ABC UK supports the licensing and use of the treatment within the NHS. Ideally more research could be commissioned to optimise the treatment regimen and to better understand the mechanism of treatment, ultimately leading to biomarkers to identify patients for whom the treatment would be most effective.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • ABC UK supports the licensing and use of the treatment within the NHS • The treatment is highly innovative • The treatment gives hope to many for whom other treatment options have been exhausted • Further research/trials to optimise the treatment and develop biomarkers would be highly desirable • Consideration should be given for research/trials for use of the treatment earlier in the disease progress and/or as a primary treatment

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you

1.Your name	[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 approx. 4,800 users, local support groups around the country 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 Roche, Merck, Pfizer, MSD, BMS, and Janssen.
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 manufacturer, amount, and purpose of funding.	Fight Bladder Cancer received a £1,000 honorarium for expert input provided during the Virtual Global Patient Advisory Board on Bladder Cancer - 9th July 2020 from Merck Healthcare KGaA Fight Bladder Cancer received a £10,000 donation from Pfizer Limited to support the production of bladder cancer patient information booklets - 11 September 2020. Fight Bladder Cancer received a £10,000 donation from Merck Serono Limited to support our Patient Information Booklets – 17 September 2020 Fight Bladder Cancer lists all clinical trials currently recruiting patients within the UK, including clinical trials for this technology

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?	We reached out to people on our private online forum of 4,800 patients and carers to ask them about advanced bladder cancer, and received 37 comments. We also spoke to our Support Services Manager, nurses, medical oncologists, and collaborated with our sister charity in Canada to better understand the patient experience.
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?	What is it like to live with the condition? Advanced urothelial cancer has a very poor prognosis. At this point in the pathway there is currently limited choice on treatments. Most current treatments are also very invasive, have significant side effects and often have quite serious side effects that significantly reduce the quality of life for the final months. It is a constant battle to delay the further growth and spread of the cancer. The condition is physically and emotionally tough with a regime of chemotherapy, a known low survival rate, and the understanding that the battle is to "prolong life" rather than resulting in a cure. Patients report that this condition has a substantial impact on their ability to work, ability to travel, and ability to exercise. “It’s like a gun to my head every single minute of the day and night” “Everything I do is tinged with a sadness and a sorrow of "will this be the last time I do this?".” “It’s totally all consuming”

	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?	For advanced/metastatic urothelial cancer, prognosis is very poor with very limited treatments being available. In addition to the chemotherapy treatments, the patients are likely to need other treatments such as radiotherapy to the part of the body where the cancer has spread, surgery to remove the cancer, surgery to unblock the ureters or urethra, and drugs to strengthen the bones. "There's a lack of understanding of bladder cancer by medical staff. Our dad's bladder cancer has taken over our whole life - even when we pretend things are normal, the next scan, the next treatment, fear of the future never go away. The physiological impact on patients and their families is truly underestimated. Supporting my dad leaves me little time or energy for much else!" "Nearly 7 years with advanced bladder cancer, 40+ operations, 3 rounds of chemotherapy, radiotherapy minus a kidney and the one remaining will have to go too. Life is different, I'm different, but I'm still here. I would not be if it wasn't for the NHS, good or bad, and I've had both experiences. They have saved my life many many times and I will be forever grateful"

8. Is there an unmet need for patients with this condition?	The existing treatments for urothelial cancer have limited effectiveness which results in the poor prognosis for those with advanced/metastatic cancer. There is a substantial unmet need for treatment options that can meaningfully improve survival and quality of life in patients with advanced bladder cancer following chemotherapy. “I would love a wonder pill, even if it could just get rid of the fatigue that comes with the procedures and stress” “Every ache or twinge makes me feel uneasy. It really does suck, especially with Covid-19 all over the place. My life consists of the internet, writing, and TV.”
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We spoke to one patient directly who had experienced avelumab, and they reported that it was a “cake walk” compared to chemotherapy. They said on chemotherapy they experienced nausea, neuropathy, and they lost all their hair. While immunotherapy often left them tired, they felt so much better than the abject fatigue and weakness from chemotherapy. This patient is now cancer free, and they feel that this result can be attributed to the combination of radical cystectomy, chemotherapy, and avelumab. We spoke to a medical oncologist, who stated that there is no doubt that the results from the JAVELIN Bladder 100 clinical trial are fantastic. They recommend that for the patients where the cancer can be initially controlled with chemotherapy and then start immunotherapy maintenance, avelumab should be the standard, unless we get better data on the other combinations.

	We spoke to a nurse who treated patients with avelumab, and they told us that in terms of side effects, the patients tolerated the treatment very well. The patients were expecting the same kind of substantial side effects from avelumab that they had from experienced from chemotherapy. After a few cycles and experiencing minimal side effects the patients were more relaxed with the new treatment.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The patient reported that the only remarkable side effect they had during avelumab was profuse sweating. The nurse reported that the main side effects that people experienced were pruritus and rash that required chlorphenamine for treatment. They also noted that the main disadvantage is the fact that the patients are coming every 2 weeks, whereas other checkpoint inhibitors are given every 3 or 4 weeks. The nurse emphasised that immunotherapy was still not very well known for the patients, and it was quite challenging for patients and relatives to understand the difference between chemotherapy and immunotherapy.

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.	This technology seems to be particularly beneficial for patients that showed only partial response or stable disease on first line chemotherapy. People whose cancer had not spread to internal organs but had spread to other parts of the body seemed to respond particularly well to this technology.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	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.
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.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Advanced bladder cancer is physically and emotionally tough with a regime of chemotherapy, a known low survival rate, and the understanding that the battle is to prolong life rather than resulting in a cure • Advanced cancer has an impact on the ability to work, ability to travel, and ability to exercise of both the patient and their family • The existing treatments for advanced urothelial cancer have limited effectiveness, which results in the poor prognosis • The results from JAVELIN Bladder 100 are fantastic, and many patients responded positively to this treatment with minimal side-effects compared to chemotherapy • Avelumab after chemotherapy could see a step change in treating advanced bladder cancer

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Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

Acknowledgements

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The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contribution of authors

Mari Imamura and Moira Cruickshank summarised and critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported within the company submission. David Cooper critiqued the statistical methods and analyses presented in the company submission and checked all the numerical results related to the review of the clinical effectiveness evidence. Dwayne Boyers and Corinne Booth critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further sensitivity analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Gordon Urquhart provided clinical advice during the appraisal. Miriam Brazzelli coordinated all aspects of the appraisal and acted as lead for the clinical effectiveness side of the appraisal. Dwayne

Boyers acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
AIC	Akaike information criterion
aRCC	advanced renal cell carcinoma
BC	Base case
BIC	Bayesian information criterion
BICR	blinded independent central review
BNF	British National Formulary
BOR	best overall response
BSC	best supportive care
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CR	complete response
CRD	Centre for Reviews and Dissemination
CS	company submission
DC	disease control
DOR	duration of response
EAMS	Early Access to Medicine Scheme
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
ERG	Evidence Review Group
FAS	full analysis set
FBlSI-18	Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
INV	investigator
irAE	immune-related adverse event

IRR	infusion-related reaction
IV	intravenous
KM	Kaplan-Meier
LN	log normal
MCC	Merkel cell carcinoma
mg	milligram
MHRA	Medicine and Healthcare Products Regulatory Agency
MVAC	methotrexate, vinblastine, adriamycin and cisplatin
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reached
OR	objective response
ORR	objective response rate
OS	overall survival
PAS	patient access scheme
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PFS-INV	progression-free survival (investigator assessed)
PK	pharmacokinetics
PR	partial response
PS	performance status
PSA	probabilistic sensitivity analysis
PSSRU	Personal and Social Services Research Unit
Q2W	every 2 weeks
QALY	quality-adjusted life-year
QoL	quality of life
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SACT	Systemic Anti-Cancer Therapy
SAE	serious adverse event
SD	standard deviation
SLR	systematic literature review
SmPC	summary of product characteristics

SoC	standard of care
TA	technology appraisal
TEAE	treatment-emergent adverse event
TNM	Tumour, Node, Metastasis Classification system
TRAE	treatment-related adverse event
TTD	time to treatment discontinuation
TTR	time to tumour response
UC	urothelial carcinoma
UK	United Kingdom
USA	United States of America
UTI	urinary tract infection
WW	watchful waiting

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). 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 1.6 explain the key issues in more detail. 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 ERG's view, not the opinion of NICE.

1.1 Overview of the evidence submitted by the company and ERG's key issues

The company submission (CS) focuses on avelumab as maintenance therapy for the first-line treatment of adult patients with locally advanced or metastatic urothelium carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy.

The clinical effectiveness evidence is provided by one ongoing Phase III, multicentre, open-label parallel two-arm randomised controlled trial (RCT), JAVELIN Bladder 100 (Study B9991001; NCT02603432). The JAVELIN Bladder 100 trial compared avelumab in combination with best supportive care (BSC) with BSC alone. The company reports the results of the interim analysis data with the data cut-off date of 21 October 2019. Main clinical outcomes that used in the economic model included overall survival (OS), progression-free survival (PFS), heath-related quality of life (HRQoL) and adverse effects of treatment. Indirect or multiple treatment comparisons were not conducted by the company for this appraisal.

The results of the JAVELIN Bladder 100 trial indicate a benefit in terms of both OS and PFS for those receiving avelumab in addition to BSC, in comparison with those receiving BSC alone.

As expected, in general, the likelihood of treatment-related and immune-related adverse events was increased for patients treated with avelumab +BSC in the JAVELIN Bladder 100 trial

compared to those receiving BSC alone. However, there are no new safety concerns regarding the safety profile of avelumab.

Table 1 presents a summary of the key issues identified by the ERG.

Table 1. Summary of the key issues identified by the ERG

Issues	Summary of issue	Report sections
Issue 1	Health-related quality of life data	Section 2.2.2; Section 3.2.7
Issue 2	Treatment effectiveness parameters (extrapolation of OS curves for avelumab and watchful waiting (WW))	Section 3.2.6
Issue 3	Definition of progression (BICR vs. INV)	Section 3.2.6
Issue 4	Time to treatment discontinuation on avelumab and duration of continued PFS and OS benefit	Section 3.2.2; Section 3.2.6 Section 5.2
Issue 5	The proportion of patients receiving subsequent (post progression) treatment in the model.	Section 3.2.8
Issue 6	The mix of subsequent (post progression) treatments included in the model	Section 3.2.8
Issue 7	Uncertainty about whether end of life criteria are met	Section 6.1

The most important differences between the company's preferred assumptions and the ERG's preferred assumptions in terms of the magnitude of impact on the ICER are around the proportion of patients receiving treatment post-progression in each arm of the model, and the types of treatment that would be used post-progression for patients treated with avelumab.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost-effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained. For the analysis of cost-effectiveness, the company have developed a partitioned survival analysis model, populated using extrapolation of PFS and OS data from the JAVELIN Bladder 100 trial.

Overall, the technology is modelled to affect QALYs by:

- Affecting OS, keeping patients treated with avelumab alive for longer than those treated with watchful waiting (WW), thereby generating life year gains from the model.
- Affecting PFS compared to WW, thereby delaying disease progression to a health state with poorer quality of life and generating QALY gains for avelumab.
- A slight reduction in QALYs due to additional adverse events for avelumab (minor impact on cost-effectiveness).

Overall, the technology is modelled to affect costs by:

- Adding additional treatment acquisition costs of avelumab to the treatment pathway – treatment acquisition costs are influenced by assumptions around the time to treatment discontinuation and any stopping rules that might be applied in clinical practice.
- Reducing the proportion of patients who require immunotherapy (e.g. atezolizumab) and chemotherapy post disease progression, for avelumab compared to WW, thereby reducing the total costs of post-progression treatments in the avelumab arm of the model.
- A slight increase in the costs of treating adverse events compared to BSC (minor impact on cost-effectiveness).

The modelling assumption that has the greatest effect on the ICER is:

- The assumption that time to avelumab treatment discontinuation and any stopping rules applied impacts only on avelumab treatment acquisition costs and has no impact on the relative treatment benefit or duration of continued treatment benefit for avelumab compared to WW.

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

The ERG considers that the decision problem addressed in the CS was in line with the final scope issued by NICE. The population and intervention included in the evidence submitted

by the company are consistent with the expected marketing authorisation. The ERG is not concerned with the difference between the licensed dose of avelumab (a flat dose of 800 mg) and a weight-based dose (at 10 mg/kg) used in the JAVELIN Bladder 100 trial.

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

The ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be acceptable and in line with current methodological standards. In the ERG clinical advisor's opinion, the study participants are reflective of patients who would be considered for maintenance treatment for locally advanced or metastatic urothelial carcinoma in clinical practice in the UK.

The ERG's key issue that relates to the clinical effectiveness evidence is described in Table 2 below.

Table 2. Issue 1. Health-related quality of life data

Report section	*Section 2.2.2 and 3.2.7*
Description of issue and why the ERG has identified it as important	The CS only reported progression-based utility values and did not present any quality of life data within each health state separately by treatment arm. In describing the EQ-5D-5L scores collected in the trial the company states the scores were not significantly different for patients treated with avelumab compared to those receiving BSC (i.e. WW in the model) alone and this would seem to be validated by supporting reference to a conference presentation. However, this seems at odds with the PFS benefit observed with avelumab in the trial where an associated improvement in HRQoL is expected.
What alternative approach has the ERG suggested?	The ERG accept that the use of progression-based utility values pooled across treatment arms is the most appropriate method, but would appreciate a greater level of data regarding quality of life outcomes (especially EQ-5D-5L) from the trial (by treatment arm and progression status) to instil greater confidence in the company base case parameter inputs.
What is the expected effect on the cost-effectiveness estimates?	The ERG consider it unlikely that this issue would change the ERG's preferred base case analysis, but further information would help provide greater confidence in the ICER reported.
What additional evidence or analyses might help to resolve this key issue?	The ERG would welcome further data from the company, reporting descriptive quality of life data (especially EQ-5D based utilities) by treatment arm and progression status. The ERG would also welcome some further explanation regarding the potential inconsistencies between a lack of observed quality of life benefit for avelumab, in light of the PFS benefit observed in the trial.

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

The ERG has five main issues with the cost-effectiveness evidence from the company's economic model, which are summarised in Tables 3-7 below.

Table 3. Issue 2. Treatment effectiveness parameters (extrapolation of OS curves for avelumab and WW)

Report section	*Section 3.2.6*
Description of issue and why the ERG has identified it as important	The ERG consider the company has chosen OS extrapolation curves (generalised gamma parametric survival curves) that may over-estimate overall survival for both the avelumab and WW arms of the model.
What alternative approach has the ERG suggested?	The ERG prefer the LN because it: • Has best statistical fit to the KM OS for avelumab; the best BIC and 2nd best AIC for WW • Has good visual match to the KM data for both arms; • Generates 5 and 10 year OS estimates for WW that are closer to the mid-point of the company's clinical expert expectations (5 year OS: 10.71%, 10 year OS: 2.90%) than the company preferred generalised gamma.
What is the expected effect on the cost-effectiveness estimates?	The implication of applying the ERG preferred OS extrapolation is only a small increase in the ICER for avelumab compared to WW.
What additional evidence or analyses might help to resolve this key issue?	The company could have provided a greater level of detail regarding how clinical expert opinion was derived, how questions were posed to the panel of experts and what methods were used to identify ranges of expected 5- and 10-year OS for both the WW and avelumab arms.

Table 4. Issue 3. Definition of progression for PFS (BICR vs. INV assessed)

Report section	*Section 3.2.6*
Description of issue and why the ERG has identified it as important	The company base case economic model prefers the use of a BICR definition of progression for use in the economic model. Whilst this may be a highly accurate measure of clinical progression, the ERG note that it may not reflect how progression is determined and how post-progression treatment choices are made in UK clinical practice.
What alternative approach has the ERG suggested?	Based on the ERG clinical expert's opinion, the ERG prefers the use of investigator assessed progression (also measured in the JAVELIN Bladder 100 trial) because it is more likely reflects how progression is determined, and how post-progression treatment decisions are made in UK clinical practice.
What is the expected effect on the cost-effectiveness estimates?	Using investigator assessed definition of progression with a 3-knot hazard and 3-knot odds survival curve for avelumab and WW respectively reduces the ICER from £29,245 in the company base case to £27,159.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that the company have provided all the necessary data in their submission document, but further clinical opinion regarding the relative advantages and disadvantages of using BICR vs. INV assessment would have been helpful to resolve this issue.

Table 5. Issue 4. Time to treatment discontinuation on avelumab and duration of continued PFS and OS benefit

Report section	*Section 3.2.2, 3.2.6 and 5.2*
Description of issue and why the ERG has identified it as important	The company base case economic model assumes that 95% of avelumab treated patients will discontinue treatment at 2 years, with the remainder stopping by year 5 (estimates that are substantially lower than fitting parametric survival curves to TTD KM data from the JAVELIN Bladder 100 trial). However, no corresponding adjustment is made to the duration of continued treatment benefit for avelumab OS and PFS in the model. The ERG consider the assumption that early treatment discontinuation will affect costs only, with no implications for PFS and OS benefit to be questionable. This is an important area of unresolved uncertainty. The potential impact of different combinations of treatment discontinuation and duration of treatment benefit assumptions could lead to substantial increases in the ICER compared to the company base case.
What alternative approach has the ERG suggested?	The ERG accept that the treatment discontinuation rules are reasonable and reflective of UK clinical practice, but prefer the use of the generalised gamma survival curve to estimate treatment discontinuation between years 2 and 5 (better fit to the KM data and allow a slower rate of discontinuation). In the absence of clear published data to determine any reduction in incremental treatment benefit (PFS or OS) over time following avelumab treatment discontinuation, the ERG retain the company approach to not further capping the duration of continued treatment benefit in terms of PFS or OS curves for the base case analysis. However, to illustrate the impact of alternative

	assumptions on the ICER, the ERG have performed several additional two-way scenario analyses for the committee's information applying different treatment discontinuation rules (at 2 and 5 years) and alternative caps to the duration of PFS and OS benefit for avelumab over WW at 2, 5 and 10 years.
What is the expected effect on the cost-effectiveness estimates?	The ERG's preferred parametric survival curve (generalised gamma as opposed to LN) to estimate treatment discontinuation between years 2 and 5 has a small impact on the ICER, increasing the company preferred base case ICER from £29,245 to £30,317. Additional ERG scenario analyses show that imposing caps on the duration of PFS and OS benefit substantially increase the ICER from £29,245 in the company base case to £36,361 (benefits capped at 10 years) and £51,545 (benefits capped at 5 years). Applying alternative treatment discontinuation assumptions in scenario analyses increase the company preferred ICER (parameterised using the company preferred LN extrapolation) to £38,657 (assuming no discontinuation at 2 years, but all stop by year 5) and £45,745 (assuming no treatment discontinuation or stopping rules).
What additional evidence or analyses might help to resolve this key issue?	The ERG would appreciate a consideration of any real-world data the company may have, or any evidence from the literature to support the company assumption that discontinuing treatment early would have no impact on effectiveness (OS and PFS) outcomes. If such data or literature are not available, at the very least, some detailed clinical explanation as to why the assumptions are justified would be beneficial in supporting the company's base case assumptions and reducing uncertainty surrounding the ICER.

Table 6. Issue 5. The proportion of patients receiving subsequent (post progression) treatment in the model.

Report section	*Section 3.2.8*
Description of issue and why the ERG has identified it as important	The proportion of patients receiving subsequent treatments is likely to be lower in clinical practice. As the treatment pathway post-progression differs between treatment arms the assumptions in the model regarding subsequent therapies are important drivers of the results. In the company's base case analysis, the proportions are derived from the JAVELIN Bladder 100 trial, but the company acknowledged these figures were likely higher than would be seen in clinical practice with reference to the Systemic Anti-Cancer Therapy (SACT) dataset. This showed a lower proportion receiving subsequent treatments. The ERG clinical advisor felt the proportion receiving subsequent treatments following progression would likely be lower than the trial as patients in practice are generally less fit, and are not monitored as closely for progression.
What alternative approach has the ERG suggested?	During the clarification process, the company was asked to provide an alternative analysis using lower proportions. The company's response provided three separate scenario analyses in addition to a threshold analysis. The ERG clinical advisor considered the analysis which used an average of the trial and the SACT dataset estimates was closer to the expected proportions who would receive subsequent treatments in practice.
What is the expected effect on the cost-effectiveness estimates?	Reducing the proportions receiving subsequent treatments from [redacted] in the avelumab arm and from [redacted] on the WW arm to [redacted] and [redacted] respectively, increases the ICER (see additional scenario analyses provided in response to clarification questions, provided in Table 27 of the main ERG report).
What additional evidence or analyses might help	The ERG acknowledge that there remains uncertainty with this parameter and would welcome some more clinical validation of the alternative estimates (see ERG report Table 24). In addition,

to resolve this key issue?	further clinical input would be helpful on the likely impact on efficacy of fewer patients receiving subsequent treatments.

Table 7. Issue 6. The mix of subsequent (post progression) treatments included in the model

Report section	*Section 3.2.8*
Description of issue and why the ERG has identified it as important	In the avelumab arm, a small proportion ([redacted]) received second-line anti-PD-1/PD-L1 treatment. However, the ERG clinical advisor did not agree that any patients would receive a second-line anti-PD-1/PD-L1 upon progression after avelumab maintenance. As atezolizumab is another immunotherapy, patients would not receive this or any other immunotherapy following avelumab maintenance in clinical practice but would instead receive chemotherapy.
What alternative approach has the ERG suggested?	Although the ERG has not identified an alternative source for this parameter, its preference is to remove the cost of atezolizumab and assume these patients will receive chemotherapy instead based on clinical advice received.
What is the expected effect on the cost-effectiveness estimates?	Following clarification, the company provided an alternative scenario where the cost of atezolizumab is removed from the avelumab arm and patients are instead assumed to receive chemotherapies. No changes are made to the efficacy estimates, which is considered a reasonable assumption. This reduces the ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG acknowledge that there remains uncertainty around this parameter, and would welcome some more clinical validation of the treatment pathway following avelumab maintenance (see ERG report, Table 24). In addition, further clinical input would be helpful on the assumption that there would be no material impact on the efficacy estimates because of this change to the model.

1.6 Other key issues: summary of the ERG's view

Section 6.1 of the main report outlines the company's case that avelumab meets the NICE criteria for end of life consideration. The ERG agrees that avelumab clearly meets the criteria of increasing life expectancy by at least three months, but some uncertainty remains whether OS on the WW arm of the model is <24 months. Table 8 summarises the issues.

Table 8. Issue 7. End of life criteria

Report section	*Section 6.1*
Description of issue and why the ERG has identified it as important	The ERG accepts that avelumab meets the end of life criteria for improvement in OS of >3 months, with modelled life year gains for avelumab close to one for both ERG and company preferred model assumptions. For the requirement that OS be <24 months without avelumab, some uncertainty remains. Median OS estimated from the JAVELIN Bladder 100 trial is <24 months for the BSC arm of the trial. The economic model predicts mean OS of 35.4 months (median: 15.9 months) and mean OS of 27.82 months (median = 15.6 months) under the company and ERG preferred base case analyses respectively. On balance, the ERG considers it plausible that avelumab meets the NICE end of life criteria.
What alternative approach has the ERG suggested?	The ERG prefers the application of mean OS projected from the economic model as opposed to median OS derived from the BSC arm of the trial because it is the mean QALY gains to which any end-of life QALY weighting would be applied.
What is the expected effect on the cost-effectiveness estimates?	If avelumab is deemed to meet the criteria for end of life consideration, and QALYs are weighted accordingly, this would reduce the ICER substantially.
What additional evidence or analyses might help to resolve this key issue?	Any further data from the JAVELIN Bladder 100 trial or the literature reporting mean OS would likely help reduce the uncertainty around whether or not avelumab meets the criteria for end of life consideration.

1.7 Summary of ERG's preferred assumptions and resulting ICER

The ERGs preferred assumptions are the same as the company's except for the following:

1. LN survival curves for OS for both avelumab and WW because they have the best statistical fit to the KM OS for avelumab, the best BIC and 2nd best AIC for WW, they provide a good visual match to the KM data for both arms, and they generate 5 and 10 year OS estimates for WW that are closer to the mid-point of the company's clinical expert expectations (5 yr OS: 10.71%, 10 yr OS: 2.90%) than the company preferred generalised gamma.

2. PFS measured according to INV assessment, parameterized using a 3-knot hazard and 3-knot odds model for avelumab and WW respectively. The ERG prefer this approach as opposed to the company base case BICR assessment because it more closely reflects decision making (e.g. regarding the initiation of post-progression therapies) in UK clinical practice.

3. Generalised gamma extrapolation curves for TTD between years 2 and 5. The ERG prefer this assumption because the company base case already over-rides the TTD curves, dropping the proportion on treatment from about [redacted] to 5% at 2 years. The ERG therefore feel that the company has preferred a LN curve that over estimates the proportion ceasing treatment between years 2 and 5. In addition, the generalised gamma is the best statistical and visual fit to the KM data.

4. Based on the ERG clinical expert's advice, the ERG prefers the company scenario analysis that applies lower subsequent treatment proportions for avelumab [redacted] and WW [redacted], calculated as an average of the subsequent treatment proportions in the SACT dataset and JAVELIN Bladder 100 trial.

5. Remove atezolizumab treatment from the post-progression treatment distribution in the avelumab arm and re-distribute the [redacted] of patients to the SOC chemotherapies.

The impact of each individual change is documented in Table 9. However, the ERG note that these results are not the most appropriate for decision making, as they do not include the

confidential PAS price available for atezolizumab, used as a post-progression treatment in the model. The ERG provide a confidential appendix, incorporating the PAS price for atezolizumab for the committee's information.

Table 9. Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER	ICER (change from company base case)
Company's preferred base case	[redacted]	[redacted]	£29,245	--
LN OS curves for Avelumab and WW	[redacted]	[redacted]	£30,629	+£1,384
INV assessed PFS (Avelumab: 3-knot hazard; WW: 3-knot odds)	[redacted]	[redacted]	£27,159	-£2,085
TTD BETWEEN YRS 2-5 (GENERALIZED GAMMA)	[redacted]	[redacted]	£30,317	+£1,073
Reduced proportions on subsequent treatment: avelumab ([redacted]%); WW ([redacted]%)	[redacted]	[redacted]	£37,543	+£8,298
Remove atezolizumab from the avelumab arm	[redacted]	[redacted]	£25,822	-£3,423
ERG's preferred base case (all changes above combined) - deterministic	[redacted]	[redacted]	£34,802	+£5,557
ERG's preferred base case (all changes above combined) - probabilistic	[redacted]	[redacted]	£33,463	N/A

Abbreviations: ERG = evidence review group; ICER = incremental cost-effectiveness ratio; INV = investigator assessed progression; LN = lognormal; LYs = life years; N/A = Not applicable; OS = Overall survival; PFS = progression free survival; QALYs = Quality adjusted life years; TTD = time to treatment discontinuation; WW = Watchful waiting

The ERG has flagged two interlinked issues (described collectively as issue number 4) which are not amended for the ERG's preferred base case analysis, due to a lack of evidence to develop alternative parameter estimates. However, there remains substantial uncertainty surrounding the most appropriate assumptions underpinning time to treatment discontinuation on avelumab and any associated impact of stopping treatment earlier in clinical practice (e.g. after two years) than in the trial (no stopping rule) on the duration of continued treatment benefit (PFS and OS) for avelumab. The ERG have therefore conducted several two-way scenario analyses exploring the impact of varying treatment discontinuation rules alone and in combination with different assumptions about the duration of continued avelumab treatment OS and PFS benefit. Further details describing the issues are provided in Section 3.2.6. Additional exploratory and sensitivity analyses conducted by the ERG to illustrate the potential variation in the ICER under different assumptions are provided in Section 5.1 of the report.

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

This submission focuses on the maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy. The company's description of urothelial cancer in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is avelumab (Bavencio®, Merck KGaA and Pfizer).

1.2 Background

Bladder cancer is the 11th most common cancer in the UK, with age-standardised incidence rate at 16.6 cases per 100,000 population in 2015-2017.(1) It is more common in men than in women (73% are in male and 27% in female), and its incidence rates rise with age from around age 50-54 in both males and females, with a sharper rise in males from age 60-64. On average 56% of patients with bladder cancer are >75 years of age.(1) In England, the National Cancer Registration and Analysis service reported 8,686 new bladder cancer cases in 2017, of which 1,464 (16.9%) were Stage IV.(2)

Nearly 75% of bladder cancer cases present as superficial (non-muscle invasive) disease and the remainder as invasive or metastatic disease.(3, 4) Most of superficial tumours do not progress to more invasive disease but have a high rate of recurrence after treatment.(4) The remaining higher risk superficial tumours or invasive disease need to be managed more intensively. Many bladder cancer patients therefore require long-term surveillance and treatment, making bladder cancer one of the most costly disease to manage from diagnosis to death.(3, 5, 6) Bladder cancers are classified as non-muscle-invasive (Stage 0-I), muscle-invasive (Stage II-III), and locally advanced or metastatic (Stage IV). According to the Tumour, Node, Metastasis (TNM) Classification system, locally advanced or metastatic bladder cancer includes disease that has invaded the pelvic or abdominal wall (T4b), has spread to one or more lymph nodes (N1-N3) or has metastasised to distant sites (M1).(7, 8)

Urothelial carcinoma (UC) is the most common type of bladder cancer, accounting for 90% of the cases.(3) UC originates in the urothelial cells (transitional cells) which form the inner

lining of the bladder, urethra, ureter, or renal pelvis.[9, 10] In line with the NICE final scope, the company submission (CS) focuses on locally advanced or metastatic urothelial cancer.

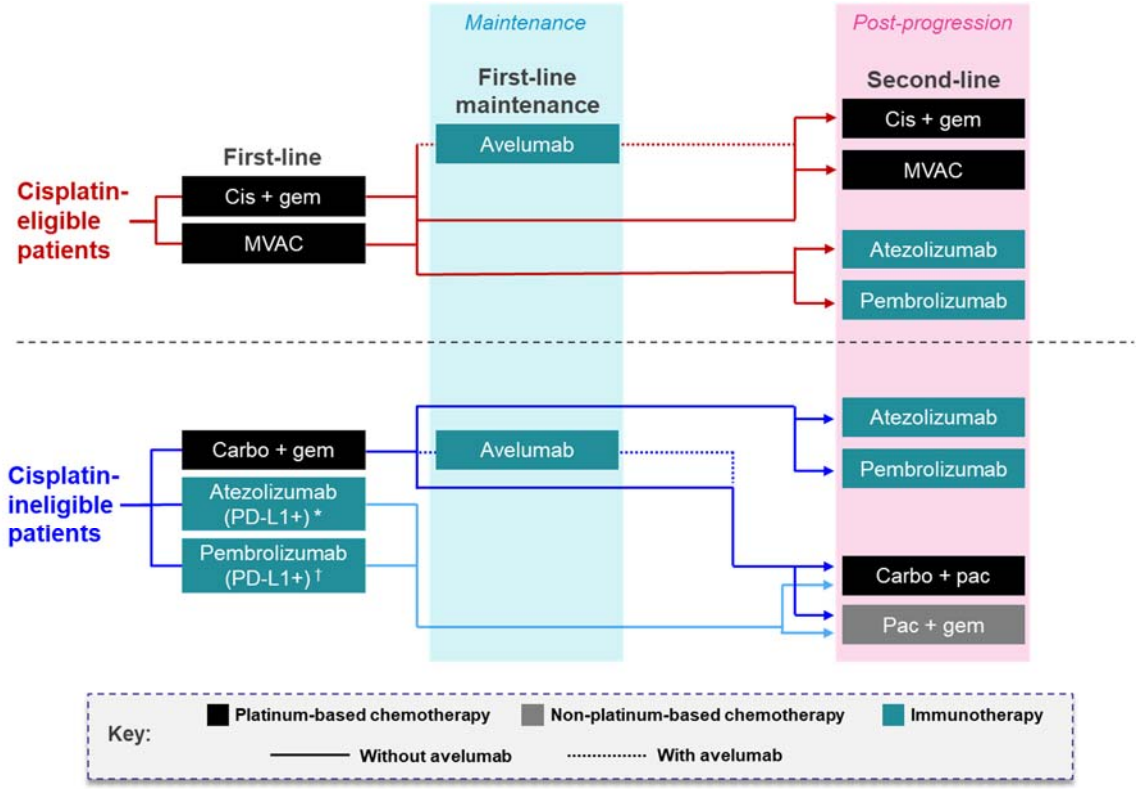
UC is usually identified by the presenting symptom of haematuria (blood in the urine). There is no screening programme for detecting UC in the UK. The symptoms of UC can be inconsistent, which can delay diagnosis until the disease is locally advanced or metastatic and is associated with a poor prognosis.[6, 11] Survival is especially poor in Stage IV disease with five-year overall survival less than 5%.[12-14]

The main aim of treatment for locally advanced and metastatic UC is to prevent disease progression, maintain health-related quality of life (HRQoL), provide relief from cancer symptoms and extend life. Presently, the NICE guidance NG2 recommends a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] in combination with granulocyte-colony stimulating factor [G-CSF]) for treatment-naïve patients with locally advanced or metastatic urothelial cancers.[6] When cisplatin is unsuitable people could be offered carboplatin in combination with gemcitabine for untreated disease, or if their tumours express PD-L1 (programmed death-ligand 1), atezolizumab or pembrolizumab is also recommended within the Cancer Drugs Fund.[15, 16] It is stated in the CS that published trials on first-line platinum-based chemotherapy for locally advanced and metastatic UC reported complete response (CR) and partial response (PR) rates of up to 29% and 55%, respectively, and objective response rates of 24-70% (Section B.1.3.6 of the CS). The NICE final scope states that there are no maintenance treatments currently licensed for use after response to first-line platinum-based chemotherapy.[17]

Avelumab is a monoclonal antibody of immunoglobulin G1 (IgG1) which binds to the PD-L1 protein molecule expressed by tumour cells and a number of immune cells. Avelumab inhibits PD-L1 from binding to its receptor, PD-1 (programmed death-1), on tumour-infiltrating T-cells, potentiating immune response to kill tumour cells.[18, 19]

The company's proposed positioning for avelumab in the clinical care pathway is presented in Figure 1 below. Avelumab is presented as maintenance treatment in the first-line setting for patients with locally advanced or metastatic UC whose disease has not progressed

following first-line platinum-based chemotherapy. The ERG clinical expert considers the company's positioning of avelumab to be reasonable and in line with current clinical practice.



Abbreviations: carbo = carboplatin; cis = cisplatin; gem = gemcitabine; MVAC = methotrexate, vinblastine, adriamycin and cisplatin; pac = paclitaxel; PD-L1 = programmed death-ligand 1; UC = urothelial carcinoma
*PD-L1 expression ≥5%; †PD-L1 with a combined positive score ≥10

Figure 1. Proposed treatment pathway with avelumab for locally advanced or metastatic urothelial carcinoma [reproduced from Figure B.1.3, Document B of the CS]

1.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 10 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

Table 10. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
Population	Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy	As per scope	Not applicable	The population described in the company's submission (CS) matches that described in the NICE final scope. The study populations in the JAVELIN Bladder 100 trial, the main source of evidence submitted by the company, comprises patients who had received a cisplatin- or carboplatin-based chemotherapy in combination with gemcitabine. The inclusion of gemcitabine aligns with current NICE recommendations on a platinum-based chemotherapy regimen.[6] The ERG's clinical advisor is of the opinion that the clinical evidence submitted by the company (JAVELIN Bladder 100 trial) reflects the characteristics of the patient population who are eligible for this treatment in the UK.

Intervention	Avelumab	As per scope	Not applicable	The intervention described in the company's submission matches the intervention described in the final scope. Avelumab (Bavencio®) has received marketing authorisation by the European Medicines Authority (EMA) for use as monotherapy for the treatment of adults with metastatic Merkel cell carcinoma, and in combination with atixinib for the first-line treatment of adults with advanced RCC.[18] A variation for a new indication of maintenance treatment of locally advanced or metastatic urothelial carcinoma was submitted to the EMA on 26 May 2020. At the time of the CS, the European Public Assessment Report (EPAR) has yet to be published. Avelumab received an Early Access to Medicine Scheme (EAMS) positive scientific opinion from the UK Medicines and Healthcare products Regulatory Agency (MHRA) on 01 September 2020 (EAMS number 11648/0003) for the first-line maintenance treatment of adults with locally

				advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy.[20] The recommended dose of avelumab according to the marketing authorisation is a single 800 mg flat-dose administered intravenously every 2 weeks.[18] Evidence submitted by the company (JAVELIN Bladder 100) used a weight-based dose at 10 mg/kg with a median dosage of 724 mg and a mean dosage of 752 mg for the avelumab +BSC arm. While the licensed dose (a flat dose of 800 mg) is different to that used in the JAVELIN Bladder 100 trial, the company explains that the fixed licensed dose would have similar clinical outcomes to the weight-based dose and therefore no adjustment to efficacy was made in the CS. This approach was accepted in a previous NICE technology appraisal on avelumab in combination with axitinib for untreated advanced renal cell carcinoma (RCC) (TA645).[21] SmPC also states that clinically meaningful differences were not expected between

				settings administered every 2 weeks at 800 mg or 10 mg/kg (section 5.2 of SmPC, Appendix C.1.1 of the CS).[18] For the purpose of this submission, the ERG considers the trial dose of 10 mg/kg to be generalisable to the 800 mg flat dose.
Comparator(s)	Established clinical management without avelumab (including but not limited to routine surveillance, symptom control and pain management [including palliative radiotherapy])	As per scope	Not applicable	The comparator treatment described in the company's submission matches that described in the NICE final scope. The company select best supportive care (BSC) as the relevant comparator. BSC includes care as deemed appropriate by the treating physician. This could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy) but not active anti-tumour therapy. The view of an expert panel elicited by the company as well as that of the ERG's clinical advisor is that, in general, the defined comparator (BSC) is reflective of current UK clinical practice.[22]

				The ERG note that BSC was administered in both avelumab and control groups. Therefore, the treatment comparison in the evidence submitted by the company was avelumab plus BSC versus BSC.
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates • Time to relapse or progression • Adverse effects of treatment • Health-related quality of life (HRQoL)		Not applicable	The outcomes described in the company's submission match those described in the NICE final scope.
Subgroups	No subgroups specified	Not specified	Not applicable	No subgroups were specified in the final scope issued by NICE. The CS reported the following pre-specified subgroups for the outcomes of overall survival, progression-free survival and objective response: • Best response to first-line chemotherapy (Complete/partial response; stable disease) • Metastatic disease site (visceral, non-visceral) • Age (<65, ≥65 years) • Gender (male, female) • Race (white, Asian, other) • Pooled geographic region (Europe, North America, Asia, Australia, Rest of the World)

				• PD-L1 status at baseline (positive, negative, unknown) • Fist-line chemotherapy regimen (gemcitabine + cisplatin; gemcitabine + carboplatin; gemcitabine + carboplatin + cisplatin) • ECOG (Eastern Cooperative Oncology Group)) performance status (0, ≥1) • Creatinine clearance at baseline (≥60 mL/min, <60 mL/min) • Liver lesions at baseline (yes, no) • Lung lesions at baseline (yes, no)
Special considerations including issues related to equity or equality	No special considerations specified	Not specified	Not applicable	The ERG agree with the company that there are no anticipated equality issues related to avelumab.

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D.1.1 of the CS. The ERG's appraisal of the company's systematic review methods is summarised in Table 11 below.

Table 11. ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details are provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, CENTRAL and DARE for primary research, HTA organisations for evidence syntheses, and relevant conference proceedings. Details are provided in Appendix D.1.1.1 of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	
Was study selection conducted by two or more reviewers independently?	Yes	See Appendix D.1.1.2 of the CS.
Was data extraction conducted by two or more reviewers independently?	Unclear	Responsibility for data extraction was not reported in the CS.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	The company used the minimum criteria listed in the NICE template section 2.5.2, adapted from the University of York Centre for Reviews and Dissemination (CRD) guidance

		(the company response to Question A3 of the clarification document).[23]
Was risk of bias assessment conducted by two or more reviewers independently?	Possibly	The appraisal was undertaken by two reviewers and then validated independently (company response to Question A3 of the clarification document).
Was identified evidence synthesised using appropriate methods?	Not applicable	As the SLR identified only one RCT, meta-analysis was not conducted.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria; results are presented in Table 12.

Table 12. Quality assessment of the company's systematic review of clinical effectiveness evidence (JAVELIN Bladder 100 trial)

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

2.2.1 Included study

Details of the key clinical effectiveness evidence are provided in Table B.2.1, Section B.2.2, of the CS and reproduced by the ERG as Table 13 below.

Table 13. Clinical effectiveness evidence [reproduced from Table B.2.1, Section B.2.2 of the CS]

Study	JAVELIN Bladder 100 (Study B9991001; NCT02603432)		
Study design	Phase 3, randomised, open-label, parallel two-arm, multicentre study		
Population	Locally advanced or metastatic UC that did not worsen during or following completion of first-line platinum-based chemotherapy		
Intervention(s)	Avelumab 10 mg/kg Q2W (4-week cycle) + BSC (N=350)		
Comparator(s)	BSC alone		
Indicate if trial supports application for marketing authorization	Yes	Indicate if trial used in the economic model	Yes
Reported outcomes specified in the decision problem	Overall survival (OS), progression-free survival (PFS), response rates, health-related quality of life (HRQoL), adverse effects of treatment		
All other reported outcomes	Time to tumour response (TTR), duration of response (DOR), disease control (DC), serious adverse events (SAEs), vital signs, physical examination, ECOG performance status, ECG, laboratory assessments, pharmacokinetics (PK), anti-drug-antibodies (ADA), biomarkers		

Abbreviations: BSC = best supportive care; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; UC = urothelial carcinoma

The evidence for the clinical efficacy and safety of avelumab (Bavencio® Merck KGaA and Pfizer) for adults with locally advanced or metastatic UC consists of one ongoing, Phase III, multicentre, open-label, parallel two-arm randomised clinical trial, JAVELIN Bladder 100 (Study B9991001; NCT02603432).[24] An overview of the study is presented in Table B.2.2, Section B.2.3 of the CS. Study methods are summarised in Section B.2.3 and the participant flow of the study is presented in Figure B.5.3, Appendix D.1.2 of the CS.

JAVELIN Bladder 100 was funded by Pfizer and Merck and investigated the efficacy of avelumab as maintenance treatment in the first-line setting for patients with locally advanced or metastatic UC whose disease did not progress following first-line platinum-based chemotherapy. A total of 700 adults were randomized in a 1:1 ratio to either avelumab (10 mg/kg as intravenous infusion once every two weeks) in combination with best supportive

care (BSC) (n = 350) or BSC alone (n = 350). Randomisation was stratified by best response to first-line chemotherapy (complete/partial response versus stable disease), and metastatic disease site (visceral versus non-visceral) at the time of initiating first-line chemotherapy.

Participants treated with avelumab + BSC had a median weight of 72.4 kg and a mean weight of 75.2 kg at baseline, equating to a dosage of 724 mg and 752 mg, respectively. Participants continued to receive avelumab until confirmed disease progression, patient withdrawal, loss to follow-up, or unacceptable toxicity. No avelumab dose modifications were permitted but infusions could be omitted due to persisting toxicity.

As of the data cut-off for the interim analysis (21 October 2019), the median duration of follow-up for overall survival analysis was 19.6 months and 19.2 months for avelumab + BSC and BSC groups, respectively.

The company performed a quality assessment of the JAVELIN Bladder 100 study using seven criteria adapted from the University of York Centre for Reviews and Dissemination (CRD) guidance (Table B.2.7, Section B.2.5, and Appendix D.1.3, of the CS).[23] The ERG generally agree with the company's assessment presented in Table B.2.7 of the CS; however, the ERG consider that concealment of treatment allocation, which was stated by the company to be 'not possible' (risk of selection bias), would have been adequate with the use of an interactive web-based response system for randomisation. Except for a lack of blinding of participants and personnel in the open-label study, as acknowledged by the company, the JAVELIN Bladder 100 study fulfils all other quality assessment criteria. *Overall, the ERG consider the JAVELIN Bladder 100 study to be of acceptable methodological quality.*

JAVELIN Bladder 100 was conducted at 197 sites in 29 countries with around 60% of the participants recruited in Europe (Table B.2.6, Section 2.3.5.3 of the CS), enrolling 19 (2.7%) participants from four trial sites in the UK (all located in England). Treatment groups were well-balanced for baseline characteristics including demographics, disease characteristics and prior therapies (Table B.2.6, Section B.2.3.5.3 of the CS, reproduced as Table 14 below). The median age of participants was 68 and 69 years for avelumab + BSC and BSC, respectively. Almost half of participants had PD-L1-positive tumours (54% for avelumab + BSC and 48.3% for BSC). For first-line chemotherapy, 56% (n = 389) of participants received cisplatin plus gemcitabine, 38% (n = 269) of participants received carboplatin plus gemcitabine and

6% (n = 40) of participants received one or more cycles of each combination. Most participants (72.1% [n = 505]) achieved a complete or partial response to first-line chemotherapy at baseline, which in the opinion of the ERG's clinical expert is a relatively higher proportion of patients than that expected in UK clinical practice. One of the main trial incorporating cisplatin plus gemicitabine in the advanced disease setting reported response rates of around 50%, which is typical of what is observed clinically.[25] *Nevertheless, the ERG consider that the majority of the characteristics of the study participants are reflective of patients who would be considered for maintenance treatment for locally advanced or metastatic UC in UK clinical practice.*

As of the data cut-off for the interim analysis (21 October 2019), a larger proportion of patients discontinued BSC treatment (92.6%), compared with avelumab + BSC (75.7%). This reflected the higher rate of discontinuation due to disease progression in the BSC group (75.1% [n = 263]) compared with the avelumab + BSC group (54% [n = 189]) (Table B.2.4, Section 2.3.5.1 of the CS).

Table 14. Demographics, baseline and disease characteristics (full analysis set) [reproduced from Table B.2.6, Section B.2.3.5.3, of the CS]

Endpoint	All patients (N=700)	
	Avelumab + BSC(N=350)	BSC (N=350)
Age, years		
Median (range)	68.0 (37.0, 90.0)	69.0 (32.0, 89.0)
Mean (SD)	[redacted]	[redacted]
<65 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
Gender, n (%)		
Male	266 (76.0)	275 (78.6)
Female	84 (24.0)	75 (21.4)
Race, n (%)		
Asian	75 (21.4)	81 (23.1)
Black	2 (0.6)	0 (0.0)
White	232 (66.3)	238 (68.0)
Other	21 (6.0)	15 (4.3)
Unknown	20 (5.7)	16 (4.6)
Geographic region, n (%)		
North America	12 (3.4)	22 (6.3)
Europe	214 (61.1)	203 (58.0)
Asia	73 (20.9)	74 (21.1)
Australasia	34 (9.7)	37 (10.6)
Rest of the World	17 (4.9)	14 (4.0)
Median time since initial diagnosis (range), months	[redacted]	[redacted]

Endpoint	All patients (N=700)	
	Avelumab + BSC(N=350)	BSC (N=350)
First-line chemotherapy regimen, n (%)		
Gemcitabine + cisplatin	183 (52.3)	206 (58.9)
Gemcitabine + carboplatin	147 (42.0)	122 (34.9)
Gemcitabine + cisplatin/gemcitabine + carboplatin	20 (5.7)	20 (5.7)
Not reported	0 (0.0)	2 (0.6)
Best response to first-line chemotherapy		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	97 (27.7)	98 (28.0)
Site of metastasis		
Visceral	191 (54.6)	191 (54.6)
Non-visceral	159 (45.4)	159 (45.4)
Histopathological classification		
Carcinoma	306 (87.4)	292 (83.4)
Carcinoma with squamous	16 (4.6)	26 (7.4)
Carcinoma with glandular	6 (1.7)	9 (2.6)
Carcinoma with variant	22 (6.3)	22 (6.3)
Other	0 (0.0)	1 (0.3)
ECOG PS		
0	213 (60.9)	211 (60.3)
1	136 (38.9)	136 (38.9)
2	1 (0.3)	0 (0.0)
3	0 (0.0)	3 (0.9)
PD-L1 status		
Positive	189 (54.0)	169 (48.3)
Negative	139 (39.7)	131 (37.4)
Unknown	22 (6.3)	50 (14.3)

Abbreviations: BSC = best supportive care; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; n = number of patients in the category; N = number of patients evaluable; PR = partial response; PS = performance status; PD-L1 = programmed death-ligand 1; SD = standard deviation

2.2.2 Primary and secondary efficacy endpoints

For all outcomes, interim analyses conducted on 21st October 2019 have been reported. These are considered by the company to be the final analyses, as the trial had achieved its primary objectives, albeit patients are still being followed up.

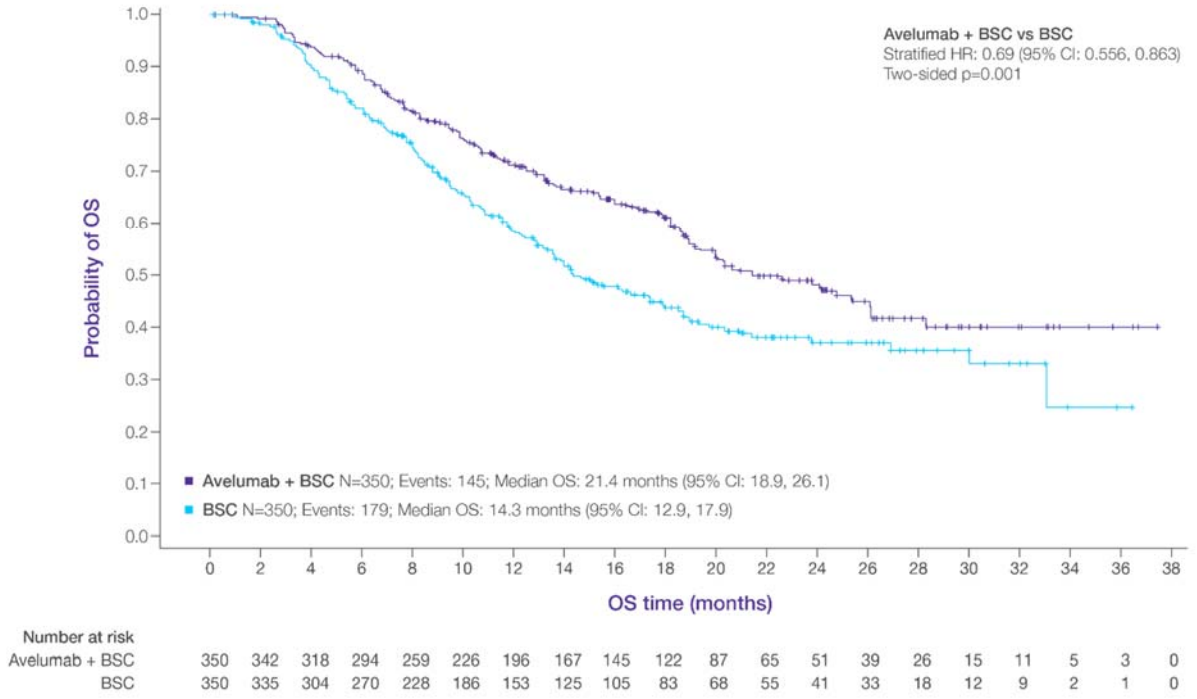
Primary endpoint

The primary efficacy endpoint in the JAVELIN Bladder 100 trial was overall survival (OS), defined as the time from date of randomisation to date of death due to any cause. At the time of the interim analysis, median duration of follow-up for OS was 19.6 (95% confidence

interval [CI] [redacted] months for the avelumab + BSC group (n=350) and 19.2 (95% CI [redacted] months for the BSC group (n=350).

Table B.2.9 of the CS reports a summary of OS in the full analysis set (FAS). Median OS was 21.4 (95% CI 18.9, 26.1) months for the avelumab + BSC group (n=350) and 14.3 (95% CI 12.9, 17.9) months for the BSC group (n=350), with a Hazard Ratio [HR] of 0.69 (95% CI 0.556, 0.863; p=0.001). A total of 205 (58.6%) participants in the avelumab + BSC group and 171 (48.9%) in the BSC group had been censored at the time of the interim analysis.

Additionally, the clinical study report (CSR) provided the following sensitivity analyses for OS: per-protocol analysis set, using an unstratified analysis, and considering actual (CRF-derived) strata. The results of these analyses were reported to be similar to those of the primary analyses. The Kaplan-Meier plot of OS in the FAS is reproduced in Figure 2 below.



Abbreviations: BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; OS = overall survival; vs = versus
Source: Pfizer Inc., 2020;[26] Powles et al., 2020[24]

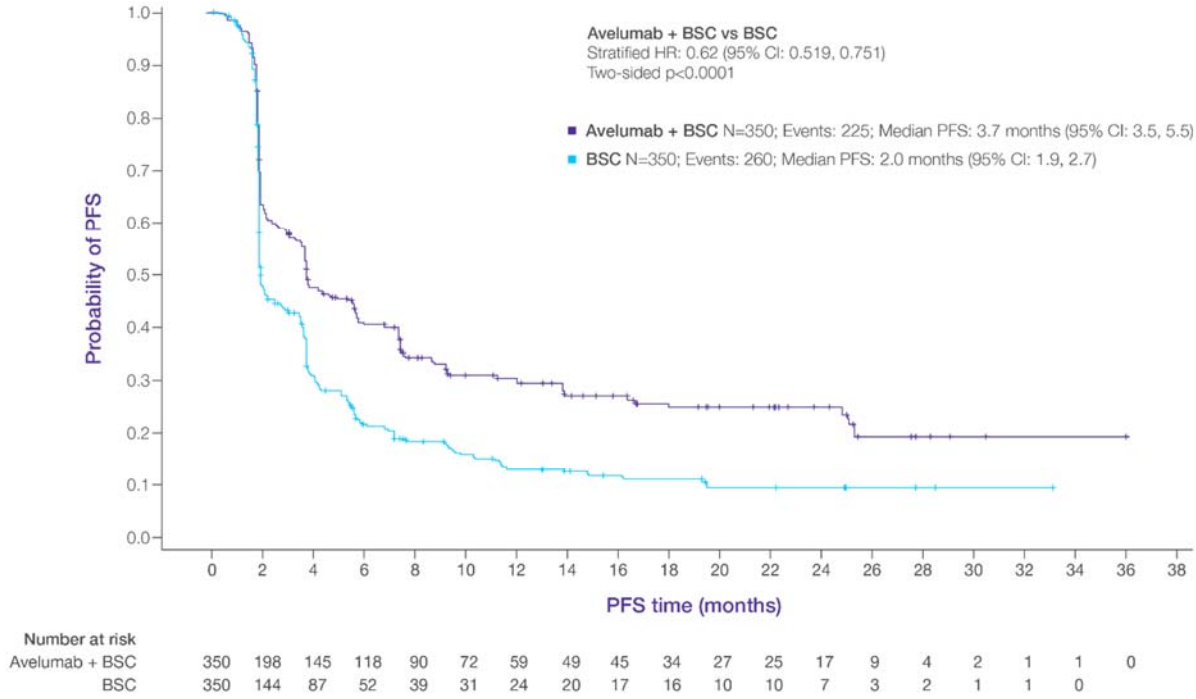
Figure 2. Kaplan-Meier plot of OS in all randomised patients (FAS; primary endpoint) [reproduced from Figure B.2.2, Section B.2.6.1.2, Document B of the CS]

Secondary endpoints

Secondary efficacy endpoints reported in the CS are as follows:

- Progression-free survival (PFS), defined as the time from the date of randomisation to the date of the first documentation of progressive disease or death due to any cause, whichever occurred first. Table B.2.10 of the CS reports a summary of PFS (based on blinded independent central review [BICR] assessment) in the FAS. At the time of the interim analysis, median **duration** of follow-up for analysis of PFS was [redacted] (95% CI [redacted] months for the avelumab + BSC group (n=350) and [redacted] (95% CI [redacted] months for the BSC group (n=350). Of 225 events (64.3%) in the avelumab + BSC group, [redacted] were assessed as progressive disease and [redacted] had died. The respective proportions in the BSC group were [redacted] progressive disease and [redacted] deaths. Median PFS was 3.7 (95% CI 3.5, 5.5) months in the avelumab + BSC group and 2.0

(95% CI 1.9, 2.7) months in the BSC group (HR 0.62, 95% CI 0.519, 0.751, p<0.0001). A total of 125 (35.7%) participants in the avelumab + BSC group and 90 (25.7%) in the BSC group had been censored at the time of the interim analysis. The Kaplan-Meier plot of PFS in the FAS is reproduced in Figure 3.



Abbreviations: BICR = blinded independent central review; BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; PFS = progression-free survival; vs = versus
Source: Pfizer Inc., 2020[26]; Powles et al., 2020[24]

Figure 3. Kaplan-Meier plot of PFS (based on BICR assessment) in all randomised patients (FAS; secondary endpoint) [reproduced from Figure B.2.3, Section B.2.6.1.3, Document B of the CS]

- Objective response rate (ORR), defined as the proportion of participants with an objective response (best overall response [BOR] of CR or PR). Table B.2.11 of the CS presents a summary of response (based on BICR) for the FAS. The ORRs for the avelumab + BSC group were 9.7% and 1.4% for the BSC group (stratified Odds Ratio 7.46, 95% CI 2.824, 24.445, p<0.0001). The confirmed BOR of CR and PR was 6% and 3.7% in the avelumab + BSC group, respectively, and 0.9% and 0.6% in the BSC group, respectively.

- Duration of response (DOR), defined as the time from the first documentation of objective response (OR) to the first documentation of progressive disease (PD) or death due to any cause, whichever occurred first (in participants with an OR). The median duration of response [redacted] at the time of the interim analysis.
- Disease control (DC), defined as BOR of CR, PR, non-CR/non-PD or stable disease, was achieved in 41.1% [redacted] of participants in the avelumab + BSC group and 27.4% [redacted] of those in the BSC group.
- Time to response (TTR), defined as the time from randomisation to first documentation of OR which was subsequently confirmed and summarized (for participants with an OR).
  [redacted] [Note. This was not reported in the CS. See section 11.1.1.2.4.1 of CSR]
- Patient-reported outcomes, as assessed by NCCN (National Comprehensive Cancer Network) Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index (FBISI-18) and EuroQoL 5-Dimenion 5-Level (EQ-5D-5L). The company stated that mean changes from baseline in FBISI-18 total scores and EQ-5D-5L index scores were similar between the two groups, though descriptive statistics or effect sizes were not reported within the CS. The company have, however, provided a reference to a conference presentation, which would appear to show very similar quality of life outcomes for both arms of the study.[27] Time to deterioration was defined as time from randomisation to a ≥3-point decrease from baseline in FBISI Disease Related Symptom-Physical (DRS-P) over two consecutive assessments. Median time to deterioration was similar in the two groups in the FBISI-18 DRS-P. In all randomised participants, median time to deterioration in the FBISI-18 DRS-P was not reached in the avelumab + BSC group as compared to 13.8 months in the BSC group (HR 1.26, 95%CI 0.90, 1.77, p=0.174).

A summary of JAVELIN bladder 100 primary and secondary outcomes is presented in Table 15 below.

Table 15. Summary of the outcomes assessed in the JAVELIN Bladder 100 trial

Outcome	Avelumab + BSC arm (n=350)	BSC arm (n=350)
Primary outcome: OS		
Events, n (%)	145 (41.4)	179 (51.1)
Censored, n (%)	205 (58.6)	171 (48.9)
Median OS (95% CI), months	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
Median OS, HR (95% CI)	0.69 (0.556, 0.863), p=0.001	
Secondary outcomes		
PFS, events, n (%)	225 (64.3)	260 (74.3)
Median PFS (95% CI), months	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)
Median PFS, HR (95% CI)	0.62 (0.519, 0.751), p<0.0001	
ORR, %	9.7	1.4
DOR, median (95% CI), months	[redacted]	[redacted]
DC, n (%)	144 (41.1)	96 (27.4)
TTR, median, months	2	2
PRO, median time to deterioration (95% CI), months	Not reached (13.9, not reached)	13.8 (12.9, not reached)

Abbreviation: BSC = best supportive care; CI = confidence interval; DC = disease control; DOR = duration of response; HR = hazard ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; TTR = time to response

2.2.3 Subgroup analyses

Subgroups for consideration were not specified in the NICE final scope. The CS reports the following pre-specified subgroups for the outcomes of overall survival, progression-free survival and objective response in Figures B.5.4, B.5.5 and B.5.6, Appendix E.1.1 of the CS:

- Best response to first-line chemotherapy (Complete/partial response; stable disease)
- Metastatic disease site (visceral, non-visceral)
- Age (<65, ≥65 years)
- Gender (male, female)
- Race (white, Asian, other)
- Pooled geographic region (Europe, North America, Asia, Australia, Rest of the World)
- PD-L1 status at baseline (positive, negative, unknown)
- Fist-line chemotherapy regimen (gemcitabine + cisplatin; gemcitabine + carboplatin; gemcitabine + carboplatin + cisplatin)
- ECOG (Eastern Cooperative Oncology Group)) performance status (0, ≥1)
- Creatinine clearance at baseline (≥60 mL/min, <60 mL/min)
- Liver lesions at baseline (yes, no)
- Lung lesions at baseline (yes, no)

The company states that all subgroups were explanatory and no adjustment for multiplicity was performed. Point estimates suggest that avelumab + BSC had a beneficial effect across all pre-specified subgroups and efficacy outcomes (overall survival, progression-free survival and objective response) (CS, page 42). Several of the subgroups have a very small number of participants and therefore show wider confidence intervals indicating uncertainty around the point estimate. The ERG notice the reduced evidence of a benefit in the female population and in those aged less than 65 years old for both overall survival and progression-free survival. For the other subgroups there is either no evidence of a difference or only a limited number of observations.

With regard to the subgroup of participants with PD-L1 positive tumours (189 randomised to avelumab + BSC and 169 to BSC), the company presents overall survival, progression-free survival and objective response in Appendix E.1.2.1 of the CS. The results supported the

consistency of the beneficial effect of avelumab in this subgroup.

[redacted], the company states that [redacted] A broad summary of outcomes in patients with PD-L1-positive and negative tumours is presented in Table 16 below.

Table 16. Summary of overall survival, progression-free survival (based on BICR assessment) and objective response (based on BICR assessment) in participants with PD-L1-positive or negative tumours in the FAS [*adapted from Tables B.5.9, B.5.10, B.5.11, B.5.14, B.5.15, B.5.16, Appendix E.1.2 of the CS*]

• **Endpoint**	**PD-L1-positive (N=358)**		**PD-L1-negative (N=270)**	
	Avelumab + BSC (N=189)	**BSC (N=169)**	**Avelumab + BSC (N=139)**	**BSC (N=132)**
Overall survival (OS)				
Median OS (95% CI), months	NR (20.3, NR)	17.1 (13.5, 23.7)	18.8 (13.3, 22.5)	13.7 (10.8, 17.8)
HR (95% CI), two-sided p-value	0.56 (0.404, 0.787), p<0.001		0.85 (0.615, 1.181)	
Progression-free survival (PFS)				
Median PFS (95% CI), months	5.7 (3.7, 7.4)	2.1 (1.9, 3.5)	3.0 (2.0, 3.7)	1.9 (1.9, 2.1)
HR (95% CI), two-sided p-value	0.56 (0.431, 0.728), p<0.0001		0.63 (0.474, 0.847)	
Objective response				
n (%)	26 (13.8%)	2 (1.2%)	[redacted]	1 (0.8%)
Odds ratio (95% CI), two-sided p-value	[redacted]		Not reported	

Abbreviations: BICR = blinded independent central review; BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; n = number of patients in the category; N = number of patients evaluable; NR = not reached; PD-L1 = programmed death-ligand 1

2.2.4 Adverse events

The safety population of JAVELIN Bladder 100 (N = 689) included all participants who received at least one dose of avelumab or received only BSC (avelumab + BSC, n=344; BSC, n=345). The methods used to assess safety are reported in Sections B.2.4.3.3 and B.2.10 of the CS and are considered appropriate by the ERG. In general, the safety profile for avelumab is as expected for patients with this clinical condition.

Table B.2.14 of the CS, reproduced as Table 17 below, summarises the frequency of participants with treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs).

Table 17. Summary of adverse events - safety analysis set [reproduced from Table B.2.14, Section B.2.10.1.3 of the CS]

	Treatment-emergent AE (TEAE), n (%)		Treatment-related AE (TRAE), n (%)	
	Avelumab + BSC (N=344)	BSC (N=345)	Avelumab + BSC (N=344)	BSC (N=345)
Adverse events (AE)	337 (98.0)	268 (77.7)	266 (77.3)	4 (1.2)
Grade ≥3	163 (47.4)	87 (25.2)	57 (16.6)	0 (0.0)
Serious	96 (27.9)	69 (20.0)	31 (9.0)	0 (0.0)
Leading to discontinuation	41 (11.9)	0 (0.0)	33 (9.6)	0 (0.0)
Leading to death	4 (1.2)	24 (7.0)	1 (0.3)	0 (0.0)

Abbreviations: AE = adverse event; BSC = best supportive care; n = number of patients in the category; N = number of patients evaluable

Commonly reported adverse events

Table 17 above shows that there was a higher incidence of TEAEs and TRAEs in the avelumab + BSC group compared with the BSC group (98.0 % and 77.7%, respectively, for TEAEs; 77.3% and 1.2%, respectively for TRAEs). Grade ≥3 TEAEs and TRAEs were also reported more frequently in the avelumab + BSC group compared with the BSC group (47.4% and 25.2%, respectively, for TEAEs; 16.6% and 0%, respectively for TRAEs).

The company has provided lists of the most common TEAEs of any grade reported in ≥10% of participants or Grade ≥3 reported in ≥5% of participants (Table B.2.15, Section B.2.10.1.4 of the CS), and the most common TRAEs of any grade reported in ≥5% of participants or Grade ≥3 reported in ≥2% of participants (Table B.2.16, Section B.2.10.1.4 of the CS). The most common TEAEs included fatigue, pruritus, urinary tract infection, diarrhoea, arthralgia,

asthenia, constipation, back pain, nausea, pyrexia, decreased appetite, cough, vomiting, hypothyroidism, rash, anaemia, haematuria, and infusion-related reaction. The company highlighted that no individual AE occurred at a frequency of ≥20% in the avelumab + BSC group.

Serious adverse events (SAEs)

Serious TEAEs occurred in 27.9% of participants in the avelumab + BSC group and 20% of participants in the BSC group (Table 17 above). The company has provided a list of the most common serious TEAEs of any grade reported in ≥2 participants (Table B.2.17, Section B.2.10.1.5 of the CS).

Serious TRAEs occurred in 9% of participants in the avelumab + BSC group (Table 17 above). Those reported in ≥2 participants were infusion-related reaction (n = 4 [1.2%]), blood creatinine phosphokinase increased (n = 2 [0.6%]) and colitis (n = 2 [0.6%]) (Table B.2.18, Section B.2.10.1.5 of the CS). There were no serious TRAEs in the BSC group.

Adverse events leading to treatment discontinuation

Within the avelumab + BSC group, TEAEs and TRAEs leading to treatment discontinuation were reported in 11.9% (n = 41) and 9.6% (n = 33) of participants, respectively (Table 17 above). The company has provided a list of TEAEs and TRAEs leading to treatment discontinuation (Table B.2.21, Section B.2.10.1.7 of the CS). The most common TEAEs leading to discontinuation of avelumab were [redacted] There were no TEAEs and TRAEs leading to treatment discontinuation in the BSC group.

Adverse events leading to death

Grade 5 (fatal) TEAEs occurred in 4 (1.2%) participants in the avelumab + BSC group and 24 (7.0%) participants in the BSC group (Table 17 above). Among the avelumab-treated participants, sepsis was the only fatal TEAE other than disease progression (Table B.2.20, Section B.2.10.1.6 of the CS).

Death was attributed to the toxicity of study treatment in 2 (0.6%) participants in the avelumab + BSC group. One participant had sepsis, 29 days after the last dose of avelumab.

The other participant had an ischemic stroke after the end of the on-treatment period, 100 days after a single dose of avelumab. Both deaths were considered to be unrelated to avelumab by the sponsor.

Adverse events leading to dose interruption or modification

A total of 140 (40.7%) participants experienced TEAEs leading to interruption of avelumab treatment and [redacted] participant experienced a TEAE of [redacted] that led to a starting dose reduction of avelumab, which was not permitted by the protocol.

Adverse events of special interest: Immune-related adverse events (irAE) and infusion-related reactions (IRR)

Within the avelumab + BSC group, 101 (29.4%) participants had adverse events that were categorized as being immune-related, of whom 24 (7%) participants had a Grade 3 event. No Grade 4 or Grade 5 immune-related adverse events (irAEs) occurred. The most frequent category of irAEs was thyroid disorders, which occurred in [redacted] participants. Infusion-related reaction (IRR) was reported in 74 (21.5%) participants in the avelumab + BSC group, including 3 (0.9%) participants with a Grade 3 event. [redacted] Grade 4 or Grade 5 IRR were reported. The company has provided a list of irAEs, serious irAE and IRRs (Tables B.2.22, B.2.23 and B2.24, Section 2.10.1.9 of the CS).

A summary of irAEs and IRRs is presented in Table 18 below.

Table 18. Summary of immune-related adverse events (irAE) and infusion-related reactions (IRR) [adapted from Tables B.2.22 and B.2.24, Section B.2.10.1.9 of the CS]

	Avelumab + BSC (N=344)		BSC (N=345)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Immune-related AE (irAE)	101 (29.4)	24 (7.0)	5 (1.4)	1 (0.3)
Infusion-related reactions (IRR)	74 (21.5)	3 (0.9)	0 (0.0)	0 (0.0)

Abbreviations: AE = adverse event; BSC = best supportive care; n = number of patients in the category; N = number of patients evaluable

2.2.5 Meta-analyses

As only JAVELIN Bladder 100 was identified by the company as relevant to address the decision problem of this appraisal, no meta-analyses were performed.

2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Indirect or multiple treatment comparisons were not conducted by the company for this appraisal.

2.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison analyses were conducted by the company.

2.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG requested the data for overall survival, progression-free survival and time to treatment discontinuation. The ERG used the provided data to reproduce the overall survival and progression free survival hazard ratios and agree with the analysis performed in the JAVELIN Bladder 100 trial, which has been presented in Tables B.2.9 and B.2.10 on pages 37 and 38 of Document B.

2.6 Conclusions of the clinical effectiveness section

Disease progression is an outcome, which cannot have its definition modified to be less subjective; so, it is the opinion of the ERG that, while a blinded independent central review took place, the quality of the JAVELIN Bladder 100 trial would have been higher had it not been open label and had the initial assessment been blinded in order to reduce bias. Nevertheless, the ERG do not consider this a particular cause of concern.

The ERG initially had concerns regarding the maturity of the overall survival data and the use of these data as the starting point for extrapolation for the cost effectiveness analyses. After reviewing the trial publications and receiving further clarification from the company, the ERG are happy that the interim analysis of the JAVELIN Bladder 100 trial is also the final analysis following the decision of the independent external data monitoring committee that the trial efficacy boundaries had been crossed, and so the data are suitable for extrapolation and results can be used for inference.

Table B.2.9 Document B shows the analysis of the primary endpoint of overall survival (OS). The ERG have reviewed these data and agree with the company that they show a benefit from avelumab + BSC compared with BSC alone. The summary statistics and Kaplan-Meier plot

show a higher percentage of participants being alive at all time points. The median overall survival is more than 7 months longer for those receiving avelumab + BSC and the confidence intervals for median OS do not overlap, which provides further evidence of a benefit in the intervention group. The hazard ratio shows a reduced risk and the confidence interval and p-value indicate that this difference is statistically significant.

The company also provide analysis of PFS and objective response as secondary end points and, in response to a query from the ERG, submitted an additional analysis of PFS using the investigator definition of progression. The ERG reviewed the analyses of PFS under both definitions and observe that under both definitions the probability of being event free is higher at all time points for those who received avelumab in addition to BSC. The median event-free time is longer for those also receiving avelumab. The hazard ratios presented show the risk of progression is reduced for those in the avelumab + BSC group and the tight confidence intervals around the hazard ratios and the p-values indicate that the difference is significant. The Kaplan-Meier plots also provide evidence of a beneficial effect from also receiving avelumab.

The ERG reviewed the analyses of objective response under both the blinded independent central review from the original submission and also using the investigator assessment, which was provided by the company at clarification. The ERG are satisfied that these data show that an overall response is more likely for those in the avelumab + BSC group.

The ERG also reviewed the analysis of OS and PFS on the PD-L1 positive and negative populations, which is presented in Appendix E of the CS. The ERG are happy that this analysis shows a significant benefit for those also receiving avelumab on both OS and PFS for patients with PD-L1 positive tumours. For patients with PD-L1 negative tumours, there is a clear benefit on PFS in the avelumab + BSC group. For the OS outcome the median survival time is longer for those receiving avelumab + BSC and the hazard ratio suggests a benefit; however, the smaller sample size and greater uncertainty around the hazard ratio indicate that this difference is not significant.

The ERG noticed that the outcome ‘time to treatment discontinuation’ is used in the cost effectiveness part of this appraisal (Figure B.3.19 and Table B.3.6, Document B), but apart from presenting adverse events, which led to treatment discontinuation, it was not discussed in

the clinical effectiveness section of the submission. The ERG have used the data provided by the company at clarification and are able to reproduce Figure B.3.19.

The ERG inspected the adverse events reported in Tables B.2.15 to B.2.24 of the CS. We agree with the company's statement that when an intervention arm is compared to best supportive care only the incidence of adverse events is likely to be higher in the intervention arm. The ERG note that Table B.2.15 shows higher rates of all adverse events (apart from haematuria) in the avelumab + BSC group when all grades of events are considered. When comparisons are restricted to events of Grade 3 and above, any differences between the groups are reduced and for some adverse events are less likely in the avelumab + BSC group. The ERG observed the proportion of urinary tract infection (UTI) shown in Table B.2.17 is higher amongst those who also receive avelumab. Tables B.2.22, B.2.23 and B.2.24 show immune-related adverse events and the ERG highlight nearly 30% of those in avelumab + BSC group have some grade of immune-related adverse events but note that when restricted to events of Grade 3 and above the rate is reduced to 7%. The ERG are not concerned with the slightly higher rate of serious immune-related events in the avelumab + BSC group and notes that no one type of event has a high frequency. Table B.2.24, which summarises infusion-related reactions, shows that the events in the avelumab + BSC group are mainly of Grade 2 or lower.

The number of deaths in the trial were already considered as part of the OS primary endpoint and, therefore, do not require further discussion as serious adverse events. At the time of clarification, the ERG did notice slight differences between tables in the number of deaths and progressions presented but are satisfied with the company's clarification that any discrepancies are due to the investigator and independent reviewer's definitions of progression and also the timing of these reviews. The ERG are not concerned with any differences in serious adverse event or adverse event rates and in the ERG's clinical expert opinion, the trial has not raised any safety signals with regard to the use of avelumab as a first-line maintenance treatment.

COST EFFECTIVENESS

3.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify previous economic evaluations of avelumab and comparators. The methods and results of the searches are described in Appendix G of the CS. Further searches were conducted for resource use, costs and HRQoL data. Appendix H of the CS describes the methodology and results of these searches.

The scope of the cost-effectiveness search included treatments for first-line, first-line induction or maintenance therapies for locally advanced or metastatic UC. The literature search identified three published cost-effectiveness analyses, two evaluating pembrolizumab vs. gemcitabine + carboplatin chemotherapy in England and the US.[28, 29] The third study evaluated the cost-effectiveness of atezolizumab, pembrolizumab or durvalumab vs. gemcitabine + cisplatin chemotherapy or gemcitabine + carboplatin chemotherapy.[30]

The company have identified a further six NICE technology appraisals of treatments for locally advanced or metastatic UC.[15, 16, 31-34] The key features of these appraisals are compared to the company's avelumab submission in Table B.3.1 of the CS. Some notable characteristics across the different technology appraisals are that all appraisals have appropriately used a 3-state partitioned survival analysis model and none included a treatment waning effect over time in the original submissions. However, the ERG note that committee documents for previous appraisals indicate that there was significant debate around the appropriateness of continuing treatment effects over the longer term, particularly when early treatment discontinuation was assumed. See for example, Section 3.13 of the FAD for TA10466 (pembrolizumab) and Section 3.12 of the FAD for TA525 (atezolizumab).[35, 36] Both FADs noted that a lifetime duration of treatment benefit would be considered implausible, but noted a lack of evidence to determine the most likely duration of treatment benefit following treatment discontinuation with immunotherapies.

None of the identified published cost-effectiveness studies or technology appraisals included avelumab and there was no cost-effectiveness evidence for any treatments used in the maintenance phase. The ERG are satisfied that the company have undertaken a thorough systematic review of the cost-effectiveness evidence and note that all searches are fully reproducible.

3.2 Summary and critique of the company's submitted economic evaluation by the ERG

3.2.1 NICE reference case checklist

Table 19 reports the ERGs assessment of the CS against the NICE reference case.

Table 19. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes. Health effects for patients have been included. The model does not consider any carer disutility.
Perspective on costs	NHS and PSS	Yes: NHS and PSS perspective costs are included.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes: A cost-utility analysis reporting incremental cost per QALY gain for avelumab vs WW was conducted.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. The model time horizon used in the base case is 25 years, which is considered sufficiently long to capture a lifetime horizon for a modelled cohort with start age of 67.5. It should be noted that the model structure is restricted to a maximum of 25 years. Therefore, any scenario analyses that might consider a younger population should be interpreted cautiously as such analyses would not necessarily reflect a lifetime horizon. The ERG accepts however that no such analyses are reported in the CS.
Synthesis of evidence on health effects	Based on systematic review	Yes. Efficacy, EQ-5D utility by progression status, and AE probability data to populate the model are all obtained from the JAVELIN

Element of health technology assessment	Reference case	ERG comment on company's submission
		Bladder 100 trial. The company conducted a systematic review of the HRQoL evidence and review of utilities used in previous NICE appraisals for UC. The review identified alternative utility values for pre- and post-progression states from TA 519 (pooled across treatment arms) and these were used in cost-effectiveness scenario analyses.[32]
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.	Mostly Yes: Health effects are expressed as QALYs obtained using EQ-5D-5L responses cross walked to EQ-5D-3L using the van Hout 2012 algorithm.[37] Utilities by progression status (data pooled across treatment arms) were estimated using a mixed effects linear model with 2 covariates (baseline utility and progression status). Disutility of adverse events were obtained from the literature, using either EQ-5D data or direct health state valuations using standard gamble. Any deviation from the NICE reference case for obtaining AE disutilities is likely to have only a minimal impact on the ICER.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes. Health related quality of life was based on patient level responses to the EQ-5D-5L questionnaire from JAVELIN Bladder 100 trial. AE disutilities are obtained from patient reported quality of life or patient level health state valuation.
Source of preference data for valuation of changes in health-	Representative sample of the UK population	Mostly Yes. EQ-5D responses cross-walked from the 5L to 3L version are valued using UK general population TTO tariffs for England using the Dolan 1997 value set.[38] Some, but not all AE disutilities were based on UK value sets. For

Element of health technology assessment	Reference case	ERG comment on company's submission
related quality of life		example, disutilities for UTI, back pain and immune-mediated hepatitis were obtained from US valuations of EQ-5D data.[38] Any deviation from the NICE reference case for obtaining AE disutilities is likely to have only a minimal impact on the ICER.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes. NHS and PSS perspective costs are included throughout the model in 2018/19 GBP values (the most recent data available to the company at the time of submission).
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes. Continuous discounting of costs and QALYs is performed at each weekly time point in the model.
AE: adverse events; EQ-5D: standardised instrument for use as a measure of health outcome; ICER: incremental cost effectiveness ratio; PSS: personal social services; QALYs: quality-adjusted life years; TTO, time trade off method; UC: urothelial cancer; UTI: urinary tract infection.		

3.2.2 Model structure

The company have submitted a partitioned survival analysis (PartSA) model, developed in Microsoft Excel® to calculate total costs, life years, QALYs and hence incremental cost effectiveness ratios for avelumab compared to watchful waiting (WW). The PartSA model

has three health states (progression free survival (PFS), progressed disease and death). Occupancy in the death and PFS state is determined as the area under survival curves fitted to kaplan meier (KM) data from the JAVELIN Bladder 100 trial for overall (1-OS) and PFS respectively. Occupancy in the progressed disease state is the area between the fitted OS and PFS curves. The model includes one line of post-progression treatment (See Section 3.2.8). The ERG agree that the company's chosen PartSA model structure is appropriate for decision making, and acknowledge that the modelling approach is consistent with six different appraisals in UC conducted by NICE.[15, 16, 31-34]

However, the ERG are concerned that the true duration of treatment benefit after discontinuation of avelumab treatment is unknown and is a significant area of unresolved uncertainty for decision making. The company have assumed that PFS and OS benefit of avelumab occurs over the full model time horizon. The company also assume that, in UK clinical practice, treatment discontinuation will occur earlier than in the clinical trial. The economic model assumes 95% of patients discontinue at 2 years, with all remaining patients stopping treatment at 5 years. Discontinuation for the 5% remaining on treatment at 2 years then follows a lognormal parametric survival curve, fitted to the time to treatment discontinuation data from the trial, until all patients have avelumab treatment stopped at 5 years.

The ERG's clinical expert notes that 2-year stopping rules are common for immunotherapy treatments for cancer, and that applying treatment discontinuation assumptions as per the company's economic model would be acceptable in UK clinical practice. The ERG also agrees with the company that there is some precedence in NICE assessments in UC to prefer early stopping rules and notes that the NICE FAD for pembrolizumab (TA519 / TA10466) considers a 2-year stopping rule to be reasonable.[35, 36]

However, the ERG are concerned that assuming a life time continued treatment effect is not evidenced based or sufficiently justified within the CS. Furthermore, because the company assumes that discontinuing treatment earlier than in the trial impacts only on costs and not on PFS or OS benefit, the ERG consider the company's base case assumptions to generate a highly optimistic estimate of the ICER for avelumab. The company have not provided any robust evidence or detailed clinical explanation in the CS to justify the assumption of lifetime duration of treatment benefit after treatment discontinuation. Furthermore, the ERG note that assumptions surrounding the duration of treatment benefit have generated considerable

uncertainty in previous NICE appraisals (see for example TA525 and TA10466 FADs).[35, 36] Further review of the committee deliberations for these assessments indicates that the committees considered a life time duration of continued treatment benefit to be implausible. To address this uncertainty, the ERG conduct several two-way scenario analyses to explore the impact of different combinations of assumptions about treatment discontinuation and caps on the duration of avelumab treatment benefit (e.g. no avelumab PFS or OS benefit after 2, 5 or 10 years) on the ICER. Further details of the scenario analyses conducted are provided in Sections 5.1 and 5.2.

3.2.3 Population

The modelled population is a cohort of patients with locally advanced or metastatic UC, who have previously had treatment with a first line platinum-based chemotherapy regimen. The baseline characteristics of the modelled cohort (age: 67.5 years, 77.3% male, mean BSA: 1.87m^2 with GFR = 68.92 ml/min/1.73m^2) are obtained from the intention to treat FAS, pooled across avelumab + BSC and BSC arms of the JAVELIN Bladder 100 trial. The ERG consider the modelled population to be in line with the NICE scope for this assessment. The ERG's clinical expert further advises that the modelled population is representative of the patients who would be eligible for treatment with avelumab as maintenance therapy following first list platinum based chemotherapy in UK clinical practice.

3.2.4 Interventions and comparators

Intervention

The modelled intervention is avelumab (Bavencio®) delivered as a flat intravenous (IV) dose of 800 mg, every 2 weeks. This modelled dose is in line with the SmPC, but is different to the dosing approach used in the JAVELIN Bladder 100 clinical trial, which was 10mg/kg of body weight every two weeks.[18, 24] Given an average body weight of 75.14kg from the JAVELIN Bladder 100 trial, the ERG note that the average total treatment dose (750mg) administered is sufficiently similar to the flat dose of 800mg to have no concerns regarding any differences in treatment effectiveness. The ERG's clinical expert further confirms that the flat dose applied in the company's model best represents how avelumab would be used in UK clinical practice. Whilst the ERG accept that the treatment discontinuation assumptions applied in the model (95% by 2 years and 100% by 5 years) would be acceptable in UK

clinical practice, they are nonetheless inconsistent with the SmPC, which states that treatment should continue *"….according to the recommended schedule until disease progression or unacceptable toxicity"*. The full SmPC documentation is available in Appendix B.5 of the CS.

Comparator

The comparator for the appraisal as specified in the NICE scope is "Established clinical management without avelumab". The comparator arm of the model is named "watchful waiting" (WW), whereas the comparator arm in the JAVELIN Bladder 100 trial is described as "best supportive care (BSC)". The company consider these to be analogous to each other, but based on clinical expert input, the company chose to name the model comparator arm "watchful waiting" to more accurately describe the potential for subsequent active treatments post-progression. The ERG note that there are no direct active treatment costs associated with "watchful waiting" pre-progression other than routine patient monitoring in the model. The ERG are therefore satisfied that the chosen model comparator is sufficiently similar to that used in the trial to enable the use of trial data in the model. The ERG also consider WW to be an appropriate comparator for decision-making and is in line with standard patient management in UK clinical practice where active treatments would not currently be used as standard practice following platinum based chemotherapy prior to disease progression.

3.2.5 Perspective, time horizon and discounting

The economic model evaluates cost-effectiveness from the perspective of the patient for health effects (QALYs) and from the perspective of the NHS and PSS for resource use and costs. The ERG is satisfied that the analysis perspective is in line with the NICE reference case.

The model time horizon used in the base case analysis is 25 years, which is considered sufficiently long to capture a lifetime horizon for a modelled cohort with start age: 67.5. The ERG consider the modelled lifetime horizon to be appropriate and necessary to capture all the cost and outcomes associated with delayed progression using avelumab. However, the ERG caution that the current model configuration means that the maximum possible time horizon in the model is 25 years. This may not necessarily reflect a lifetime horizon in any scenarios varying the age of the cohort and the model does not currently include configuration to

perform these analyses. However, as no such scenario analyses are reported, there are no implications for cost-effectiveness results.

Costs and QALYs were discounted in line with the NICE reference at a rate 3.5% per annum, applied continuously for each week in the model (i.e. the discount factor is determined at the weekly, rather than the annual level). The company note that life years were not discounted to aide interpretation of survival curve output. The annual discount rate for costs and QALYs was reduced to 0% for scenario analyses. The ERG consider the company's time horizon, analysis perspective and approach to discounting to be appropriate.

3.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness was measured using survival models of time to event outcomes (PFS and OS) fitted independently by treatment arm to KM data from the JAVELIN Bladder 100 trial and extrapolated over the model's 25-year time horizon. The process for selecting the most appropriate survival curve followed NICE DSU recommendations and involved inspection of log cumulative hazard plots, and assessing different survival curves in terms of visual fit to the KM data, goodness of fit statistics (AIC and BIC) and validation with UK clinical oncologists experienced in treating patients with locally advanced or metastatic UC.[39]

The ERG acknowledge that the company submitted economic model includes the functionality to fit a full range of parametric OS models and parametric and spline based PFS models, which enables full exploration of the uncertainty associated with the curve fitting process. The ERG consider the company approach to selecting survival curves to be transparent and in line with NICE DSU recommendations.[39] Unless stated otherwise in the following sections, the ERG agree with the company's selected survival curves.

Overall survival (OS)

OS is modelled using a single curve crossing both pre and post-progression health states. The ERG note that OS is likely to be higher after disease progression but accept that the company will not have sufficient data to populate state specific OS curves. The ERG therefore accept the company's use of a single OS curve, noting that the net impact of any biases on the ICER is unclear. A single OS curve may underestimate OS benefit for avelumab by not counting the OS advantage of preventing disease progression. However, conversely, OS may be over-

estimated because avelumab patients may not achieve any additional benefit of receiving immunotherapy post progression.

The process for selecting the OS curve is fully described in section B.3.3.3.1 (Figures B.3.3 to B.3.7) of the CS. Briefly, log cumulative hazard plots show that proportional hazard assumptions are unlikely to hold and it was deemed appropriate to fit survival curves independently by model treatment arm. Six alternative survival models were considered (exponential, generalised gamma, gompertz, log-logistic, lognormal and weibull). Visual inspection against the KM data indicated that lognormal, log-logistic and generalised gamma provided the best fits to the KM data for both treatment arms.

For the avelumab arm, the lognormal had the best statistical goodness of fit according to both AIC and BIC. However, the company selected the generalised gamma curve for avelumab OS on the basis that it predicted 5 and 10 year OS most closely aligned with the expert opinion of 8 clinical oncologists for 5 year OS of 20-30% and 10 year OS between 10-15% with avelumab treatment. The ERG noted that the company preferred generalised gamma generated the most optimistic 5 and 10 year OS for avelumab. The ERG also notes that the company have not provided any evidence that the clinical experts discounted the best fitting LN curve as being inappropriate. Given that 5 and 10-year OS for avelumab is essentially unknown, the ERG prefers the use of the more conservative LN curve for avelumab as it has the best statistical fit. Furthermore, the ERG's clinical expert deemed the LN predictions to be reasonable.

For WW, generalised gamma had the best AIC, whereas the lognormal had the best BIC, though AIC / BIC scores were essentially similar for both lognormal and generalised gamma. The company's expert opinion suggested 5 and 10 year OS of 5-15% and 2-7% respectively under WW. The company selected the generalised gamma, which generated the most optimistic estimates of 5 and 10 year OS that were close to the upper end of the clinician's expectations. The ERG however prefer the use of the LN curve as it generates 5-year (10.71%) and 10-year (2.90%) OS predictions that are closer to the mid-point of the clinical expert expectations. The ERG's clinical expert agreed that the LN curve predictions were reasonable.

For all OS curves, the company apply an adjustment to ensure that the probability of death does not fall below that of UK general population all-cause mortality probabilities and the ERG consider this appropriate. The ERG note that the company use clinical expert expectations of 8 UK clinical oncologists regarding 5 and 10 year OS for avelumab and WW to inform the most appropriate survival curve selection. The ERG consider this reasonable, but note that it was unclear from the CS how the experts views were elicited, what exact questions were posed to the experts, and whether they answered individually or as a group to come to these OS expectations. Further information on how the elicitation work was carried out and direct ranges of estimates obtained from each clinical expert, if available to the company, would help to resolve some uncertainty and further support the company's choice of OS extrapolation curves used in the model.

Progression free survival

The proportion of the cohort in the pre-progression health state is determined by fitting survival curves to the KM data and extrapolating independently by treatment arm over the model's 25-year time horizon. The process for selecting the PFS curves for avelumab and WW is fully described in section B.3.3.3.2 (Figures B.3.9 to B.3.15) of the CS.

PFS curves are fitted for two alternative definitions of progression in the company economic model, blinded independent clinical review (BICR) assessed and investigator (INV) assessed. In real world clinical practice, the ERG's clinical expert is of the view that INV assessed progression is more likely to be used to make decisions about disease progression and guide treatment decisions in clinical practice. The ERG therefore considers models parameterised using the INV definition of progression to be more appropriate for decision making on the grounds of cost-effectiveness. In response to clarification queries, the company provided a full set of analyses using the INV definition to complement the BICR definition data reported in Section B.3.3.3.2 of the CS. The company model allows selection of either progression definition.

For both definitions of progression, the company rejected the use of any of the six standard parametric survival curves because none were sufficient to capture both the initial sharp drop in the KM curves around 2 months and the longer tail at the end of the curves. The company then explored the use of spline based parametric models to improve the accuracy PFS estimation relative to the KM curves. Models were fitted with one, two, or three knots and

three functional forms, hazard (extension of Weibull model), odds (extension of log logistic) and normal (extension of lognormal) were considered for each. All nine models were evaluated according to visual fit, AIC and BIC scores, and clinical validity. The ERG agree with the company that three-knot spline models are most appropriate for modelling both investigator and BICR assessed PFS.

For the company base case, BICR assessment, the company preferred the use of a 3-knot-normal spline-based model for both avelumab and WW as it generated a good visual fit to the KM data, had acceptable AIC and BIC scores and was considered plausible by the company clinical experts. The ERG consider the selected curves to be appropriate for modelling BICR assessed progression. However, as noted, the ERG prefer the use of INV assessed progression. Following the same process as outlined above for BICR assessment, the ERG prefer INV assessed PFS estimated using 3-knot hazards and 3-knot odds for avelumab and WW respectively. The ERG's clinical expert considers the 5 and 10 year PFS projections to be appropriate and the ERG also note that the projections are in line with the expectations of the company's clinical experts. The implication is a small reduction in the ICER for avelumab.

Time to treatment discontinuation

The ERG critique of the company's treatment discontinuation assumptions (95% at 2 years and 100% at 5 years) is provided in Section 3.2.2. This section describes the approach used to estimate treatment discontinuation between years 2 and 5 in the company model, by fitting parametric survival curves to the TTD KM data from the JAVELIN Bladder 100 trial. The ERG note that the generalised gamma has the best visual and statistical fit, but the company have chosen a lognormal curve because the generalised gamma proportion remaining on treatment at 5 years (7.5%) was deemed too high to be plausible in clinical practice. The ERG's clinical expert opinion would generally agree that this is appropriate, with a substantial proportion of people coming off treatment over time. However, given that the company have applied treatment discontinuation assumptions at two years and five years that over-ride the projections of the survival curves, the ERG considers it reasonable to apply the curve that fits the KM data best up to 2 years to extrapolate between 2 and 5 years for the proportion that remain on treatment. Furthermore, the ERG consider that if accepting the 2 and 5 year discontinuation and stopping rules, then it is appropriate to apply a slower rate of discontinuation between years 2 and 5. The implication of using the ERG preferred

extrapolation is a small increase in the ICER. However, the more fundamental uncertainty for decision-making is the assumption of lifetime continued treatment benefits, regardless of avelumab treatment discontinuation or stopping rules (See Section 3.2.2).

Adverse events:

Adverse events were obtained directly from the JAVELIN Bladder 100 trial.[24] The following AEs were included in the model:

- Grade ≥ 3 TEAEs occurring in ≥ 1% of patients in either treatment arm.
- Grade ≥ 3 TRAEs occurring in ≥ 1% of patients in the avelumab arm
- Grade ≥ 3 irAEs occurring in ≥ 1% of patients in the avelumab arm
- Any Grade non-irAEs occurring in ≥ 5% of patients in either treatment arm
- Grade ≥ 3 non-irAEs occurring in ≥ 2% of patients in either treatment arm

The model did not explicitly consider the cost and utility implications of adverse events associated with downstream, post-progression treatments. As avelumab is likely to lengthen the time to progression, it is likely that any bias from omitting adverse events of post progression treatment would favour WW in the model, though the magnitude of any bias is likely to be very small. The ERG note that the company have not provided any justification for the criteria they used to select the most appropriate adverse events for inclusion in the model. Given the relatively short duration of adverse events, the ERG consider it to be unlikely that amending the criteria for selecting adverse events for inclusion in the model would make a material difference in the ICER, though any biases generated by excluding a full set of adverse events would likely favour avelumab.

3.2.7 Health related quality of life

Health-related quality of life is included in the model through the use of utility weights applied to each health state and utility decrements for adverse events. A utility weight is applied to the progression-free health state, with a lower value applied post-progression. Utility decrements are applied for adverse events of Grade ≥3 as described in section 3.2.6.

Utility weights

EQ-5D-5L data were collected in the JAVELIN Bladder 100 trial and used in the model to derive utility weights for each health state. Data were collected at each 28-day treatment cycle, at the end of treatment, and at follow-up visits at 30, 60 and 90 days after

discontinuation. In order to be consistent with the NICE reference case, EQ-5D-5L responses were 'crosswalked' to estimate EQ-5D-3L values using the algorithm by van Hout et al. (2012) along with the EQ-5D-3L value set from Dolan et al. (1997).[37, 38] Utility values were also adjusted for sex and age over the model time horizon using the baseline age (67.5) and the proportion of males (77.3%) from JAVELIN Bladder 100. Patients were included in the analysis if they had EQ-5D data collected at baseline and at one or more follow-up visits. Of the 700 patients in the ITT population, 47 were excluded due to missing observations resulting in 653 patients with sufficient observations for the analysis. The ERG sought additional clarification regarding the sample size used to estimate the utility values in each health state from JAVELIN Bladder 100 trial as a frequent limitation of quality of life data collected in clinical trials is the lack of data collected post-progression. While the sample size is smaller for the estimation of utilities in the progressed disease health state compared to the progression-free state, the ERG was satisfied with the overall number of patients and observations used to estimate the utility values. See response to question B7 of clarification questions for more details.

A mixed-effects regression model with two covariates (baseline utility and progression status) was fitted to the EQ-5D data to produce the following equation for estimating utility values:

Utility = 0.772 + 'progressed' x (-0.0075).

Note 'progessed' takes the value of 1 for patients who have progressed and 0 for patients who are progression-free. 0.772 is the mean utility at baseline applied to patients who are progression-free. Alternative utility values are explored in a scenario analysis using values from NICE TA519.[32] The values are lower than those derived from the JAVELIN Bladder 100 trial, which the company state is expected given the patients eligible to receive avelumab maintenance are likely to have a higher quality of life as patients receive treatment after achieving stable disease or PR/CR. Despite the difference between the patient populations the utility values from NICE TA519 were considered by the ERG to provide a lower bound of expected utility values in each health state. The values used in this scenario analysis are shown in Table 20 below.

Table 20. Utility values used in model base case and scenario analysis (Source: Company submission, document B, table B.3.12)

State	JAVELIN Bladder 100 (base-case)	TA519 (scenario)
Progression-free	0.772	0.731
Post-progression	0.698	0.641

The ERG note the company only presented progression-based utility values and did not present utility values within each health state separately by treatment arm. In describing the EQ-5D-5L scores collected in the trial the company states the scores were not significantly different for patients treated with avelumab compared to those receiving BSC alone. However, this seems at odds with the PFS benefit observed with avelumab in the trial where an associated improvement in HRQoL may be expected. The ERG note the use of progression-based utility values pooled across treatment arms would generally be considered more appropriate than applying separate treatment specific utility values within each health state, but additional clarification on the potential inconsistencies between the EQ-5D-5L data and the PFS benefit with avelumab would be helpful.

Another potential issue identified by the ERG relates to the post-progression utility value. The subsequent treatment options following avelumab maintenance and WW are quite different ([redacted] of patients received atezolizumab following progression after WW, whereas following avelumab maintenance patients would mostly receive chemotherapies). Further discussion of the treatments used post progression is provided in Section 3.2.8. Given the subsequent treatment pathways are quite different in each arm, it was considered whether patients on the more active treatment (atezolizumab) would experience better quality of life post progression as the treatment is more actively treating the progression. However, the ERG clinical expert indicated any differences in quality of life post-progression would likely be small. Overall, the ERG was satisfied with the utility values applied in the model base case using the EQ-5D data from the JAVELIN Bladder 100 trial.

Utility decrements

The quality of life impact of adverse events of grade ≥ 3 in either treatment arm were included separately in the model by applying utility decrements sourced from a range of

published studies combined with the adverse event rates from the JAVELIN Bladder 100 trial. The durations of the disutilities were based largely on TA581, TA378, on published studies and on assumptions. See table B.3.9 in the CS for details of the disutilities and durations of adverse events applied in the economic model.

The utility decrements are taken from a range of different studies and included a number of assumptions but no discussion was provided on the comparability of the data sources with patients who would be eligible to receive avelumab maintenance. In addition, the ERG note some of the values were not consistent with the NICE reference case, such as EQ-5D scores valued using the US value set and utility decrements elicited using the standard gamble method. While there is some uncertainty in the utility decrements, the QALY loss associated with adverse events in each arm was small [redacted] and [redacted] in the avelumab and WW arms respectively) due to the low rates and short duration of grade 3 and above adverse events in the JAVELIN Bladder 100 study. Therefore, any bias resulting from the approach used will have minimal impact on the cost-effectiveness results.

3.2.8 Resources and costs

Avelumab treatment acquisition costs

The cost of avelumab included in the model is based on a flat dose of 800mg administered by IV infusion once Q2W as per the anticipated licensed dose for avelumab. Avelumab is available as a 200mg vial at a list price of £768 per vial. A patient access scheme (PAS) is available for avelumab which reduces the price by [redacted] to [redacted] per 200mg vial. A single administration cost of £183.54 was applied per two-weekly treatment cycle. No active treatment costs were included for WW.

The expected licensed dose of avelumab is different from the dose used in the JAVELIN Bladder 100 trial where avelumab was administered using a weight-based dose of 10mg/kg. No adjustment was applied to account for this difference as efficacy outcomes are expected to be the same with a flat dose of 800mg. This approach was accepted by NICE in a previous avelumab appraisal for its use in untreated advanced or metastatic renal cell carcinoma (TA645) and the ERG clinical advisor confirmed the efficacy estimates would be similar.[21] The company also highlighted that the fixed dose lies between the mean dose in the trial ([redacted]) and the volume of avelumab required when accounting for wastage ([redacted]). Instead of using relative dose intensity (RDI) estimates to account for missed or delayed doses, an alternative approach was used to calculate the mean number of infusions per 2-weekly treatment cycle due to the differences between the licensed dose and the weight-based dosing used in the trial. Based on a mean treatment duration of [redacted] weeks and a mean number of infusions of [redacted] given every 2 weeks, a ratio of the mean number of infusions per treatment cycle was estimated at [redacted]. A summary of dosing information applied in the model is provided in Table 21 below.

Table 21. Avelumab dosing information applied in the model (reproduced from Table B.3.13, Document B of the CS)

Component	Value
Dose	800 mg
Vial size	200 mg
Cost per vial	£768.00
Cost per mg	£3.84
Cost per treatment (list price, unadjusted)	£3,072.00
Administration information	IV infusion once every 2 weeks

Component	Value
Mean duration of treatment in JAVELIN Bladder 100	[redacted]
Mean number of infusions in JAVELIN Bladder 100	[redacted]
Estimate of planned doses per cycle	[redacted]
Cost per treatment (list price, adjusted)	[redacted]

Abbreviations: RDI = relative dose intensity; IV = intravenous

Source: Pfizer Inc., 2020[26]

[A] ERG note, reported as [redacted]% in the CS, but correct value of [redacted]% used in economic model.

Additional clarification was sought from the company to understand how the approach used in the model differed from the RDI based on the JAVELIN Bladder 100 trial data. The response stated that the mean and median RDI estimates for avelumab in the trial were [redacted] and [redacted] respectively. However, RDI does not distinguish between dose delay, dose reductions or missed doses. As avelumab is expected to be licensed at the 800mg flat dose meaning all patients receive 4 vials of avelumab, the RDI is expected to be higher than observed in the trial. To explore this uncertainty further, two additional sensitivity analyses were provided which used mean RDI of [redacted] and median RDI of [redacted] resulting in the company base case ICER decreasing to £23,002 and £25,144 respectively. The ERG is satisfied that the additional clarification provided by the company supports their base case approach that the RDI of the flat dose of avelumab will likely be higher than that resulting from the weight-based dosing in the trial.

BSC

BSC was included in both arms of the JAVELIN Bladder 100 trial according to local clinical practice and included treatments such as antibiotics, nutritional support, hydration, pain management and radiotherapy for isolated lesions. As BSC was included in both arms, no active treatment costs were included.

Resource use

Resource use estimates included in the model are based on previous NICE submissions for urothelial cancers (TA492, TA522 and TA272) but adjusted for the avelumab maintenance population using clinical expert opinion.[15, 16, 31] Resource estimates are included separately

according to health state but do not differ by treatment arm. Unit costs were sourced from Personal and Social Services Research Unit (PSSRU) and NHS reference costs (2018-19).[40, 41] See tables B.3.16 and B.3.17 in the CS for details of resource use frequencies included in the base case.

A scenario analysis is provided using alternative resource use frequencies from TA272. A comparison of the base case and scenario analysis costs is provided in Table 22.

Table 22. Resource use costs per model cycle (source: Table B.3.19, Document B and company economic model)

	Cost per model cycle	
Health State	**Base case**	**Sensitivity analysis (TA272 resource use frequencies)**
Pre-progression	£67.76	£172.29
Progressed	£108.03	£161.53

The sensitivity analysis shows that the results are sensitive to using the alternative resource use estimates. Following discussions with the clinical advisor, the ERG is satisfied that the company's base case resource use estimates are broadly reflective of the resource use requirements in clinical practice, and in particular, the higher cost associated with progressed disease.

Other resource use costs

In addition to the health state costs a one-off terminal care cost is applied to account for resource use associated with palliative care based on a published study (Round et al., 2015).[42] A cost of £4,507 is applied in each arm according to the proportion of patients who die in each cycle. It is not clear how the study used was selected or whether alternative sources were considered, but the cost is applied in both arms and is not a key driver of the results. Adverse event costs are included based on the frequency reported in JAVELIN Bladder 100 multiplied by the relevant unit cost (see CS table B.3.20 for details of adverse event unit costs) resulting in a cost of £234.41 for avelumab and £174.11 for WW applied in the first model cycle.

Subsequent treatment costs

Costs of subsequent treatments following progression are included in the model based on the JAVELIN Bladder 100 trial but are adjusted to reflect the treatments available in UK clinical practice. The proportions receiving subsequent treatments and the type of treatments received differ by treatment arm. From the trial data, in the avelumab arm [redacted] of patients who progress following avelumab maintenance are assumed to receive subsequent active treatments, and of these [redacted] received subsequent anti-PD-1/PD-L1 immunotherapies. The corresponding proportions for the WW arm are [redacted] and [redacted] respectively.

A key concern identified by the ERG is the proportion of patients receiving subsequent treatments in the trial is likely to be higher than clinical practice. As patients in practice are generally less fit than patients in the trial, and also are not monitored as closely, fewer patients will receive subsequent treatment upon progression. Further clarification and analysis was sought from the company to explore the impact of assuming a lower proportion of patients receive subsequent treatments in the model. In the CS, estimates from the Systematic Anti-Cancer Therapy (SACT) dataset showed the proportion of patients in UK clinical practice who receive a second-line therapy following first-line platinum-based chemotherapy was 41.9%, which was lower than the proportion in the JAVELIN Bladder 100 trial. Following clarification the company explained this figure was not directly comparable with the proportions receiving subsequent treatments in JAVELIN Bladder 100 which included only patients achieving at least stable disease (and therefore may be considered fitter and more likely to receive subsequent treatment). To explore this issue further, an alternative analysis was provided using an average of the proportion observed in the JAVELIN Bladder 100 trial ([redacted] and [redacted] in the avelumab and WW arms respectively) and the 41.9% from the SACT dataset, resulting in [redacted] and [redacted] for avelumab and WW respectively. Note that this sensitivity analysis adjusts the costs only with no adjustment made to account for changes to efficacy data as a result of fewer patients receiving subsequent treatments in practice.

This alternative analysis shows the results are sensitive to relatively small changes in this parameter, which can be explained by the higher cost of subsequent treatments in the WW arm due to greater use of more costly immunotherapies. The ERG clinical advisor agreed

that the lower proportions used in this sensitivity analysis are closer to clinical practice and therefore should be included in the ERG preferred base case.

The treatments included post-progression were adjusted from the subsequent active treatments patients received in the JAVELIN Bladder 100 trial to closer reflect practice. In the WW arm, [redacted]% received a second-line anti-PD-1/PD-L1 treatment (not avelumab). In the avelumab arm, the majority received second-line chemotherapy with a small proportion ([redacted]) receiving second-line anti-PD-1/PD-L1 treatment. Some of the subsequent anti-PD-1/PD-L1 treatments in JAVELIN Bladder 100, namely nivolumab, pembrolizumab and durvalumab, are not routine second-line treatments in England and Wales. For the purposes of costing in the model an assumption is made that only atezolizumab is included as the second-line anti-PD-1/PD-L1 in the base case. A scenario analysis was conducted using the treatments used in the trial. See Table 23 for details.

Table 23. Subsequent anti-PD-1/PD-L1 treatments (base-case and scenario analysis) (source: Table B.3.21, Document B of the CS)

Treatment	Base case		Scenario analysis (JAVELIN Bladder 100)	
	Avelumab	Watchful waiting	Avelumab	Watchful waiting
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	-	-	[redacted]	[redacted]
Pembrolizumab	-	-	[redacted]	[redacted]
Durvalumab	-	-	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse Abbreviations: PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1; TA = technology appraisal

The ERG agree it is appropriate to assume that atezolizumab would be used for all anti-PD-1/PD-L1 treatment and to exclude nivolumab, pembrolizumab and durvalumab costs from the model. This also assumes these treatments are equally efficacious, which was considered an appropriate simplifying assumption. However, for the avelumab arm the ERG does not agree that patients would receive a second-line anti-PD-1/PD-L1 upon progression after avelumab maintenance based on clinical expert advice. As atezolizumab is another immunotherapy,

patients would not receive this or any other immunotherapy following avelumab maintenance in clinical practice but would instead receive chemotherapy.

The ERG's clinical expert explains that atezolizumab like avelumab is an humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%. It is not licenced nor has it been evaluated in patients previously treated with an alternative PD-L1 inhibitor. Given the shared mechanism of action treatment with atezolizumab following progression of disease on treatment with avelumab in an advanced disease setting is not expected to provide any significant benefit nor expected to improve the end points of overall survival.

Following clarification, the company provided an alternative scenario where the cost of atezolizumab is removed from the avelumab arm and patients are instead assumed to receive chemotherapies. Based on the ERG's clinical expert advice, the ERG therefore prefer the application of the company scenario to remove atezolizumab from the subsequent treatment basket in the avelumab arm with no further adjustment to OS outcomes. A comparison of the base case, JAVELIN Bladder 100 trial and the ERG preferred base case assumptions for costing subsequent treatments is provided in Table 24.

Table 24. Comparison of base case, trial and ERG preferred base case assumptions for subsequent treatment

Treatment	Company preferred base case		Scenario analysis (JAVELIN Bladder 100)		ERG preferred base case	
	Avelumab	Watchful waiting	Avelumab	Watchful waiting	Avelumab	Watchful waiting
Any subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapies						
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC chemotherapies						
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse Abbreviations: PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1; SoC = Standard of care; TA = technology appraisal.

The ERG preferred base case assumptions summarised in Table 24 are closer to clinical practice. However, no adjustment has been made to the model to account for the impact on efficacy of fewer patients receiving subsequent treatments or assuming no patients in the avelumab arm receive subsequent atezolizumab. Although the ERG considers it is unlikely that changing these parameters will have no impact on efficacy, the lack of alternative approach to account for this uncertainty means on balance it is reasonable to apply these.

4 COST EFFECTIVENESS RESULTS

4.1 Company's cost effectiveness results

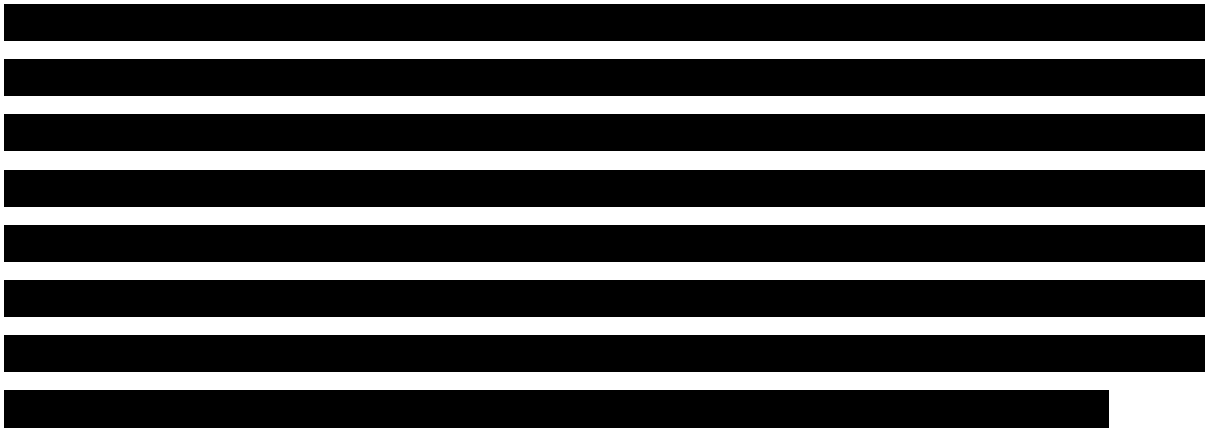
The company have presented an incremental cost-effectiveness analysis comparing avelumab vs. WW. The company's cost-effectiveness results include a PAS where the cost of avelumab is subject to a [redacted] simple discount. All reported ICERs are based on the agreed PAS price. The company preferred base case analysis remained unchanged after clarification queries, though the company did provide several additional analyses in response to ERG requests for clarification. The company preferred base case deterministic and probabilistic ICERs for avelumab versus WW are reported in Table 25.

Table 25. Company preferred base-case cost-effectiveness analyses

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company preferred base case deterministic ICER							
Avelumab	[redacted]	[redacted]	[redacted]				
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,245
Company preferred base case probabilistic ICER							
Avelumab	NR	NR	NR	[redacted]	[redacted]	[redacted]	£27,506
Watchful waiting	NR	NR	NR				

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; NR = Not Reported; QALY = quality-adjusted life year

Health state occupancy and time to treatment discontinuation under the company preferred base case assumptions are reproduced in Figure 4 below.



Abbreviations: BSC: Best Supportive Care (considered the same as watchful waiting by the company); PFS: Progression Free Survival; OS: Overall Survival; TTD: Time to Treatment Discontinuation

Figure 4. Company preferred results (reproduced from the company submitted economic model)

Disaggregated costs from the company model are reported in Appendix J of the CS (Table B.5.26), reproduced in Table 26 below. The disaggregated costs show that the main drivers of incremental costs are the additional avelumab treatment acquisition costs ( ), partially offset by reductions in subsequent treatment costs for progressed disease ( ).

Table 26. Disaggregated costs (reproduced from Table B.5.26, appendix J of the CS)

	Costs avelumab	Costs watchful waiting	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU: PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU: PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subs tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A summary of QALYs gained by health state are provided in Appendix J, Table B.5.28 of the CS. As expected, the main driver of QALY differences is the difference in PFS and OS between the model treatment arms. The ERG note that adverse events have little impact on either incremental costs or incremental QALYs and are less important in terms of determining the most appropriate ICER for decision making.

4.2 Company's sensitivity analyses

Deterministic and scenario analyses

The company conducted a comprehensive range of one-way deterministic sensitivity and scenario analyses. A tornado diagram illustrating the results of one-way sensitivity analyses for the 10 most influential model parameters shows that the most influential parameters in terms of the ICER are avelumab dose adjustment, and subsequent treatment acquisition costs (proportions and duration of treatment assumptions). Table B.3.33 of the CS shows the impact of 18 different scenario analyses on the ICER. In response to a clarification query from the ERG, the company reproduced these analyses providing further details of total costs, total QALYs by arm as well as incremental costs, QALYs and ICERs for completeness. These results are provided in Table 27 below.

Table 27. Results of company conducted scenario analyses (reproduced from Tables 4, 5, 7, 9, 10 & 13 of the company response to the ERG's clarification points)

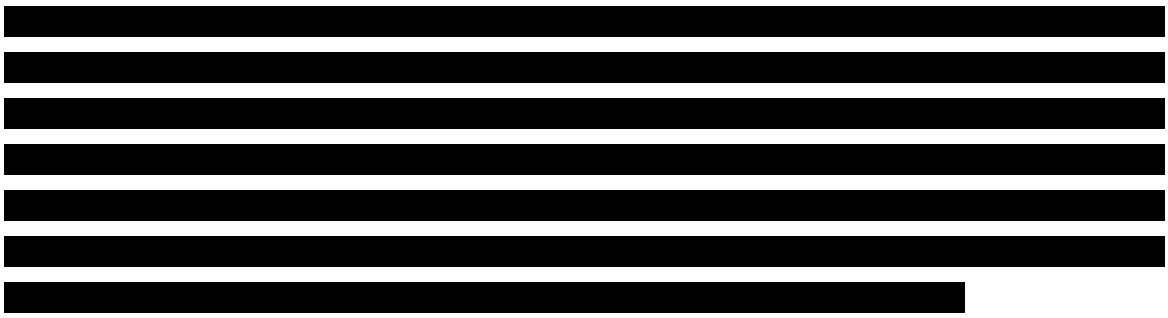
Analysis	Avelumab total			WW total			Incremental			
	Costs	Lys	QALY	Costs	LYs	QALY	Costs	LYs	QALY	ICER
Company preferred base case:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,245**
Scenario analyses conducted in the Company Submission (full results provided in response to clarification)										
10 year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,971
20 year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,961
0% discounting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,969
Log logistic OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,185
Lognormal OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,629
PFS: BICR (Gen gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,991
PFS: BICR (3-knot odds)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,750
PFS: BICR (3-knot hazard)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,677
PFS: INV (3-knot normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,069

Analysis	Avelumab total			WW total			Incremental			
	Costs	Lys	QALY	Costs	LYs	QALY	Costs	LYs	QALY	ICER
TTD: LN; no 2 year drop; stop @ 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,657
TTD: GG; 2 year drop to 5%; stop @ 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,317
TTD: LN; no 2 year drop; no stop @ 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,745
PFS/PPS utility: TA519	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,558
No utility age adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,144
No treatment wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,221
Resource use from TA272	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,747
Subs treatment: IOs not redistributed to atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,032
No avelumab dose adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,166
Additional scenario analyses provided in response to clarification queries										

Analysis	Avelumab total			WW total			Incremental			
	Costs	Lys	QALY	Costs	LYs	QALY	Costs	LYs	QALY	ICER
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,330
tx proportions: Avelumab ([redacted]%); WW ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,544
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,822
RDI: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,002
RDI: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,144

Abbreviations: BICR: blinded independent central review assessment of progression; GG: generalised Gamma; ICER = incremental cost-effectiveness ratio; INV: investigator assessed progression; IOs = immune-oncology; LL: log logistic; LN: Lognormal; LY = life-year; OS = overall survival; PFS: progression free survival; PPS: post progression survival; QALY = quality-adjusted life year; RDI = relative dose intensity; Subs tx : subsequent treatment; TA: technology appraisal; WW = watchful waiting.

In response to clarification queries, the company also provided a threshold analysis (Figure 5) showing the impact on the ICER of varying the cost savings from subsequent therapies. In the base case, the savings due to subsequent treatments are [redacted]. Note that in Figure 5, analysis 1 assumes 100% of patients in both arms receive subsequent treatment upon progression and analysis 3 uses the lower proportions described in section 3.2.8 ([redacted] and [redacted] for avelumab and WW respectively). Details of analysis 2 are not provided in the clarification response, but analysis conducted by the ERG where the proportion receiving subsequent treatments was assumed to reflect the SACT dataset (41.9%) increased the ICER to [redacted], which appears to reflect analysis 2 in Figure 5.



Abbreviations: ICER = incremental cost-effectiveness ratio

Figure 5. Threshold analysis on subsequent therapy cost savings (source: Figure 1, company's clarification response to question B2)

Probabilistic sensitivity analyses (PSA):

The company conducted a PSA, with 2000 sampling iterations, which was sufficient to achieve convergence and provide stable estimates of the ICER. Full details of the PSA parameters, sampling distributions and chosen sampling bounds are provided in Appendix L of the CS. The ERG are satisfied with the company's PSA approach and note that is an accurate representation of sampling uncertainty in the model. However, the ERG also note that the PSA results may not fully describe the uncertainty surrounding alternative combinations of assumptions surrounding treatment discontinuation and continued treatment effectiveness over time. Figures 6 and 7 below illustrate the PSA scatter plot and CEACs respectively for the company's base case analysis. The probability that avelumab is cost-effective at threshold values of WTP for a QALY gain of £20,000, £30,000 and £50,000 is [redacted]%, [redacted]% and [redacted]% respectively.

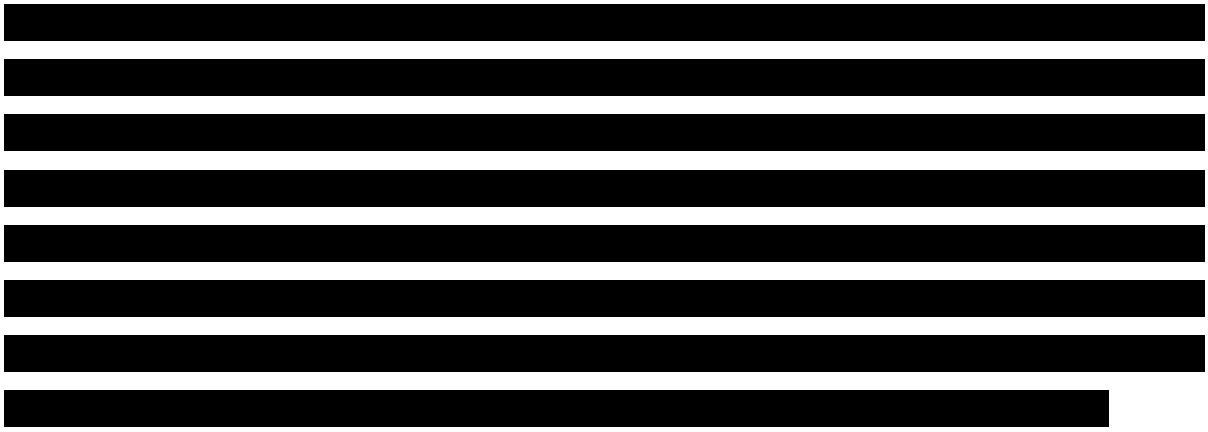


Figure 6. PSA scatter plot (source: Figure B.3.25 of the CS)

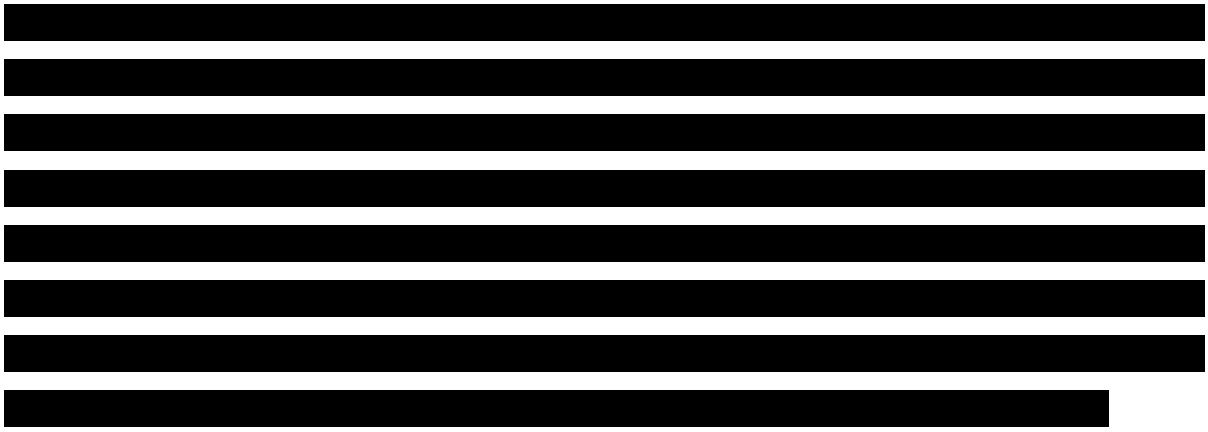


Figure 7. Cost-effectiveness acceptability curve (source: Figure B.3.26 of the CS)

Summary

The company conducted scenario analyses show that the ICER is most sensitive to assumptions about treatment discontinuation, the type of post-progression treatments received (immunotherapy or chemotherapy) and the proportion of patients receiving those post-progression therapies. These scenario analyses impact only on costs in the model and are assumed to have no implications for PFS, OS, life years or QALYs. The company analyses do not fully illustrate the uncertainty surrounding combinations of assumptions about treatment discontinuation rules and the duration of continued avelumab treatment benefit in terms of OS and PFS. The ERG conduct additional scenario analyses around these key assumptions in section 5.1 and 5.2.

4.3 Model validation and face validity check

The CS states that an advisory board meeting and one-to-one discussions with 8 practicing UK oncologists were used to consult on key model parameters, including long term OS and PFS outcomes for avelumab and watchful waiting as well as progression based utilities, resource use and duration of treatment with avelumab. However, the submission provides very little detail of how the discussions took place or exactly how parameters were elicited from the experts. Importantly, there is no mention in the CS as to whether the key assumption of early treatment discontinuation with no reduction in OS or PFS effectiveness of avelumab were discussed extensively and whether they were deemed clinically plausible. The ERG considers further clinical validation and explanation of this assumption to be important to resolve remaining uncertainty surrounding the most appropriate ICER for decision-making. The company also conducted an internal quality control check of the model.

The ERG has undertaken a range of further verification tests, based on an adaption of those proposed by Tappenden et al.[43] The results of these verification checks are provided in Table 28 below, applied to the company preferred base case analysis. The ERG further checked the company's survival functions and patient flow in the model for both treatment arms. The company model passed all the ERGs quality control checks.

Table 28 'Black box' verification checks conducted on the company submitted model (adapted for Part SA model)

Model component	Model test	Unequivocal criterion for verification	Issues identified
Clinical trajectory	Apply avelumab PFS and OS curve data as well as AE probabilities to the WW arm of the model	All treatments produce equal estimates of mean OS, PFS and total LYGs and total QALYs	None
	Sum health state occupancy at any model timepoint	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0, set all adverse event disutilities to 0, set discount rate QALY = 0[A]	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments & no impact on costs	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero for all treatments	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range $0 \leq x \leq 1$ etc.)	None
General	Set all treatment-specific parameters equal for all treatment groups (implemented by setting all avelumab parameters = WW parameters)	Costs and QALYs equal for all treatments	None
	Amend value of each individual model parameter*	ICER is changed	None

ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year
* Note this assumes that the parameter is part of the total cost function and/or total QALY function
[A] Note for this check, it is necessary to set the discount rate for QALYs = 0 because the model does not discount LYG projection

5 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the ERG

Following the critique of the CS from Chapter 3, the ERG have conducted several additional scenario analyses to further explore the impact of varying key assumptions on the ICER. Table 29 describes the additional analyses carried out.

Table 29. Description of additional analyses conducted by the ERG

#	Description of company base case assumption	Description of ERG change	Justification / Relevance	ERG report
1	PFS assessed by BICR	PFS assessed by investigator review, 3-knot hazard (avelumab) and 3-knot odds (WW)	INV assessment is more reflective of how progression is determined in clinical practice and more closely aligns with treatment decisions post-progression.	Section 3.2.6
2-13	**TTD:** drop to 5% @ 2yr, stop @ 5 years **Cap on duration of PFS & OS benefit:** - None	**TTD** - 5% @ 2yr, stop @ 5 yr. - No drop @ 2yr, stop @ 5 yr. - No drop @ 2yr, no stop @ 5 yr. **Cap on duration of PFS & OS benefit:** - None - 10 years - 5 years - 2 years	Several two-way scenario analyses to illustrate the impact of varying treatment discontinuation assumptions alone or in combination with different caps on the duration of PFS and OS benefit for avelumab.	Section 3.2.2

Abbreviations: BICR = blinded independent central review of progression; ERG: Evidence review group; INV = investigator assessed progression; OS = Overall survival; PFS = progression free survival; TTD = time to treatment discontinuation; WW = Watchful waiting.

5.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 30 describes the impact of the additional analyses on the cost-effectiveness findings. The ERG note that applying the ERG preferred assumption of INV assessment reduces the ICER for avelumab slightly. As noted in Section 3.2.2, the ERG question the validity of the company assumption that early treatment discontinuation (relative to estimates of treatment discontinuation obtained using survival curves fitted to the JAVELIN Bladder 100 trial data) has no impact on the duration of continued OS or PFS. The ERG are concerned that the company have not provided sufficient clinical validation or any supporting data to show that early treatment discontinuation can be achieved with no impact on treatment effectiveness (i.e. the continued duration of treatment benefit from avelumab). The ERG therefore consider the company preferred base case to represent an optimistic scenario for avelumab, where early discontinuation can reduce incremental costs but with no impact on LY or QALY gains.

Selecting an appropriate alternative assumption is difficult because treatment-stopping rules were not applied in the JAVELIN Bladder 100 trial and as such, there are no data to robustly estimate what, if any, decrement to treatment effectiveness would be appropriate if early discontinuation rules were applied in clinical practice. The ERG have therefore undertaken a range of different scenario analyses varying the treatment discontinuation / stopping rules at 2 and 5 years and applying treatment benefit caps for PFS and OS at 2, 5 and 10 years. Applying shorter durations of continued treatment benefit for avelumab increases the ICER substantially. The ERG accepts that some combinations from Table 30 may be less plausible. For example, it is unlikely that analyses 10-13 would represent a fair combination of assumptions for avelumab because PFS and OS benefit would be capped before all treatment had ceased. Therefore, a plausible range for the ICER might be somewhere between £29,245 (most optimistic company base case) and £68,804 (less optimistic assumptions).

Table 30 Impact of additional ERG analysis on the ICER

#	Analysis		Avelumab total			WW total			Incremental			
			Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
BC	**Company preferred base case:**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,245**
1	PFS – INV, 3-knot hazard (avelumab) & 3-knot odds (WW)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,159
Scenarios around duration of continued treatment benefit, with alternative treatment discontinuation rules for avelumab												
	Duration of continued treatment benefit:	**TTD assumptions**										
2	As per treatment specific PFS and OS curves	5% @ 2yrs, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,245
3		No 2 yr drop, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,657
4		No 2 yr drop, No stop @ 5yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,745
5	No additional benefit beyond 10 years	5% @ 2yrs, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,361

6		No 2 yr drop, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,187
7		No 2 yr drop, No stop @ 5yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,094
8	No additional benefit beyond 5 years	5% @ 2yrs, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,545
9		No 2 yr drop, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,804
10		No 2 yr drop, No stop @ 5yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,801
11	No additional benefit beyond 2 years	5% @ 2yrs, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£115,734
12		No 2 yr drop, stop @ 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£156,227

13		No 2 yr drop, No stop @ 5yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£186,724

Abbreviations: BC = Base case; ICER = incremental cost-effectiveness ratio; INV = investigator assessed progression; LY = Life years; OS = Overall survival; PFS = progression free survival; QALY: Quality adjusted life year; WW = Watchful waiting

5.3 ERG's preferred assumptions

The ERGs preferred assumptions are the same as the company's except for the following amendments:

1. LN survival curves for OS for both avelumab and WW. The ERG prefer LN curves because they have the best statistical fit to the KM OS for avelumab, the best BIC and second best AIC for WW. Furthermore, they provide a good visual match to the KM data for both arms, and they predict 5 and 10 year OS estimates for WW that are closer to the mid-point of the company's clinical expert expectations (5 year OS: 10.71%, 10 year OS: 2.90%) than the company preferred generalised gamma.

2. PFS measured according to INV assessment, parameterized using a 3-knot hazard and 3-knot odds model for avelumab and WW respectively. The ERG prefer this approach as opposed to the company base case BICR assessment because it more closely reflects decision making (e.g. regarding the initiation of post-progression therapies) in UK clinical practice.

3. Generalised gamma extrapolation curves for TTD between years 2 and 5. The ERG prefer this assumption because the company base case already over-rides the TTD curves, dropping the proportion on treatment from about [redacted]% to 5% at 2 years. The ERG therefore feel that the company has preferred a LN curve that over estimates the proportion ceasing treatment between years 2 and 5. In addition, the generalised gamma is the best statistical and visual fit to the KM data.

4. Based on the ERG clinical expert's advice, the ERG prefers the company scenario analysis that applies lower subsequent treatment proportions for avelumab ([redacted] and WW ([redacted] calculated as an average of the subsequent treatment proportions in the SACT dataset and JAVELIN Bladder 100 trial.

5. Remove atezolizumab treatment from the post-progression treatment distribution in the avelumab arm and re-distribute the [redacted] of patients to the

SOC chemotherapies because another immune-oncology treatment would not be used following avelumab in UK clinical practice.

Table 31 describes the impact of each of the ERG preferred assumptions on the ICER and the cumulative impact of these to generate the ERG preferred base case analysis. The ERG preferred investigator assessment for PFS and removal of atezolizumab from the avelumab arm reduce the ICER compared to the company preferred base case assumptions. The remaining scenarios lead to minor (scenarios 1 and 3) or moderate (scenario 4) increases in the ICER. The ERG preferred analysis with the greatest impact on the ICER is adjusting the proportion of patients who would receive subsequent treatment post progression. The combined impact of the ERG's preferred assumptions on the ICER is an increase to £34,802, compared to £29,245 in the company base case. The ERG preferred probabilistic ICER is £33,463 and illustration of the uncertainty in the results can be found in figures 8 and 9 reporting results using scatter plots of the cost-effectiveness plane and cost-effectiveness acceptability curves respectively. Under the ERG's preferred set of assumptions, the probability that avelumab is cost-effective at £20,000, £30,000 and £50,000 per QALY gained is [redacted]%, [redacted]% and [redacted]% respectively.

Table 31. Impact of ERG preferred assumptions on the ICER

#	Analysis	Avelumab total			WW total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
Company preferred base case:		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,245**
1	LN OS curves for Avelumab and WW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,629
2	INV assessed PFS (Avelumab: 3-knot hazard; WW: 3-knot odds)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,159
3	TTD between yrs 2-5 (generalized gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,317
4	Reduced proportions on subsequent treatment: avelumab ([redacted]%); WW ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,543
5	Remove atezolizumab from the avelumab arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,822
ERG preferred base case (1-5) (deterministic)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,802
ERG preferred base case (1-5) (probabilistic)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,463**

Abbreviations: ICER = incremental cost-effectiveness ratio; INV = investigator assessed progression; LN = lognormal; LYs = life years; OS = Overall survival; PFS = progression free survival; QALYs = Quality adjusted life years; TTD = time to treatment discontinuation; WW = Watchful waiting

Figure 8. PSA scatter plot - ERG preferred assumptions (source: reproduced from the company economic model)

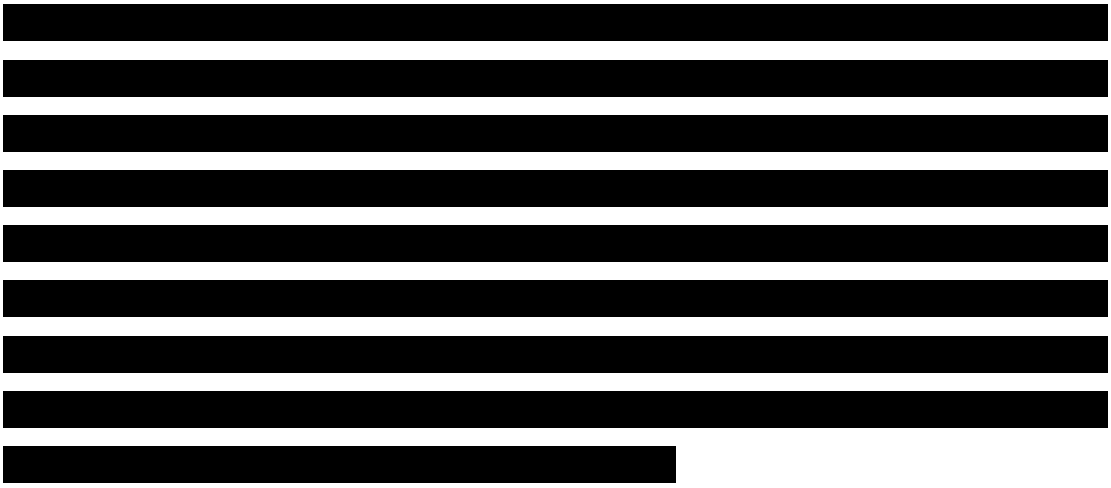


Figure 9. Cost-effectiveness acceptability curve - ERG preferred assumptions (source: reproduced from the company economic model)

Table 32 provides the results of two-way scenario analyses varying treatment discontinuation assumptions and applying different caps on the duration of continued avelumab treatment PFS and OS benefit. Excluding less plausible scenarios where duration of treatment benefit is less than maximum treatment duration, the ERG consider a plausible range of ICERs to lie between £34,802 and £81,150 per QALY gained.

Table 32. Two-way scenario analyses of treatment discontinuation and duration of continued treatment effect applied to the ERG preferred ICER

Continued treatment effect assumption	Treatment discontinuation assumption								
	Drop to 5% @ 2yrs, stop @ 5 yrs			No 2 yr drop, stop @ 5 yrs			No 2 yr drop, No stop @ 5yrs		
	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER
As per treatment specific PFS and OS curves	[redacted]	[redacted]	£34,802	[redacted]	[redacted]	£49,048	[redacted]	[redacted]	£70,802
No additional benefit beyond 10 years	[redacted]	[redacted]	£40,656	[redacted]	[redacted]	£57,485	[redacted]	[redacted]	£78,622
No additional benefit beyond 5 years	[redacted]	[redacted]	£57,069	[redacted]	[redacted]	£81,150	[redacted]	[redacted]	£110,835
No additional benefit beyond 2 years	[redacted]	[redacted]	£133,457	[redacted]	[redacted]	£191,634	[redacted]	[redacted]	£263,349

Abbreviations: ICER = incremental cost-effectiveness ratio; OS = Overall survival; PFS = progression free survival; QALYs = Quality adjusted life years;

5.4 Conclusions of the cost effectiveness section

The ERG agree that the company's chosen PartSA model structure is appropriate for modelling the cost-effectiveness of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy compared with watchful waiting. The key drivers of cost-effectiveness in the economic model are:

- The treatment acquisition costs for avelumab, and in particular time to treatment discontinuation
- PFS and OS benefit for avelumab vs. WW, informed by extrapolations of time to event data from the JAVELIN Bladder 100 trial.
- The proportion of patients receiving immunotherapy and chemotherapy treatments post progression in both arms of the models and the types of treatments used.
- The duration of continued treatment benefit for avelumab vs. WW after treatment discontinuation

The ERG preferred base case ICER is slightly higher than that preferred by the company. However, the greatest uncertainty lies in the most appropriate combination of assumptions around treatment duration with avelumab and duration of continued treatment PFS and OS benefit. Both the company and ERG base case analyses assume that 95% of patients discontinue treatment at 2 years and all stop by 5 years. The discontinuation assumptions applied in the model indicate a substantially high proportion of patients discontinuing treatment compared to in the JAVELIN Bladder 100 trial. However, no adjustment is made to the fitted OS and PFS survival curves to reflect the potential that early discontinuation of treatment might be associated with reduced effectiveness compared to that modelled based on trial data. Whilst the early treatment discontinuation assumptions are likely to be reflective of UK clinical practice use of avelumab, the resultant ICERs, which have no adjustment to effectiveness parameters, might be considered optimistic for avelumab. The ERG believe that further data is required to justify these assumptions, or at the very least, a detailed clinical explanation as to why early treatment discontinuation would be possible without any reduction in the duration of continued treatment benefit with avelumab.

6 END OF LIFE

Section B.2.13.3 and Table B.2.25 of the CS make the case that avelumab meets the NICE criteria for end of life care. The NICE methods guide states that end of life considerations may apply when:

i. "**The treatment is indicated for patients with a short life expectancy, normally less than 24 months".** The company provide three sources of evidence to show that life expectancy is less than 24 months, ranging from 9.3 to 18.5 months across several different studies. Furthermore, a study of adult patients diagnosed with Stage III-IV UC in England between 2013 and 2017 showed median OS of [redacted] months (95% CI: [redacted] to [redacted] months). Specifically to this appraisal, the JAVELIN Bladder 100 trial reported median OS of 14.3 (12.9 to 17.9) months for the BSC arm. However, mean OS from the JAVELIN Bladder 100 trial was not provided within the submission. The ERG notes that the economic model predicts mean OS of 35.4 months (median: 15.9 months) and mean OS of 27.82 months (median = 15.6 months) under the company and ERG preferred base case analyses respectively. Whilst the ERG preferred model generates lower mean OS for the WW arm, the estimate remains slightly above the 24 months specified in the NICE criteria. A judgement call is therefore required as to whether avelumab satisfies the first criteria for end of life consideration, but on balance the ERG consider it plausible that criteria 1 is met.

ii. **"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".** Section B.2.6.1.2 of the CS reports an unadjusted improvement in median OS of 7.1 months for avelumab + BSC compared to BSC alone. The economic model predicts an increase in mean OS of 12 months (median = 6.9 months) and mean OS of 11.4 months (median = 6.7 months) under the company and ERG preferred base case assumptions respectively. The ERG therefore agree with the company that avelumab clearly meets the 2nd criteria for end of life consideration as it increases OS by more than 3 months.

7 References

1. Cancer Research UK. Bladder cancer incidence statistics 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence.

2. National Cancer Registration and Analysis Service. TNM stage group by CCG by tumour type for 10+3 tumour types, 2012-2017. 2019. Available from: http://www.ncin.org.uk/publications/survival_by_stage.

3. Boustead GB, Fowler S, Swamy R, Kocklebergh R, Hounsome L. Stage, grade and pathological characteristics of bladder cancer in the UK: British Association of Urological Surgeons (BAUS) urological tumour registry. BJU Int. 2014;113(6):924-30.

4. Metts MC, Metts JC, Milito SJ, Thomas CR, Jr. Bladder cancer: a review of diagnosis and management. J Natl Med Assoc. 2000;92(6):285-94.

5. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics. 2003;21(18):1315-30.

6. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management [NG2] 2015. Available from: https://www.nice.org.uk/guidance/ng2.

7. European Association of Urology. Non-muscle-invasive bladder cancer (TaT1 and CIS) 2018. Available from: https://uroweb.org/wp-content/uploads/EAU-Guidelines-Non-muscle-invasive-Bladder-Cancer-TaT1-CIS-2018.pdf.

8. European Association of Urology. Muscle-invasive and metastatic bladder cancer 2018. Available from: https://uroweb.org/wp-content/uploads/EAU-MIBC-Guidelines-2018V2.pdf.

9. Cancer Research UK. Bladder cancer 2018 updated 2018. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/types-stages-grades/types.

10. American Cancer Society. What is bladder cancer? 2019. Available from: https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html.

11. Yaxley JP. Urinary tract cancers: An overview for general practice. J Family Med Prim Care. 2016;5(3):533-8.

12. Northern Ireland Cancer Registry. Cancer incidence, prevalence and survival statistics for Northern Ireland: 1993-2017. Bladder cancer (C67) 2019. Available from: https://www.qub.ac.uk/research-centres/nicr/CancerInformation/official-statistics/BySite/bladder/.

13. Yu XQ, Baade PD, O'Connell DL. Conditional survival of cancer patients: an Australian perspective. BMC Cancer. 2012;12:460.

14. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2016 Bethesda, MD: National Cancer Institute; 2019. Available from: https://seer.cancer.gov/csr/1975_2016/.

15. National Institute for Health and Care Excellence. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA492] 2018. Available from: https://www.nice.org.uk/guidance/ta492.

16. National institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA522] 2018. Available from: https://www.nice.org.uk/guidance/ta522.

17. National Institute for Health and Care Excellence. Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy: Final scope [Data on file]. London/Manchester: National Institute for Health and Care Excellence; 2020.

18. Merck Europe BV. Bavencio (avelumab) summary of product characteristics. 2020.

19. Medicines Complete. British National Formulary London: Royal Pharmaceutical Society; 2018. Available from: https://www.medicinescomplete.com/mc/bnf/current/index.htm.

20. Medicines and Healthcare Products Regulatory Agency. Avelumab in the treatment of bladder cancer 2020. Available from: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-avelumab-in-the-treatment-of-bladder-cancer.

21. National Institute for Health and Care Excellence. Avelumab with axitinib for untreated advanced renal cell carcinoma [TA645] 2020. Available from: https://www.nice.org.uk/guidance/ta645/.

22. Merck–Pfizer Alliance. Urothelial cancer virtual UK advisory board (2 July 2020): Meeting report. [Data on file]. 2020.

23. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care. University of York: 2009. Available from: URL: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm.

24. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020;383(13):1218-30.

25. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000;18(17):3068-77.

26. Pfizer. JAVELIN Bladder 100 (Study B9991001): Interim Clinical Study Report [Data on file]. 2020.

27. Powles T, Kopyltsov E, Su P, Parnis F, Park S, Yamamoto Y, et al. 745P - Patient-reported outcomes (PROs) from JAVELIN Bladder 100: Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma (UC). Ann Oncol. 2020;31:S550-S.

28. Fung C, Pandya C, Guancial E, Noyes K, Sahasrabudhe DM, Messing EM, et al. Impact of bladder cancer on health related quality of life in 1,476 older Americans: a cross-sectional study. J Urol. 2014;192(3):690-5.

29. Smith AB, Jaeger B, Pinheiro LC, Edwards LJ, Tan HJ, Nielsen ME, et al. Impact of bladder cancer on health-related quality of life. BJU Int. 2018;121(4):549-57.

30. Roychowdhury DF, Hayden A, Liepa AM. Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol. 2003;21(4):673-8.

31. National Institute for Health and Care Excellence. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract [TA272] 2013. Available from: https://www.nice.org.uk/guidance/ta272.

32. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA519] 2018. Available from: https://www.nice.org.uk/guidance/ta519.

33. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525] 2018. Available from: https://www.nice.org.uk/guidance/ta525.

34. National Institute for Health Care Excellence. Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy [TA530] 2018. Available from: https://www.nice.org.uk/guidance/ta530.

35. National Institute for Health and Care Excellence. Final appraisal document: Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinumcontaining chemotherapy 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10466/documents/final-appraisal-determination-document.

36. National Institute for Health and Care Excellence. Final appraisal determination: Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinumcontaining chemotherapy 2018. Available from: https://www.nice.org.uk/guidance/ta525/documents/final-appraisal-determination-document.

37. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.

38. Dolan P. Aggregating health state valuations. J Health Serv Res Policy. 1997;2(3):160-5.

39. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Sheffield: NICE Decision Support Unit; 2013. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf.

40. Curtis L. Unit Costs of Health and Social Care 2017. Canterbury: Personal Social Services Research Unit.; 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/.

41. NHS England. National Cost Collection for the NHS. Available from: https://www.england.nhs.uk/national-cost-collection/.

42. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015;29(10):899-907.

43. Tappenden P, Chilcott JB. Avoiding and identifying errors and other threats to the credibility of health economic models. Pharmacoeconomics. 2014;32(10):967-79.

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ERG report – factual accuracy check and confidential information check

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

'*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 Monday 4 January 2021** 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 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Section 1.3 – page xvi. Incorrect spelling of the name of the avelumab RCT (randomised controlled trial).	The correct name of the trial is Javelin Bladder 100.	Correct name of the avelumab RCT.	We accept the proposed minor amendment and have revised the report accordingly.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Table 10 – page 4. Incorrect spelling of the name of the avelumab RCT (randomised controlled trial).	The correct name of the trial is Javelin Bladder 100.	Correct name of the avelumab RCT.	We accept the proposed minor amendment and have revised the report accordingly.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Table 10 – page 6. The ERG report states: "*Evidence submitted by the company (JAVELIN Bladder 100) used a weight-based dose at 10 mg/kg with a mean dosage of 724 mg and 752 mg for the avelumab and BSC groups, respectively*." This is inaccurate as the BSC arm	The sentence should state: Evidence submitted by the company (JAVELIN Bladder 100) used a weight-based dose at 10 mg/kg with a median dosage of 724 mg and a mean dosage of 752 mg for the avelumab +BSC arm.	To accurately reflect mean and median dosage used in the CS as well as that a mean dosage for the BSC arm was not included in the CS.	We accept the proposed amendment and have revised the report accordingly.

was not treated with avelumab and therefore does not have a mean dosage. Instead the dosage of 724 mg refers to a median value and the dosage of 752 mg is a mean value. The CS states in page 57 of 124 (Document B): "*In JAVELIN Bladder 100, patients treated with avelumab + BSC had a median weight at baseline of 72.4 kg, and a mean weight of 75.2 kg (equating to a dosage of 724 mg, and 752 mg, respectively).*"			

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Section 2.2.3 – page 22 and Table 16 page 22. The ERG report states: "*Although the study was not powered to identify a clinical benefit in patients with PD-L1-negative tumours, the company states that positive outcomes were still observed for patients in the avelumab + BSC arm (n =*	Change "*N=131*" to "N=132" as per the Javelin Bladder 100 CSR.	To accurately capture the Javelin Bladder 100 data.	The statement in the ERG report reflects what is reported on page 83 of Appendix E.1.2 and presented in Tables B.5.14, B.5.15, B.5.16 of the same Appendix, which show a sample size of 131, not 132, for the BSC control arm. However, as the company have now requested to change N=131 to N=132, we have revised our

139) compared to the BSC arm (N = 131) (Appendix E.1.2.2)" There is a typing error in the CS regarding the PD-L1-negative BSC sample size. The Javelin Bladder 100 CSR reports N=132 for the BSC arm.			report accordingly.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Section 2.2.3 – Table 16 PD-L1-positive BSC arm sample size is incorrect.	Should change PD-L1-positive BSC arm sample size from "*N=139*" to N=169.	To accurately capture the Javelin Bladder 100 data.	We accept the proposed amendment and have revised the report accordingly.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Section 3.2.2 – page 34. The ERG report states: "*The ERG's clinical expert notes that 2-year stopping rules are common for immunotherapy treatments for cancer, and that applying stopping rules as per the company's economic model would be acceptable in UK clinical practice*." The company would like to clarify	Suggest changing "*and that applying stopping rules as per the company's economic model…*" to "and that applying treatment discontinuation assumptions as per the company's economic model…"	Accurate terminology of the treatment discontinuation assumptions included in the CS economic model.	We accept the proposed minor amendment and have revised the report accordingly.

that the company's economic model does not apply a 2-year stopping rule. In JAVELIN Bladder 100, no formal stopping rule was mandated, and continued treatment was at the discretion of the investigator. However, in clinical practice, it is anticipated that treatment for the majority of patients will have been discontinued by 2 years. Therefore, the company base-case analysis assumes that by 2 years, 95% of patients will have discontinued treatment. The remaining 5% of patients are then assumed to follow the pattern of discontinuation per the selected parametric model, before discontinuing at a maximum of 5 years. The treatment discontinuation assumptions were introduced in the CS in order to better reflect what happens in clinical practice in the UK.			

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Friday 12 February 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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.

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.

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)	**Merck Serono/Pfizer Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Health-related quality of life data	**Yes (Analysis of utility data from JB100)**	***The ERG accept that the use of progression-based utility values pooled across treatment arms is the most appropriate method, but would appreciate a greater level of data regarding quality of life outcomes (especially EQ-5D-5L) from the trial (by treatment arm and progression status) to instil greater confidence in the company base-case parameter inputs. The ERG would also welcome some further explanation regarding the potential inconsistencies between a lack of observed quality of life benefit for avelumab, in light of the PFS benefit observed in the trial.*** Table 1 below presents the mean utility in the progression-free and disease progression states predicted by the EQ-5D utility model including progression for avelumab + best supportive care (BSC) and BSC (Watchful Waiting (WW)) treatment arms. The mean progression-free health state utilities based on the EQ-5D utility model including progression were slightly higher in the avelumab arm; [redacted] and [redacted] in the avelumab + BSC and BSC arm, respectively. We note that the ERG questioned whether there was a utility benefit for avelumab in the PFS health state given the PFS benefit seen in the Javelin Bladder 100 study (JB100), the results below show that there is an observed utility benefit in the avelumab arm. The mean progressed health state utilities were lower in the avelumab + BSC arm ([redacted]) than in the BSC arm ([redacted]).

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Table 1: Estimated Mean EQ-5D-3L Utility Scores (mapped from EQ-5D-5L using the van Hout algorithm)

Health states	Number of Patients	Number of Observations	Mean EQ-5D	SE	95% LCI	95% UCI
Avelumab + BSC						
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC						
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D = EuroQoL-Five Dimensions; LCI = lower confidence interval; SE = standard error; UCI = upper confidence interval

On balance, while there is some evidence to suggest that utility may be higher for avelumab patients versus WW patients within the progression-free health state, it was considered reasonable for the purpose of informing the model to pool the utility values across treatment arms.

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<td>Key issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)</td>
<td>No</td>
<td>

The company could have provided a greater level of detail regarding how clinical expert opinion was derived, how questions were posed to the panel of experts and what methods were used to identify ranges of expected 5- and 10-year OS for both the WW and avelumab arms.

Eight consultant oncologists specialising in the treatment of advanced urothelial cancer from various hospitals in the UK were consulted for this appraisal in August 2020 to support the modelling for PFS and OS. The oncologists were asked to provide an estimate of OS at 5 and 10 years with current standard of care and with avelumab maintenance for patients who have achieved at least stable disease to first-line platinum-based chemotherapy and have not yet progressed. Notably, this is not the same as considering OS for a first-line population as non-responders are excluded.

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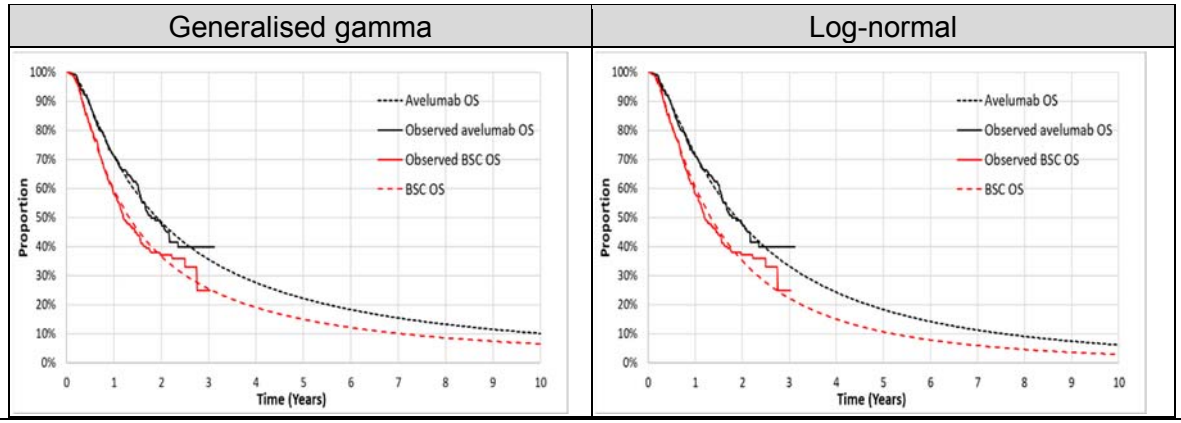
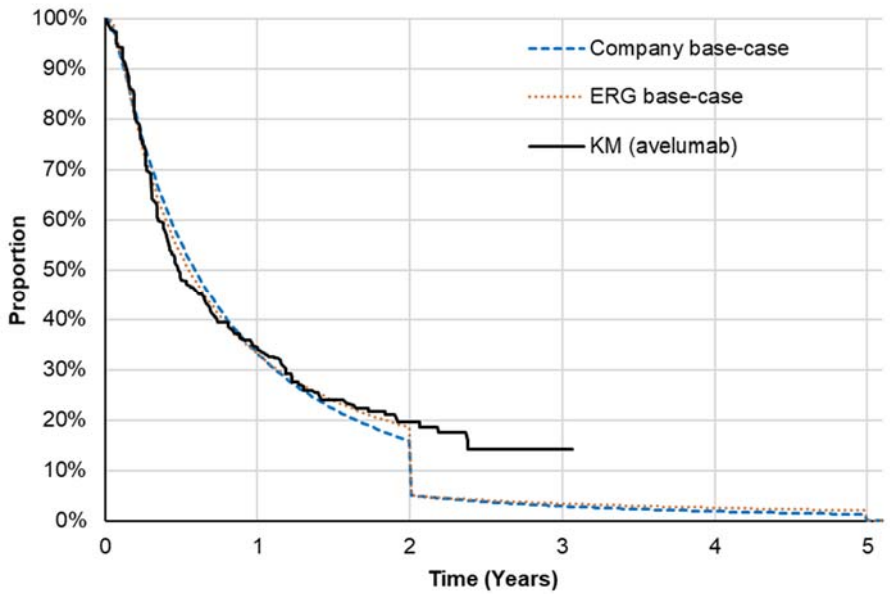
		Feedback from clinicians suggested that 5-year OS for patients managed with avelumab maintenance is expected to be between 20% and 30%, and 10-year OS is expected to be in the region of 10–15%. For the watchful waiting arm, clinicians suggested that 5-year OS is expected to be in the region of 5–15%, and that 10-year OS could be between 2% and 7%, with an estimate of 10% considered extremely optimistic. ***The ERG consider the company has chosen OS extrapolation curves (generalised gamma parametric survival curves) that may over-estimate overall survival for both the avelumab and WW arms of the model.*** The generalised gamma model was considered the most suitable extrapolation to inform the avelumab arm, based on it being the only model to provide an estimate of 10-year survival within the bounds estimated by UK consultant oncologists. Furthermore, the AIC difference compared to the statistically best fitting model is less than two which demonstrates that the best fitting and second best-fitting models are essentially equivalent in terms of statistical goodness of fit to the observed data. However, the log-normal model provides a 10-year OS estimate of 6.18% which is less than half the mid-point of the estimated range provided by the 8 KOLs. For the watchful waiting arm, the generalised gamma model provided the best AIC score, and the second-best BIC score, a good visual fit to the Kaplan-Meier curve, and a clinically plausible extrapolation. We accept that the generalised gamma may be considered optimistic for WW and note that the estimates of 5- and 10-year OS (15.00% and 6.48%, respectively) are closer to the upper bounds suggested by the clinicians. We accept that both the generalised gamma and log-normal models may be helpful to consider in decision making, but our revised base-case analysis considers the use of the lognormal model, aligned with the ERG's preferred base-case setting, given the similarities in projections.

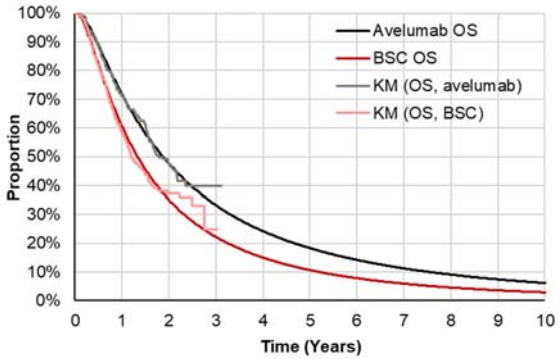
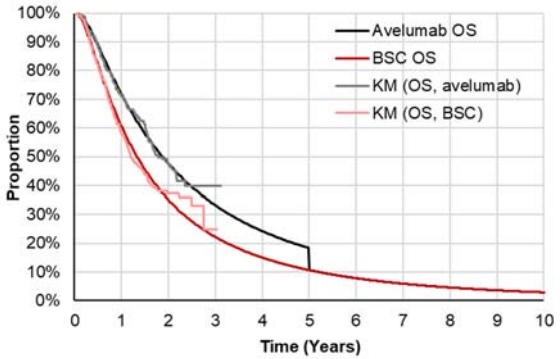
		Figure 1: Comparison of Company- and ERG-preferred extrapolations of overall survival 
Key issue 3: Definition of progression (BICR vs. INV)	**Yes (Clinical expert opinion)**	***The ERG believes that the company have provided all the necessary data in their submission document, but further clinical opinion regarding the relative advantages and disadvantages of using BICR vs. INV assessment would have been helpful to resolve this issue.*** Two estimates of progression are available for consideration within the economic analysis: (a) blinded independent central review (BICR) defined progression, and (b) investigator assessed (INV) defined progression. In our original submission, BICR-defined progression was considered in the base-case analysis. This was based on the expectation that BICR-defined progression would minimise the risk of bias in the JAVELIN Bladder 100 trial (see CS Table B.2.7). However, INV-assessed progression was explored as a sensitivity analysis (see CS Section B.3.3.3.2) for completeness. The implications of BICR- and INV-assessed progression are related to the context to which they are applied. With this in mind, eight consultant oncologists from various hospitals in the UK were consulted individually to inform this technical engagement response. Please find a summary of this clinician feedback in the additional evidence submitted alongside this response (Additional Evidence Appendices). All of the clinicians consulted agreed with the feedback received by the ERG that INV-assessed PFS does better reflect how progression is

		determined in clinical practice. In light of this feedback, we accept the ERG's view that INV-defined progression is more likely to be a better representation of how progression would be assessed in NHS practice, and so we support the use of INV-defined progression within the base-case analysis.
Key issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	**Yes (Clinical expert opinion and treatment waning effect scenarios included in additional evidence appendices)**	***The ERG accept that the treatment discontinuation rules are reasonable and reflective of UK clinical practice, but prefer the use of the generalised gamma survival curve to estimate treatment discontinuation between years 2 and 5 (better fit to the KM data and allow a slower rate of discontinuation).*** In our base-case analysis, a log-normal model was fitted to time-to-treatment-discontinuation (TTD) data from the JAVELIN Bladder 100 trial up until a timepoint of 2 years. At 2 years, it was assumed that 95% of patients would have discontinued treatment with avelumab (due to disease progression, toxicity, patient choice etc.). Although in clinical practice, it is anticipated that treatment for the majority of patients will have been discontinued by 2 years, no formal stopping rule was mandated in JB100, and continued treatment was at the discretion of the investigator. This expectation was echoed in clinical advice provided to NICE as part of its previous assessment of avelumab in MCC and RCC, wherein clinical advisers explained that for many immunotherapies used in other diseases, when there is a durable response and patients remain well, treatment tends to be stopped by 2 years for the majority of patients (1). The remaining 5% of patients on treatment at 2 years in our analysis were then assumed to follow the pattern of discontinuation per the selected parametric model until year 5. At 5 years, it was assumed that 100% of patients would have discontinued avelumab, as UK consultant oncologists considered it highly unlikely that patients would continue treatment beyond this point. This resulted in the extrapolation provided in CS Figure B.3.21 but reproduced in Figure 2 below for comparison with the ERG's method. The ERG applied the same TTD assumptions at 2 and 5 years after the start of treatment when the majority, and all, patients discontinue respectively. The difference, however, is the ERG have opted for use of a generalised gamma model to inform the rate of discontinuation. A

		comparison of the extrapolations is provided in Figure 2 for context. Both extrapolations yield similar estimates of TTD over time. ***Figure 2: Comparison of Company- and ERG-preferred extrapolations of time to treatment discontinuation***  Both the company's and ERG's extrapolations of TTD reflect an expectation that the majority of patients will have discontinued treatment by 2 years, while also acknowledging that some patients (in this case, 5%) may continue receiving maintenance therapy after 2 years. We believe that the log-normal is the most suitable model for TTD as it exhibited a good visual and statistical fit to the Kaplan-Meier curve (second-best AIC and BIC score), whilst providing the lowest proportion of patients on treatment at 5 years (4%, prior to adjustment at 2 years) of the models, whereas the generalised gamma predicts a relatively large proportion of patients remaining on treatment at 5 years (7.5%, prior to adjustment at 2 years). As such, we believe that the log-normal model for TTD should be used to inform the base-case analysis as it

		presents the best fit to both the Kaplan-Meier curve and the clinical input received about the long-term treatment duration. ***The ERG would appreciate a consideration of any real-world data the company may have, or any evidence from the literature to support the company assumption that discontinuing treatment early would have no impact on effectiveness (OS and PFS) outcomes. If such data or literature are not available, at the very least, some detailed clinical explanation as to why the assumptions are justified would be beneficial in supporting the company's base-case assumptions and reducing uncertainty surrounding the ICER*** In the ERG's additional analyses, a range of scenarios are presented concerning "*treatment benefit caps*" for the outcomes of PFS and OS at 2, 5 and 10 years. It is our understanding that the intention of these analyses is to establish the impact on the ICER when assuming no further beneficial effects of avelumab as maintenance therapy on the main two clinical outcomes used within the model (i.e., OS and PFS) after a specific point in time. An important limitation of the ERG's model is the method used to apply this cap. Rather than adjusting the treatment effect of avelumab in terms of the ratio of the hazards between the arms, the ERG assumed the avelumab curve was identical to the WW curve after the cap time. This results in a sudden spike in the hazard function occurring at the cap time (in the example below, at 5 years) such that there is a very sharp drop in the avelumab survival curves and an immediate loss of treatment effect, with ~8% of patients instantly dying. This is demonstrated in Figure 3, using the ERG's preferred base-case analysis of log-normal models for the outcome of OS and applying the cap at 5 years.

Figure 3: ERG's application of treatment benefit cap

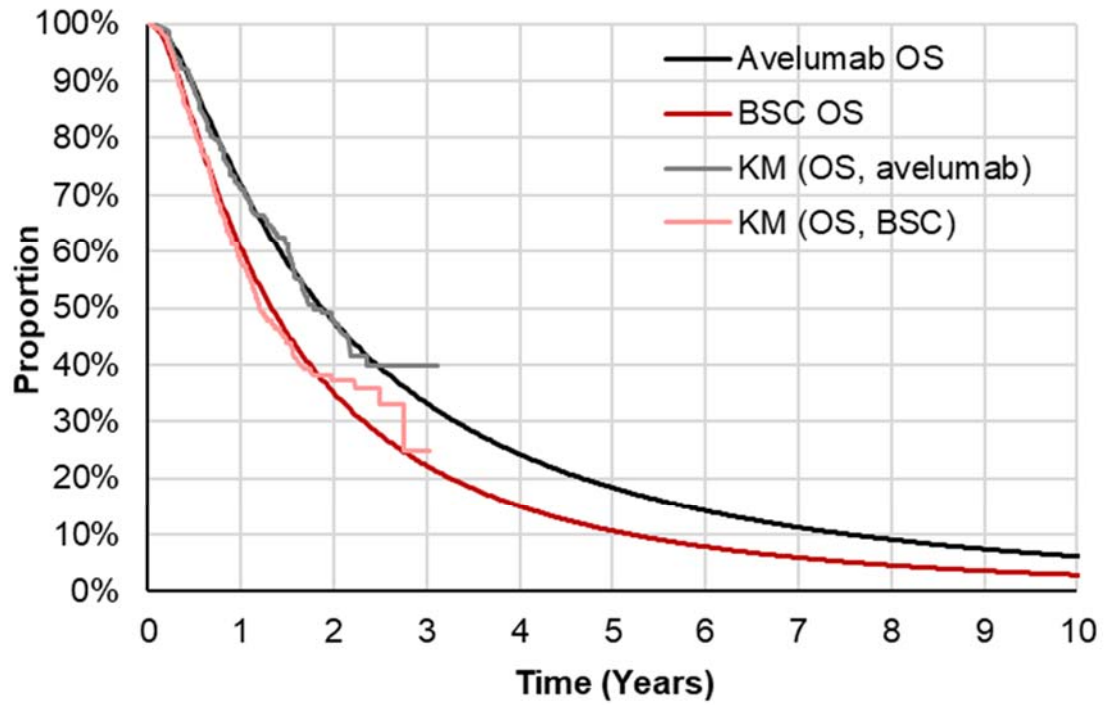
No cap applied	Cap applied at 5 years
	

It is our view that this approach, which is inconsistent with established methodology used in previous IO appraisals, is clinically implausible and inappropriate to inform decision making. As an alternative, we propose that the hazard of death for avelumab patients be set equal to that of the WW arm at the cap time. This would have the effect of assuming no additional benefit in terms of the hazard of death, but without assuming a sharp drop in survival itself. This method has been considered and accepted by NICE committees previously (2-5).

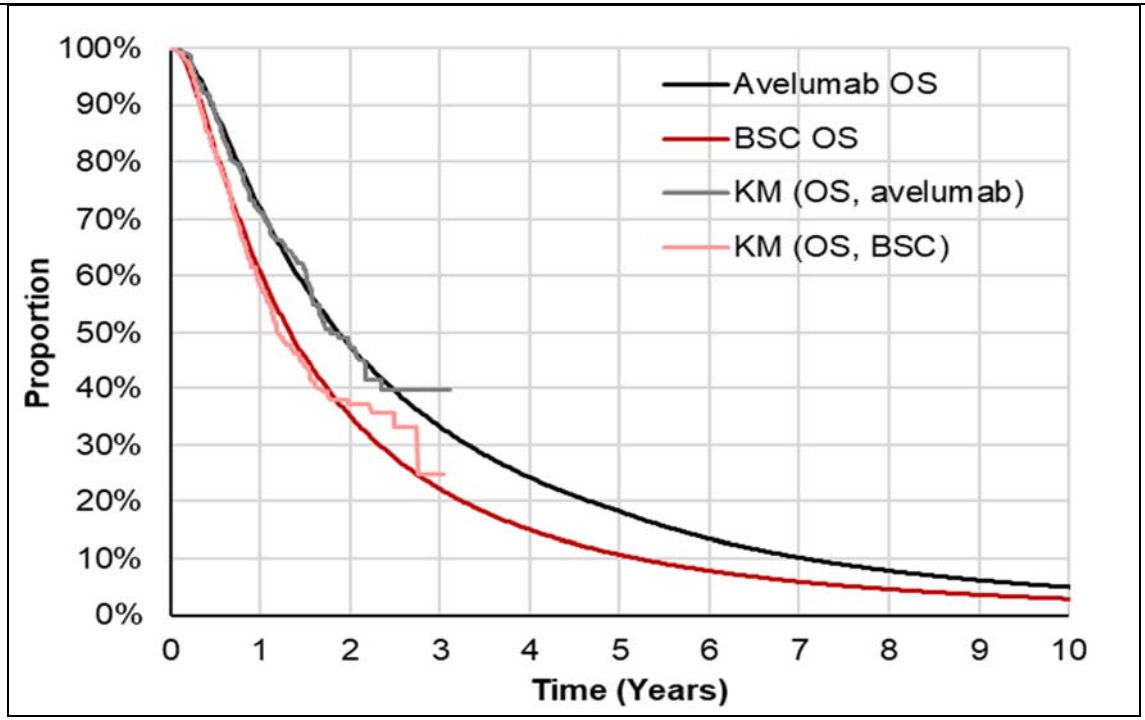
- Our preferred application, as agreed with the NICE technical team and ERG during the technical engagement call, is shown in

Figure **4** for comparison to the ERG's application. As can be inferred from the plot, the introduction of a treatment benefit cap at 5 years has a relatively small impact on the OS curves themselves owing to the fact that the projected tails are relatively similar (given that both are based on log-normal models, per the ERG's preferred base-case analysis).

		Figure 4: Company's application of treatment benefit cap 



Cap applied at 5 years



Using the approach described above, we have performed additional scenario analyses exploring treatment waning effect. The results of these scenarios are presented in more detail in the Additional Evidence Appendices submitted alongside this response.

We do not agree with the ERG's 2-year treatment waning scenario as no stopping rule has been applied in our submission, and at 2 years, patients are still projected to be receiving treatment in the model (up to 5 years). Treatment effect waning is often used to adjust for post-treatment immunotherapeutic survival benefits when a stopping rule is applied. The ERG's 2-year treatment waning scenario is extremely conservative in the absence of a

		stopping rule and is not reflective of recent approaches by Evidence Review Groups and Appraisal Committees. We have explored treatment waning scenarios applied at 5 years (where there is an instant loss of treatment benefit when all patients stop treatment, HR=1) up to 8 years (which assumes 3 years of continual treatment benefit after stopping treatment before treatment waning is applied). We consider the 5-year treatment waning scenario to represent a conservative scenario as for these patients (who are considered well enough to stop treatment, and are likely durable responders) it seems unfeasible that their treatment benefit would immediately cease. This is supported by the opinion of the oncologists we consulted as part of this response, who agreed there is a sustained benefit for immunotherapy once patients discontinue treatment. It is also important to note that there is no available evidence to inform the scenarios exploring treatment waning given that avelumab is the first IO to be used in this maintenance setting. However, in our Additional Evidence Appendix we have shared the results of treatment waning scenarios that have been explored (5 to 8 years, as mentioned above) in previous NICE appraisals of immunotherapies in mUC (5-8) as well as gradual treatment waning scenarios.
Key issue 5: The proportion of patients receiving subsequent (post progression) treatment in the model	**Yes (Clinical expert opinion)**	***The ERG acknowledge that there is still uncertainty with regard to this parameter, and would welcome some more clinical validation of the alternative estimates (see ERG report Table 24). In addition, further clinical input would be helpful on the likely impact on efficacy of fewer patients receiving subsequent treatments.*** We disagree with the ERG's modelling of subsequent treatments in its base-case analysis. Although we presented scenarios as part of our response to the ERG clarification questions which incorporated data on subsequent treatments from SACT, the aim of these scenarios was to explore the model's sensitivity to these parameters and not inform the base-case. We have since received clinical feedback that further supports the use of JB100 data to inform the proportion of patients receiving subsequent treatments. The eight UK-based clinicians that were consulted during technical engagement confirmed that the SACT dataset is not reflective

		of the population of interest in JB100. The company also elicited estimates of the proportion of patients who receive subsequent treatments following a response to chemotherapy in clinical practice and clinicians provided a range between 60-85%, which is in line with the data from JB100. It is important to acknowledge that all patients in JB100 achieved either stable disease (27.9%) or a PR/CR (72.1%) following first-line chemotherapy, and thus were eligible to receive avelumab maintenance (though may have been randomised to either treatment arm). This patient population may therefore be considered to be in a relatively better health state compared to patients who did not respond to chemotherapy (i.e. did not achieve stable disease, PR or CR) and are therefore more likely to receive subsequent treatments. The SACT data includes patients who have progressed during chemotherapy, or immediately after, and therefore does not reflect the same maintenance population as the clinical trial. Furthermore, the SACT data collected between January 2013 – March 2018 does not reflect recent NICE recommendations for immunotherapies in mUC which increased the options of efficacious treatment and in turn the proportion of patients receiving subsequent treatments in clinical practice. We therefore believe that the JB100 trial data is the only relevant data in this population and therefore should be considered the primary data source to inform the model base-case. We appreciate that the proportion of subsequent therapies should be explored in sensitivity analysis; however, reducing the proportion receiving subsequent treatments is likely to have a detrimental impact on the efficacy estimates in both treatment arms. Whilst there are no data available to support these adjustments, it should be noted that the proposed ERG approach reduces the proportion receiving a subsequent treatment by a larger amount in the BSC arm, both relatively and absolutely, and therefore a greater reduction in efficacy should be expected. Moreover, patients in the WW arm are eligible to receive subsequent immunotherapy, indicating that WW patients are likely to derive greater benefit from subsequent treatments. The company believe that the ERG's application of the average between the SACT and JB100 trial data in their base-case is arbitrary and biases against

		avelumab by reducing the subsequent treatment costs for the WW arm by more than the avelumab arm with no adjustment to efficacy. In conclusion, the SACT data does not reflect clinical practice where avelumab is used in the maintenance setting (for patients with CR, PR or SD following treatment with chemotherapy) and therefore it is not an appropriate data source to inform the proportion of patients receiving subsequent treatment in the model. Consequently, we consider the ERG's scenario (which reduces the proportion of patients receiving subsequent treatments) to be clinically implausible and therefore should not be considered in the base-case analysis.
Key issue 6: The mix of subsequent (post progression) treatments included in the model	**Yes (Clinical expert opinion)**	***The ERG acknowledge that there is still uncertainty around this parameter, and would welcome some more clinical validation of the treatment pathway following avelumab maintenance (see ERG report, Table 24). In addition, further clinical input would be helpful on the assumption that there would be no material impact on the efficacy estimates because of this change to the model.*** We agree with the ERG's clinical expert that patients treated with avelumab as maintenance would not receive subsequent anti PD-1/PD-L1 treatments in clinical practice. We have consulted with eight UK-based clinicians to inform this response and we asked whether or not patients would receive atezolizumab after avelumab maintenance treatment. All eight clinicians agreed with the ERG's clinical advice that patients would not receive a subsequent immunotherapy after progressing on a different immunotherapy agent and would instead receive chemotherapy. This is because clinicians would not expect patients who had progressed on maintenance immunotherapy to derive benefit from a sequential immunotherapy due to the shared mechanism of action. Consequently, we agree with the ERGs view and support its preference to remove the cost of atezolizumab following avelumab in the base-case analysis and assume these patients will receive chemotherapy instead.

Key issue 7: Uncertainty about whether end of life criteria are met	**Yes (Clinical expert opinion)**	***Any further data from the JAVELIN Bladder 100 trial or the literature reporting mean OS would likely help reduce the uncertainty around whether or not avelumab meets the criteria for end of life consideration.*** In our base-case analysis, the modelled median survival estimated for the WW arm was 15.87 months (versus 15.98 months in the ERG's base-case analysis), whilst median survival from the JB100 trial for WW was 14.3 months (95% CI: 12.9 to 17.9 months). However, it is important to interpret median survival within the context of the shape of the survival curve, as a proportion of patients are expected to benefit from treatments given after progression (and those that progressed prior to 15.87 months would have had limited capacity to benefit from). Despite some limitations as a measure of "average" survival, median survival does provide a helpful measure for clinicians when describing likely outcomes associated with a given treatment. Another measure that may be helpful to consider is the proportion of patients expected to survive for longer than 24 months, which is 36.58% for the WW arm in our base-case analysis, versus 35.05% in the ERG's base-case analysis. From this estimate, it can be inferred that approximately one-third of patients on the WW arm are expected to survive beyond 2 years, whereas two-thirds are estimated to have died prior to this landmark. From this result, it can be seen that the majority of patients do not survive for longer than 2 years. Phase 3 randomised controlled trials have reported median overall survival (OS) of 12.5–18.0 months for first-line cisplatin-based regimens (9-15), and 9.3 months for first-line carboplatin + gemcitabine (16). Similarly, in a meta-analysis of seven Phase 2 and 3 studies of cisplatin-based chemotherapy in metastatic UC, the median OS was 13.5 months (17). Outcomes in single-arm studies of atezolizumab and pembrolizumab have been similar to those observed with first-line chemotherapy (median OS of 12.3–18.5 months) (18-20). Furthermore, recent Phase 3 data have failed to demonstrate superiority of atezolizumab or pembrolizumab over first-line chemotherapy in extending OS (21, 22). These studies all provide evidence that suggest that the average life expectancy for patients in this setting is < 24 months.

		Interviews with eight UK based clinicians as part of this response included a question about the average life expectancy of patients who respond to chemotherapy and receive current standard of care in the UK. Estimates elicited from the clinical experts ranged from 12-18 months and it was confirmed that there is no evidence currently available which suggests that average overall survival is > 24 months in this patient population. These estimates were informed by their knowledge of the literature and their own experience with patients in clinical practice. We note that the ERG on balance agrees that EOL criteria are met. This has been supported by the additional interviews with clinicians as part of this TE response. We also believe that the overall survival gain should be taken into consideration alongside the estimated average survival in this patient population. JB100 reported an unadjusted improvement in median OS of 7.1 months for avelumab + BSC compared to BSC alone and the economic model predicts an increase in mean OS of 12 months (median = 6.9 months) and mean OS of 11.4 months (median = 6.7 months) under the company and ERG preferred base-case assumptions respectively. Therefore, we believe that avelumab unequivocally meets the life extension criterion for end of life consideration, as it increases OS by substantially more than 3 months.

Additional issues

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 (e.g. at the clarification stage).

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: 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 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]**

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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 ICER

Company base-case	-	£29,245
ERG base-case	ERG base-case includes the following changes: • **Models for OS changed to lognormal (both arms)*** • **Assessment of PFS based on investigator assessment*** • **Models for PFS changed to 3-knot hazard spline (avelumab) and 3-knot odds spline (WW)*** • Models for TTD changed to generalised gamma (both arms) • Proportions for subsequent therapy changed to ERG's preference • **Subsequent immunotherapy costs removed for the avelumab arm*** Changes in **bold** and marked with an asterisk (*) are accepted in our revised base-case analysis	£34,802 (+£5,557)

Issue 2. Treatment effectiveness parameters (extrapolation of OS curves for avelumab and WW)	As outlined in the table above the generalised gamma model was considered the most suitable extrapolation to inform the avelumab arm, based on it being the only model to provide an estimate of 10-year survival within the bounds estimated by UK consultant oncologists. Furthermore, the AIC difference compared to the best fitting model is less than two which demonstrates that the best fitting and second best-fitting models are essentially equivalent. For the watchful waiting arm, the generalised gamma model provided the best AIC score, and the second-best BIC score, a good visual fit to the Kaplan-Meier curve, and a clinically-plausible extrapolation.	The company accept that both the generalised gamma and log-normal models are appropriate for decision making. In our revised base-case, we apply the ERG's preferred OS extrapolation (log-normal) for avelumab and WW.	£30,629, (+£1,384 from company base-case)

Issue 3. Definition of progression for PFS (BICR vs. INV assessed)	The company base-case economic model uses the BICR definition of progression. This was based on the expectation that BICR-defined progression would minimise the risk of bias in the JAVELIN Bladder 100 trial.	Eight consultant oncologists from various hospitals in the UK were consulted individually to inform this technical engagement response and all agreed with the feedback received by the ERG that INV-assessed PFS does better reflect how progression is determined in clinical practice. In light of this feedback, we accept the ERGs view that INV-defined progression is a better representation of how progression would be assessed in NHS practice, and therefore support the use of INV-defined progression within the base-case analysis.	£27,159 (-£2,086 from company base-case)
Issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	Our base-case economic model uses lognormal models for TTD. The ERG's base-case analysis uses generalized gamma models.	Our revised base-case analysis is unchanged from its original base-case analysis, as the choice of TTD models is reverted to lognormal.	No change from company base-case analysis

Issue 5: The proportion of patients receiving subsequent (post progression) treatment in the model	Our base-case economic model uses data from JB100 to inform the proportion of subsequent therapies. The ERG's base-case analysis uses alternative assumptions based on SACT data.	Our revised base-case analysis is unchanged from its original base-case analysis, as proportions that receive subsequent therapy are set as per the submitted model.	No change from company base-case analysis
Issue 6. The mix of subsequent (post progression) treatments included in the model	Patients in JAVELIN Bladder 100 received subsequent nivolumab, pembrolizumab and durvalumab (as second-line anti-PD-1/PD-L1 treatments). These treatments are not considered standard of care nor part of routine commissioning in England or Wales as second-line therapy. Therefore, a simplifying assumption was made, costing these patients as receiving atezolizumab (an anti-PD-L1 treatment) instead in both avelumab and WW arms.	As outlined above, the company agrees with the ERG's clinical expert and does not expect patients to receive subsequent anti PD-1/PD-L1 treatments following avelumab in clinical practice. Therefore, the company support the ERG's preference to remove the cost of atezolizumab following avelumab in the base-case analysis and assume these patients will receive chemotherapy instead with no adjustments to the efficacy estimate.	£25,822 (-£3,423 from company base-case)
Company's preferred base-case following technical engagement	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	**£24,721**

References

1. National Institute for Health and Care Excellence. Avelumab for treating metastatic Merkel cell carcinoma. 2018. https://www.nice.org.uk/guidance/ta517

2. National Institute for Health and Care Excellence. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [TA557]. https://www.nice.org.uk/guidance/ta557/documents/final-appraisal-determination-document-2

3. National Institute for Health and Care Excellence. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy [TA655]. https://www.nice.org.uk/guidance/ta655/documents/final-appraisal-determination-document

4. National Institute for Health and Care Excellence. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer [TA654]. https://www.nice.org.uk/guidance/ta654/documents/final-appraisal-determination-document

5. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA519]. https://www.nice.org.uk/guidance/ta519/documents/final-appraisal-determination-document

6. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525]. https://www.nice.org.uk/guidance/ta525

7. National Institute for Health and Care Excellence. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA492]. https://www.nice.org.uk/guidance/ta492

8. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable [TA522]. https://www.nice.org.uk/guidance/TA522

9. Bamias A, Dafni U, Karadimou A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol. 2013;24(4):1011-7.

10. 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.

11. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001;19(10):2638-46.

12. Dreicer R, Manola J, Roth BJ, et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. Cancer. 2004;100(8):1639-45.

13. Siefker-Radtke AO, Millikan RE, Tu SM, et al. Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. J Clin Oncol. 2002;20(5):1361-7.

14. Bamias A, Aravantinos G, Deliveliotis C, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol. 2004;22(2):220-8.

15. 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.

16. 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.

17. Galsky MD, Krege S, Lin CC, et al. Relationship between 6- and 9-month progression-free survival and overall survival in patients with metastatic urothelial cancer treated with first-line cisplatin-based chemotherapy. Cancer. 2013;119(16):3020-6.

18. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389(10064):67-76.

19. ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (MK-3475-052/KEYNOTE-052) 2020 [Available from: https://clinicaltrials.gov/ct2/show/results/NCT02335424.

20. Vuky J, Balar AV, Castellano DE, et al. Updated efficacy and safety of KEYNOTE-052: A single-arm phase 2 study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol. 2018;36(15_suppl):4524.

21. Galsky MD, Arija JAA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10236):1547-57.

22. Merck & Company Inc. Merck Provides Update on Phase 3 KEYNOTE-361 Trial Evaluating KEYTRUDA® (pembrolizumab) as Monotherapy and in Combination with Chemotherapy in Patients with Advanced or Metastatic Urothelial Carcinoma 2020 [Available from: https://investors.merck.com/news/press-release-details/2020/Merck-Provides-Update-on-Phase-3-KEYNOTE-361-Trial-Evaluating-KEYTRUDA-pembrolizumab-as-Monotherapy-and-in-Combination-with-Chemotherapy-in-Patients-with-Advanced-or-Metastatic-Urothelial-Carcinoma/default.aspx.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Technical Engagement

Additional Evidence Appendices

February 2021

File name	Version	Contains confidential information	Date
ID3735_Avelumab_UC_TE_appendices_FINAL_12Feb21_ACIC	1.0	Yes	12 Feb 2021

Contents

List of tables

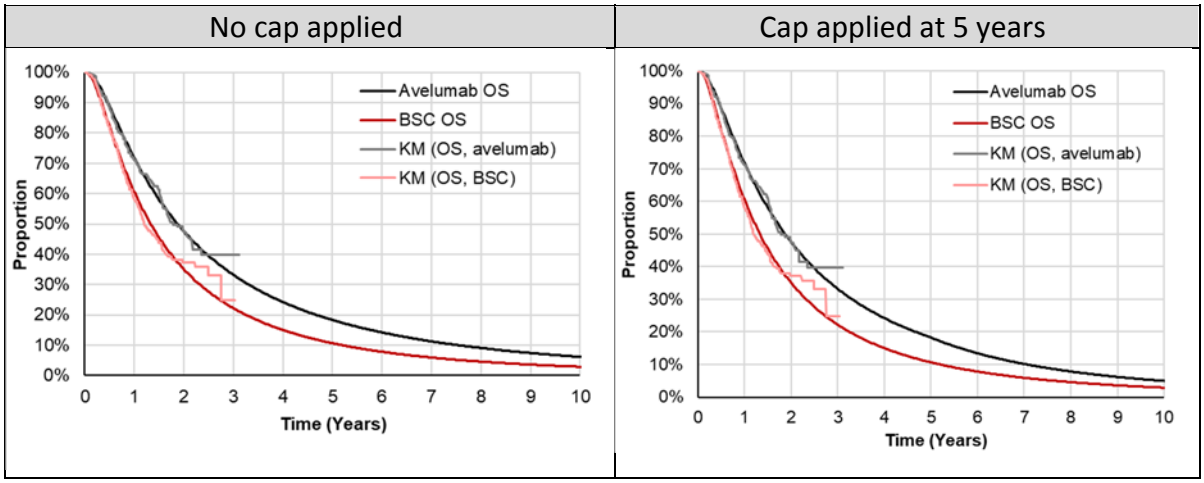
List of figures

1. Treatment waning effect

As discussed in our response to technical engagement, we have identified an important limitation of the ERG's approach to treatment waning as the method used to apply this cap, causes a sharp drop in the avelumab curve such that it is then identical to the WW curve after the cap time rather than adjusting the treatment effect of avelumab in terms of the ratio of the hazards between the arms. As an alternative, we would suggest instead that the hazard of death for avelumab patients be set equal to that of the WW arm (HR = 1) at the cap time. This would have the effect of assuming no additional benefit in terms of the hazard of death, but without assuming a sharp drop in survival itself. This methodology has been considered by NICE committees in previous appraisals and was agreed with the NICE technical team and the ERG during the technical engagement call (1-4).

Our preferred application is shown in Figure 1 for comparison to the ERG's application. As can be inferred from the plot, the introduction of a treatment benefit cap at 5 years has a relatively limited impact on the overall survival (OS) curves themselves owing to the fact that the projected tails are relatively similar (given that both are based on log-normal models, per the ERG's preferred base-case analysis).

Figure 1: Company's application of treatment benefit cap



We have explored treatment waning scenarios applied at 5 years (where there is an instant loss of treatment benefit when all patients stop treatment, HR=1) up to 8 years (which assumes 3 years of continual treatment benefit after stopping treatment before treatment waning is applied).

It is important to note that there is no available evidence to support the scenarios exploring treatment waning given that avelumab is the first immunotherapy to be used in this maintenance setting. In the absence of evidence to support treatment waning scenarios we have applied assumptions from prior NICE appraisals. A maximum 8-year treatment waning effect was based on the prior NICE appraisal TA525 (Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) where a 3-year treatment effect cap after stop of treatment was considered by the Committee. In our analysis this would correspond to an additional 3 years of treatment effect after all patients stop at 5 years, resulting in treatment effect waning at 8 years. As discussed in our main response, we do not agree with the scenarios whereby treatment waning is applied

before 5 years as patients in the model can continue on treatment up to 5 years. Table 1 presents the results of the treatment waning scenario analyses applied at year 5 to 8. The ICER results remain relatively stable with all scenarios under £30,000 (ranging from £25,720 to £27,760).

Table 1: Company TE response: Company revised base case with treatment waning effect applied.

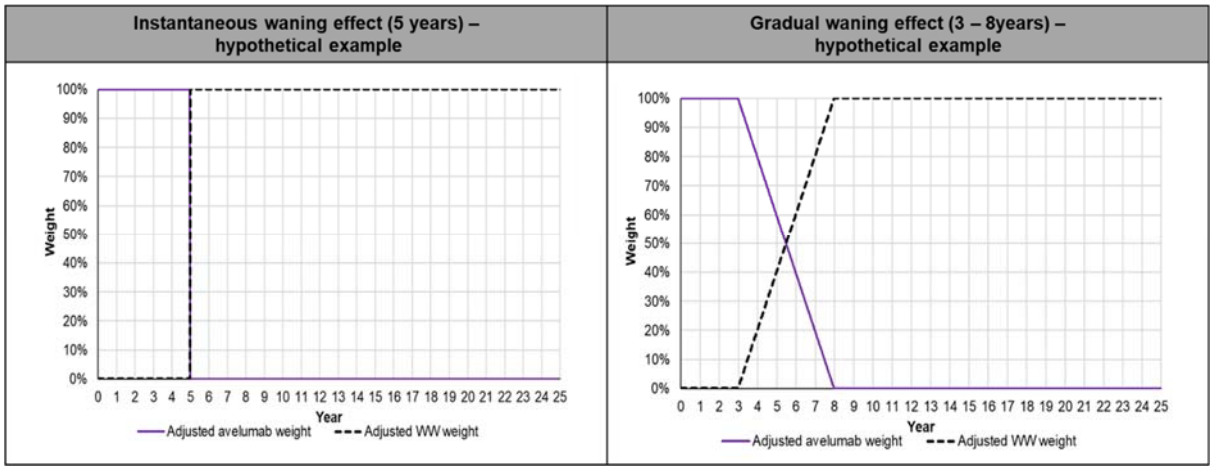
Treatment waning effect	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Applied at 5 years					
Avelumab	[redacted]	[redacted]			
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	£27,760
Applied at 6 years					
Avelumab	[redacted]	[redacted]			
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	£26,759
Applied at 7 years					
Avelumab	[redacted]	[redacted]			
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	£26,133
Applied at 8 years					
Avelumab	[redacted]	[redacted]			
Watchful waiting	[redacted]	[redacted]	[redacted]	[redacted]	£25,720

2. Gradual treatment waning effect

In a real-world setting the loss of treatment effect is unlikely to occur instantaneously and instead it is more realistic to consider this effect occurring gradually over time, particularly when considering a cohort of patients rather than individual patient cases.

As such, a gradual treatment waning effect (TWE) has also been applied in the model. This approach produces a weighted hazard based on the stratified PFS and OS curves for avelumab and BSC arms from JAVELIN Bladder 100. The gradual effect occurs linearly with a weighted hazard being produced at each cycle, to generate an adjusted avelumab OS and PFS estimate. Figure 2 illustrates this approach in comparison to an instantaneous TWE. Applying a gradual TWE methodology avoids a sudden change in the hazards (of both progression and death) that may sometimes be seen with applying an instantaneous effect to immune-oncology treatments versus BSC (watchful waiting) extrapolations.

Figure 2: Comparison of instant versus gradual treatment waning approaches: weights applied to generate adjusted hazards for avelumab



Given there is no long-term evidence of avelumab (or any other treatment) in the maintenance setting post-chemotherapy for mUC patients, it is not yet possible to determine a) whether a TWE is appropriate to apply, or b) if so, for how long. Therefore, the model has flexibility to apply the gradual TWE across various time-points (ranging between 5 and 10 years). This differs to the treatment effect waning scenario described in Section 1 of this Appendix document, where waning effect is applied instantaneously at different time points. Given that the implementation of a waning effect may be considered a driver of cost-effectiveness, we have explored two-way sensitivity analysis exploring various start and endpoints for the treatment waning (5 to 10 years). The results of this analysis can be seen in Table 2 for our original base case, Table 3 for the ERG base case and Table 4 for the our revised base case.

Table 2 (our base case at submission) highlights that across all gradual TWE scenarios the ICER remains relatively stable with all scenarios under £40,000 (ranging from £29,749 to £31,716). Table 3 shows the effect on the ERG base case. Although results are slightly higher in this scenario, all scenarios remain below £40,000. Table 4 (our revised base case) highlights that across all gradual TWE scenarios the ICER remains under £30,000 (ranging from £25,257 to £27,760).

Table 2: Company submission: base case with gradual treatment waning effect applied.

Gradual waning effect	End Year: 5	End Year: 6	End Year: 7	End Year: 8	End Year: 9	End Year: 10
Start Year: 5	£31,716	£31,329	£31,034	£30,801	£30,613	£30,460
Start Year: 6		£30,983	£30,733	£30,531	£30,370	£30,238
Start Year: 7			£30,503	£30,330	£30,188	£30,071
Start Year: 8				£30,169	£30,044	£29,940
Start Year: 9					£29,927	£29,835
Start Year: 10						£29,749

Table 3: ERG report: ERG base case with gradual treatment waning effect applied.

Gradual waning effect	End Year: 5	End Year: 6	End Year: 7	End Year: 8	End Year: 9	End Year: 10

Start Year: 5	£39,231	£38,469	£37,898	£37,458	£37,112	£36,834
Start Year: 6		£37,794	£37,319	£36,947	£36,656	£36,425
Start Year: 7			£36,891	£36,577	£36,327	£36,130
Start Year: 8				£36,291	£36,078	£35,909
Start Year: 9					£35,885	£35,740
Start Year: 10						£35,606

Table 4: Company TE response: Company revised base case with gradual treatment waning effect applied.

Gradual waning effect	End Year: 5	End Year: 6	End Year: 7	End Year: 8	End Year: 9	End Year: 10
Start Year: 5	£27,760	£27,229	£26,832	£26,527	£26,288	£26,097
Start Year: 6		£26,759	£26,429	£26,172	£25,972	£25,814
Start Year: 7			£26,133	£25,916	£25,745	£25,611
Start Year: 8				£25,720	£25,575	£25,461
Start Year: 9					£25,444	£25,347
Start Year: 10						£25,257

Overall, when considering both instantaneously and gradually applied treatment waning effect scenarios at different time points, all ICER results remain below £40,000 per QALY and well within the threshold for medicines considered against EOL criteria.

3. Clinician interviews

We agree with the ERG's view that additional clinical opinion would be useful in helping to resolve some of the key issues identified in the technical report. Consequently, we have conducted individual interviews with eight consultant oncologists specialising in the treatment of advanced bladder cancer from various hospitals across the UK to help inform the technical engagement response.

Key Issue 3

The eight clinicians were asked whether blinded independent centrally reviewed (BICR) or investigator-assessed (INV) definition of progression would better reflect the way progression would be assessed in clinical practice. All eight clinicians confirmed that INV-assessed progression is more closely aligned with clinical practice in the UK.

Key Issue 4

The eight clinicians were asked whether, in their experience, patients would continue to derive clinical benefit from avelumab following treatment discontinuation. Seven out of eight clinicians confirmed that there is a sustained treatment benefit with immunotherapies for patients who discontinue treatment (with one clinician stating that additional benefit is unknown).

Key Issue 5

Clinicians were also presented the subsequent treatment data from SACT and JB100 and asked which estimates they felt were more appropriate to use in the model. They were also

asked as to provide an estimate of proportion of patients who receive subsequent treatment from their clinical practice.

Seven of the clinicians interviewed noted that the SACT data was not reflective of the trial population as it included patients who had progressed on chemotherapy and would therefore be less likely to receive a subsequent treatment. It was also noted that clinical practice has changed in recent years due to the recent NICE recommendations of immunotherapies in mUC and therefore the proportion of patients receiving subsequent treatment has been increasing and the SACT data will not reflect this as it is Jan 2013 – March 2018 data.

Seven of the clinicians were able to provide estimates of the proportion of patients who receive subsequent treatment after BSC in clinical practice. This produced a range of estimates from 60-85%, with a mean of 71.36%

Key Issue 6

The clinicians were asked whether they would expect patients to receive an immunotherapy (atezolizumab) subsequent to avelumab in UK clinical practice and whether they would expect patients to derive benefit from this treatment.

All of the clinicians stated that patients who had received avelumab would not be treated with subsequent immunotherapy based on current NICE recommendations and lack of evidence to support this treatment pathway. The clinicians acknowledged that there is no evidence they are aware of investigating the efficacy of sequential immunotherapies. However, five of the clinicians stated that they would not expect patients to derive any benefit based on the shared mechanism of action, rather they would expect cross-resistance to immunotherapies following progression with any one immunotherapy.

Key Issue 7

Finally, the clinicians were asked whether the life expectancy for patients with mUC is under 24 months with current treatment options.

All eight clinicians were very strong in their opinion that life expectancy is less than 24 months for this patient population, noting that there is no evidence to suggest that life expectancy is above 24 months for these patients. The clinicians estimated that life expectancy in clinical practice for these patients is 14-18 months, which is aligned with the median OS for patients in the BSC arm in JB100.

Several clinicians noted that patients with metastatic bladder cancer have particularly poor life expectancy even compared to other metastatic cancers and that this life expectancy has not changed much for a long time.

4. References

1. National Institute for Health and Care Excellence. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [TA557]. https://www.nice.org.uk/guidance/ta557/documents/final-appraisal-determination-document-2

2. National Institute for Health and Care Excellence. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy [TA655]. https://www.nice.org.uk/guidance/ta655/documents/final-appraisal-determination-document

3. National Institute for Health and Care Excellence. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer [TA654]. https://www.nice.org.uk/guidance/ta654/documents/final-appraisal-determination-document

4. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA519]. https://www.nice.org.uk/guidance/ta519/documents/final-appraisal-determination-document

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Clinical expert statement & technical engagement response form

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Thank you for agreeing to comment on the 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 you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues is provided in the executive summary at the beginning of the ERG report.
- 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. In part 2 of this form we have included any of the issues raised by the ERG where we think having 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.

Please return this form by **5pm** on **Friday, 12th February 2021.**

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- Do not include medical information about yourself or another person that could identify you or the other person.
- 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. 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.

PART 1 – Treating a person with metastatic urothelial cancer after platinum-based chemotherapy, and current treatment options	
About you	
1. Your name	**Dr Alison J Birtle FRCP FRCR MD**
2. Name of organisation	**Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust**
3. Job title or position	**Consultant Oncologist & Honorary Senior Lecturer**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition?

	☐ a specialist in the clinical evidence base for this condition 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)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**
The aim of treatment for this condition	

8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Advanced bladder cancer has poor overall survival and there have been no survival improvements seen over the last 20 years in the UK. Progressive disease has a huge impact on quality of life, with patients needing intensive and costly input from urologists, interventional radiologists, palliative care team members both hospital and community or hospice based, district nurses, oncologists and specialist nurses. The use of primary care is also significant. Patients develop ureteric obstruction, go into renal failure, have profound haematuria, significant pain from both local and metastatic disease, anaemia, and fatigue. Staying in an early or stable disease state for longer will enable more patients to have a vastly improved quality of life and also with improved survival during that time. This will mean there use of healthcare resource globally will be significantly less. Palliative radiotherapy, nephrostomies, bladder irrigation, palliative TURBT resections, ureteric stents are in particular all costly to patient in terms of time and discomfort, and to the provider. Avelumab improves both overall and progression free 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.)	The vast majority of patients will relapse quickly after first line chemotherapy, and second line chemotherapy has been shown to lead to median Progression free survival of 3.2 months, overall survival of 8 months.(Pluto Trial, JCO Powles et al, 2016). Gemcitabine/cisplatin or gemcitabine /carboplatin produces responses in around 70% and 45 % of patients respectively but this is not maintained in the majority. To be able to keep these patients in an early disease state, progression free is a highly **clinically** significant achievement. Avelumab maintains response in each patient group; those with either a partial or complete response to first line chemotherapy or those with stable disease, equally.
10. In your view, is there an unmet need for patients and healthcare professionals in metastatic urothelial cancer after platinum-based chemotherapy?	Absolutely- second line chemotherapy has a response rate of around 18% and PFS of 3.2 months, Second line immunotherapy has a response rate of around 23 %. Approximately half of patients do not go onto receive second line treatment as they relapse too quickly for it to be initiated. There is a clinically meaningful improvement with maintenance Avelumab compared with BSC (21.4 months compared with 14.3 months)
What is the expected place of the technology in current practice?	

11. How is the condition currently treated in the NHS?	Patients complete first ,line chemotherapy with either gemcitabine cisplatin or gemcitabine-carboplatin to a maximum of six cycles and are then under observation. It would be standard to do a CT scan after 3 cycles, at the end of chemotherapy and then every 3 months or so. However many patients progress within that window and would have an earlier scan based on clinical/biochemical progression. Outside of a clinical trial, there is no other maintenance treatment. Combination treatment with immunotherapy and chemotherapy has been proven not to be of benefit based on the ImVigor 130 and Keynote 361 Trials . Second line treatment is with immunotherapy, or less commonly with second line chemotherapy as documented above.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines for first line treatment of advanced bladder cancer (although some of the regimes stated are not and have never been commonplace) , European Society of Medical Oncology Guidelines, and European urological Association Guidelines.
• 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.)	There may be subjective differences of patients' fitness for treatment for either first or second line chemotherapy. There will be no difference in terms of what happens at the end of chemotherapy. Pathways for these patients are well established.
• What impact would the technology have on the current pathway of care?	The patients are already in the oncology clinic and can be provided with the expectation and information on potential suitability for maintenance treatment at an early stage during their first line chemotherapy. The impact would be that more patients would be given life extending treatment and be held in an early less costly disease state. Immunotherapy would be brought further forward in care, and as with other cancers, this approach of earlier treatment improves patient outcomes while maintaining or improving quality of life.
12. Will the technology be used (or is it already used) in the same	Avelumab is currently available via an EAMS programme in the UK and so clinicians may already have experience of this, in addition to the centres who took part in the Javelin 100 trial. All centres have extensive experience of using PDL-1 or PD1 inhibitors across urothelial cancer and other cancer types. Current care is surveillance only therefore this would be additional to that, with patients starting avelumab and continuing until progression; treatment must be

way as current care in NHS clinical practice?	started within 4-10 weeks of last dose of chemotherapy. Other immunotherapy drugs are used currently in second line setting after progression and some patients never receive it.
• How does healthcare resource use differ between the technology and current care?	Patients will receive immunotherapy with Avelumab every two weeks- this does not mean they need a clinic appointment two weekly. Standard treatment will be CT scans every three months or earlier dependent upon symptoms and second line treatment with immunotherapy (Pembrolizumab or Atezolizumab) started at time of progression if the patient is fit enough at that stage .
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics- can be the cancer units as well as the cancer centres. All are well versed in delivery of checkpoint inhibitors in urothelial and other cancers and well versed in management of toxicity. The patient will receive Avelumab in the same setting as where they received their chemotherapy
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No real additional investments- we already use second line immunotherapy in urothelial cancer. This will provide access to more patients as more will be fit enough to have maintenance rather than to give at time of progression where patients are less fit, and also response to second line much poorer.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The registration study published in 2020 by Poles et al, following on from oral presentations at all of the Global Oncology Congresses demonstrates that this approach has been widely acclaimed as standard of care. With large patient numbers treated in the study, significant improvements in overall survival across all subgroups of patients and maintenance of quality of life. This “ ticks all the boxes” as s the Moderator at one of the global meetings concluded.
• Do you expect the technology to increase length of life more than current care?	Yes, the median survival improvement was 7.1 months in favour of maintenance Avelumab.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes- keeping patients in an earlier disease state as per Q 8 above, with good quality of life, very manageable side effects (in keeping with known side effects of check point inhibitors)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	All subgroups benefitted substantially (whether stable disease, complete response or partial response post chemotherapy) and whether they had 4, 5 or 6 cycles of chemotherapy. There was an even stronger signal and hazard ratio in the PDL-1 positive group but the technology was effective across all subgroups, unlike other agents where PDl-1 negative can be through to be disadvantaged- This is not the case with maintenance Avelumab.
The use of the technology	
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.)	All clinicians treating urothelial cancer are familiar with delivery and monitoring of patients on checkpoint inhibitors; hence there is no additional concern. The only extra resource implication is that Avelumab is given two weekly rather than 4 to 6 weekly. However we are bringing treatment earlier in the disease history, meaning the usage of other palliative interventions such as nephrostomies, palliative radiotherapy/ bladder resections etc are likely to be less.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A maximum of two years duration of treatment as per the trial would be reasonable as this is the basis of other checkpoint inhibitor treatment. Other reasons would be toxicity or disease progression. Few patients in Javelin 100 continued beyond two years.
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?	Yes- these patients die with significant complications of their cancer. This technology will allow improved substantial beyond that we have ever previously seen , with maintenance of good quality life and far less usage of other health care resource as above.
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?	Hugely innovative- combination treatment of checkpoint inhibitor with chemotherapy has not worked. Second line immunotherapy benefits a subset. Maintenance after chemotherapy will have a large contribution on health related benefits for bladder cancer patients
• Is the technology a 'step-change' in the management of the condition?	Yes- already adopted globally as the new standard of care.

• Does the use of the technology address any particular unmet need of the patient population?	Yes, please see previous comments.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	All clinicians and chemotherapy nurses and acute oncology teams are well versed in the identification and treatment of immune mediated side effects and there are national algorithms
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• 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?	Patients living longer, in terms of months, with good quality life. Little has been done to show this in the last 20 years for urothelial cancer patients. The trial had robust end points.
• If surrogate outcome measures were used, do they adequately predict	The study measured overall survival and was strongly clinically and statistically significant.

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No; we have been using this class of drugs in urothelial cancer for years and the adverse effects were those we would expect and know how to identify and manage.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	At the American Society of Medical Oncology Genitourinary Symposium Feb 10-13 2021, Grivas et al presented a poster, outlining adoption of Maintenance avelumab in the US. Of those surveyed 71% of the 18 centres were using the Javelin 100 system as standard of care. In addition Loriat et, had an oral presentation at the same meeting (abstract 438) avelumab first-line maintenance plus BSC in advanced urothelial carcinoma:Javelin Bladder 100 subgroup analysis based on duration and cycles of chemotherapy. This showed that the Overall survival benefit was seen in patients who had had 4, 5 or 6 cycles of chemotherapy. Therefore for patients who were struggling with any toxicity from chemotherapy but were responding well, there is now evidence to support an earlier switch to maintenance avelumab, reducing side effect burden for the patient and additional cycles of chemotherapy. This allows the clinician to tailor the treatment to the individual patient
22. How do data on real-world experience compare with the trial data?	The trial population is representative of patients in the UK with bladder cancer in terms of disease characteristics and response to chemotherapy. I have not seen any real world data other than the poster mentioned above by Grivas et al in terms of usage in the USA
Equality	

23. a) Are there any potential equality issues that should be taken into account when considering this treatment?	There have been many technology assessments in other cancer types over the last 20 years , far fewer for bladder cancer and far fewer that have been positive. I would state that the inequity here is for urothelial cancer as a whole and would urge the Committee to consider this equity.
23. b) Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. In current NHS practice, for people who would otherwise be considered for avelumab maintenance therapy: a) What is the typical life expectancy of a person in this indication? b) What proportion of people who would you expect to be alive after 5, 10 and 15 years?	Around 12 -14 months Survival is dismal. Less than 5% alive at 5 years, and less than 1% at 10 or 15 years. Hence the need for survival improvement

25. If avelumab maintenance therapy continued in NHS practice with no stopping rule, how many people would you expect to still be on treatment after 5 years?	Very few would be on beyond 2 years in the trial; therefore the numbers after 5 years would be trivial. Certainly less than 1 % and the exception.
26. If avelumab maintenance therapy were stopped, how much longer would you expect the avelumab treatment effect to last?	We don't know this. We know that with this group of drugs, ongoing benefit can be seen after stopping treatment (ie patient has reached their allotted time on treatment and is still benefitting at time of stopping) I have seen patient continue to benefit for more than 12 -18 months after stopping checkpoint inhibitors.
27. In current NHS practice, for people who would otherwise be considered for avelumab maintenance therapy: a) What proportion people would you expect to receive another active treatment after disease progression?	Second line treatment in Uk around 50% or less; third line around 1 in 4 or 1 in 5 patients

b) Which subsequent therapies would be considered for these people? Please describe specific treatments, e.g. chemotherapies and immunotherapies.	Weekly Taxol chemotherapy Response rate around 18% or less. Other than this clinical trials including early phase study ie no guarantee of benefit.
28. Compared with current NHS practice, if a person had been treated with avelumab maintenance therapy: a) Would you be more or less likely to consider subsequent therapies after disease progression? b) Would the specific subsequent treatments considered be different?	Difficult to say as we will be monitoring more closely as they will be having Avelumab two weekly as well as Ct scans and therefore a relapse on clinical, biochemical or radiological grounds is highly likely to be detected earlier and thus the patient will be more able to go onto second line treatment. However treatment with current standard does not have a high response rate (see above) More I think for the reasons above. Yes they would already have had a checkpoint inhibitor. They would therefore be offered clinical trials or second line taxol
29. Following disease progression with avelumab maintenance	We don't have that evidence

therapy, would you expect subsequent treatment with another immunotherapy to provide any clinical benefit?	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your thoughts on the key issues below, but you do not have to respond to every issue. 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 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.	
Key issue 1: Health-related quality of life data	Maintained Quality of life on Avelumab maintenance across all subgroups
Key issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)	Maintenance Avelumab improves overall survival and progression free survival in a strongly significant clinically and statistically significant was
Key issue 3: Definition of progression (blinded	See above Q 16 please

independent assessment vs. investigator assessment)	
Key issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	
Key issue 5: The proportion of patients receiving subsequent (post progression) treatment in the model	
Key issue 6: The mix of subsequent (post progression) treatments included in the model	
Key issue 7: Uncertainty about whether end of life criteria are met	

Are there any important issues that have been missed in ERG report?	No

PART 3 – Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Avelumab keeps patient in an early disease state and improves survival in a way not seen before
- The benefit of avelumab can be seen across all subgroups irrespective of whether they had a complete or partial response or stable disease after first line chemotherapy
- Quality of life was maintained or improved across all subgroups
- Maintenance with avelumab is now standard of care, practice changing across the rest of the world
- Bladder cancer progression is costly to the patient and to the Provider; patients have few options and this is the forgotten cancer

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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Clinical expert statement & technical engagement response form

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Thank you for agreeing to comment on the 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 you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues is provided in the executive summary at the beginning of the ERG report.
- 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. In part 2 of this form we have included any of the issues raised by the ERG where we think having 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.

Please return this form by **5pm** on **Friday, 12th February 2021.**

NICE National Institute for Health and Care Excellence

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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. 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.

PART 1 – Treating a person with metastatic urothelial cancer after platinum-based chemotherapy, and current treatment options	
About you	
1. Your name	**Syed A Hussain**
2. Name of organisation	**University of Sheffield**
3. Job title or position	**Professor of Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition?

	☐ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for this condition	

8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improvement in progression free survival, improvement in 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.)	Improvement in overall survival by 3 months with Hazard ratio of 0.70 or better favouring the experimental treatment. Treatment has to be well tolerated helping patients maintain good quality of life
10. In your view, is there an unmet need for patients and healthcare professionals in metastatic urothelial cancer after platinum-based chemotherapy?	The median survival in patients with metastatic urothelial cancer remains 14-15 months. 2nd line treatments in the form of Immune check point inhibitors has improved outcome and improved survival in a subset of patients. Avelumab as maintenance treatment post platinum treatment improved median survival significantly compared with best supportive care. (21.4 months versus 14.3 months favouring Avelumab HR 0.69, 95% confidence interval 0.56-0.86; p=0.001). This overall survival is measured from randomisation within the Avelumab maintenance trail. As patients were randomised after 4-6 cycles of first line chemotherapy, this will bring median survival for these patients from the start of their platinum based chemotherapy well over 2 years.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Patients are followed up with surveillance CT scans. At progression, patients receive 2nd line immune check point inhibitors.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Nice guidelines
• 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.)	The pathway is well defined. After first line chemotherapy patients undergo surveillance scans and on progression patients who are fit , are offered 2nd line immune check point inhibitors.
• What impact would the technology have on the current pathway of care?	The technology will bring the use of immune check point inhibitors to an earlier maintenance setting. In this way this will catch all patients responding to first line platinum based chemotherapy with atleast stable disease as the best response and will be offered Avelumab. Moving Avelumab to maintenance setting this will reduce number of patients receiving 2nd line immune check point inhibitors.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Immune check point inhibitors are used in 2nd line setting. This technology (Avelumab) will significantly improve the outcome for patients by bringing it to an earlier stage in maintenance setting.
• How does healthcare resource use differ between the technology and current care?	Patients will receive Avelumab post platinum based chemotherapy rather than having surveillance CT scans at 3 months intervals and receiving Atezolizumab or Pembrolizumab at the time of disease progression.
• In what clinical setting should the technology be used? (For example,	Should be used in Oncology clinics.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There are no additional investments required as immune check point inhibitors are routinely used in clinical practice in 2nd line setting. The introduction of this technology will bring the use of Immune check point inhibitor Avelumab to an earlier setting as maintenance treatment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This trial published in NEJM, September 2020 reported by Powles et al showed maintenance Avelumab plus best supportive care significantly prolonged overall survival compared to best supportive care alone, among patients with urothelial cancer who had disease that had not progressed on first line chemotherapy. JAVELIN Bladder 100 study was a large randomised trial, that recruited 700 patients. The improvement in progression free survival and overall survival was clinically and statistically significant and the benefit was seen across all groups of patients. There were no new safety signals of concern and the treatment was generally well tolerated. In view of that I expect the technology provides clinically meaningful benefits compared with current care.
• Do you expect the technology to increase length of life more than current care?	Yes. Trial reported median survival of 21.4 months v 14.3 months favouring technology
• Do you expect the technology to increase health-related quality of life more than current care?	By improving progression free survival and overall survival and with manageable toxicity reported with the technology this is likely to improve health related quality of life compared to current care.
14. Are there any groups of people for whom the technology would be more or less effective	The technology was found to be effective across different groups of patients (Hazard ration 0.69), though it was more effective in PDL positive population (Hazard ratio 0.56).

(or appropriate) than the general population?	
The use of the technology	
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.)	As 2nd line immune check point inhibitors are already in routine use, the technology approval will bring the use to an earlier stage. Therefore this will not lead to any additional requirements for treatment to be used across the country, or cause any difficulties in acceptance of this treatment. As this treatment is given at 2 weekly intervals this will increase resource utilisation in delivery of this treatment compared to 4 weekly or 6 weekly immune check point inhibitors given as 2nd line treatment.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The trial recruited patients and were treated with Avelumab till progression of disease or treatment was discontinued in view of treatment related toxicity. In the Avelumab arm reason for discontinuation was progressive disease in 189 patients (54%), adverse events in 39 patients (11.1%), withdrawal of consent in 16 (4.6%) and death in 5 (1.4%) patients. The median duration of treatment in Avelumab arm was 24.9 weeks (range 2.0-159.9 weeks). Patients can continue till disease progression based on the trial design, though as very few patients received treatment over 2

	years, a 2 years maximum use can be considered by the committee as with other immune check point inhibitors in 2nd line setting.
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?	Yes the use of technology will improve survival significantly.
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?	The standard of care is best supportive care with surveillance CT scans at 3 months intervals. This technology brings the use of immune check point inhibitors earlier in the disease pathway and brings substantial impact on health related benefits for this group of patients.
• Is the technology a 'step-change' in the management of the condition?	Yes, it is a step change in the management of this condition.
• Does the use of the technology address any particular unmet need of the patient population?	As above

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects encountered with immune check point inhibitors are treated with specific guidelines and protocols used by individual hospitals. Earlier identification of toxicities and earlier management has improved the outcome for these patients improving the quality of life.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes the clinical trial on technology reflect current UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	N-A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in robust end point of overall survival. Improvement in progression free survival
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Primary end point of over all Survival was met.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Clinical trials reported toxicities usually seen with this class of drugs (immune check point inhibitors). There were no new safety signals.
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?	There is no reported real word data with Avelumab in this setting
Equality	
23. a) Are there any potential equality issues that should be taken into account when considering this treatment?	No
23. b) Consider whether these issues are different from issues with current care and why.	-

Topic-specific questions	
24. In current NHS practice, for people who would otherwise be considered for avelumab maintenance therapy: a) What is the typical life expectancy of a person in this indication? b) What proportion of people who would you expect to be alive after 5, 10 and 15 years?	14-15 MONTHS < 5% to be alive after 5 years <1% to be alive after 10 and 15 years
25. If avelumab maintenance therapy continued in NHS practice with no stopping rule, how many people would you expect to still be on treatment after 5 years?	< 1%

26. If avelumab maintenance therapy were stopped, how much longer would you expect the avelumab treatment effect to last?	There is no trial data to help answer this question in bladder cancer, in my view If Avelumab maintenance treatment is stopped, the treatment benefit may last for over 12 months
27. In current NHS practice, for people who would otherwise be considered for avelumab maintenance therapy: a) What proportion people would you expect to receive another active treatment after disease progression? b) Which subsequent therapies would be considered for these people? Please describe specific treatments, e.g. chemotherapies and immunotherapies.	About 20 % of patients may benefit from 3rd line treatment Clinical trials Weekly Paclitaxel chemotherapy.

28. Compared with current NHS practice, if a person had been treated with avelumab maintenance therapy: a) Would you be more or less likely to consider subsequent therapies after disease progression? b) Would the specific subsequent treatments considered be different?	Depending on fitness we will anticipate approximately 20% of patients for further treatment based on fitness. More regular use of scans may help to find patients earlier with radiological disease progression bringing more fitter patients to receive further line of treatment. As patient would have already received immune check point inhibitors, subsequent therapies will include clinical trials, further use of chemotherapy.
29. Following disease progression with avelumab maintenance therapy, would you expect subsequent treatment with another immunotherapy to provide any clinical benefit?	There is no data to suggest the use of further immunotherapy after patient has progressed on Avelumab maintenance treatment.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your thoughts on the key issues below, but you do not have to respond to every issue. 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 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.	
Key issue 1: Health-related quality of life data	-
Key issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)	Significant benefit in median survival and progression free survival.
Key issue 3: Definition of progression (blinded	Benefit in progression free survival seen across all groups.

independent assessment vs. investigator assessment)	
Key issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	As discussed in my report above, please see answer to Q 16
Q	
Key issue 6: The mix of subsequent (post progression) treatments included in the model	-
Key issue 7: Uncertainty about whether end of life criteria are met	-

Are there any important issues that have been missed in ERG report?	The report covers it thoroughly.

PART 3 – Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Improvement in Median survival
- Improvement in progression free survival
- Benefits seen across all groups of patients
- No new safety signals
- Clinically and statistically significant results that are practice changing.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

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

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NICE National Institute for Health and Care Excellence

Patient expert statement & technical engagement response form

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

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. In part 2 of this form we have included any of the issues raised by the ERG where we think having 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.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday, 12th February 2021.**

Completing this form
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. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want 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 15 pages.

PART 1 – Living with or caring for a person with metastatic urothelial cancer and current treatment options	
About you	
1.Your name	**Kevin Gorman**
2. Are you (please tick all that apply):	☑ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition?

	☑ 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 below and provide answers where 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/experience (e.g. 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. ☐ 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

Living with the condition	
6. What is your experience of living with metastatic urothelial cancer? If you are a carer (for someone with this condition) 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.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for metastatic 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 has spread. How to tell their partner? Their children? 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. The bottom line is that currently available treatments afford little in the way of hope. Outcomes are depressingly poor. It would be easier for patients and carers to endure the condition if Avelumab were an available option offering a more positive outcome. It would bring some hope.

8. If there are disadvantages for patients of **current NHS treatments** for metastatic urothelial cancer (for example how avelumab is given or taken, side effects of treatment etc) please describe these	Poor outcome.
Advantages of this treatment	
9a. If there are advantages of avelumab over current treatments on the NHS please describe these. For example, the impact 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 avelumab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	Both the company and the ERG agree that the data show better outcomes and generally acceptable side effects. This would be very much welcomed by patients, providing them with greater optimism and hope for the future.

Disadvantages of this treatment	
10. If there are disadvantages of avelumab over current treatments on the NHS please describe these? For example, are there any risks with avelumab If you are concerned about any potential side affects you have heard about, please describe them and explain why.	We are not aware of any.
Patient population	
11. Are there any groups of patients who might benefit more from avelumab 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	We are not aware of any significant differences for subgroups of patients with locally advanced or metastatic urothelial cancer receiving Avelumab or current alternatives.
Equality	
12. Are there any potential equality issues that should be taken into account when considering metastatic	We are not aware of any.

urothelial cancer and avelumab? Please explain if you think any groups of people with this condition 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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
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 of relatively short duration. This has perhaps inevitably led to several differences between the company and the evidence review group on which

	model best fits the data for extrapolation, how to interpret the mean and median, 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. It can be difficult to explain to patients why a drug has not been recommended if the underlying reason is a difference of opinion in extrapolation from a dataset which is both small and of short duration. We therefore hope that, where there is reasonable doubt, the committee will accept the interpretation of the data proposed by the company in support of its application. We remain of the view that this new treatment offers real hope for this group of very poorly served patients.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the key issues below, but you do not have to respond to every issue. If you think an issue that is important to 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 patient organisation that nominated you has 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.	
Key issue 1: Health-related quality of life data	

Key issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)	
Key issue 3: Definition of progression (blinded independent assessment vs. investigator assessment)	
Key issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	
Key issue 5: The proportion of patients receiving subsequent (post progression) treatment in the model	

Key issue 6: The mix of subsequent (post progression) treatments included in the model	
Key issue 7: Uncertainty about whether end of life criteria are met	
Are there any important issues that have been missed in ERG report?	

PART 3 – Key messages

16. 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 very many years.
- Diagnosis of advanced or metastatic bladder cancer is devastating for patients and carers, given the very poor outcomes at present.
- Avelumab offers real hope for this poorly served group of patients, offering much better outcomes without significantly worse adverse effects than current treatments.

• The committee may be faced with conflicting interpretations of data which could lead to different conclusions on affordability. We hope, where reasonable doubt exits, the committee accepts the baseline submission by the company seeking approval.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Friday 12 February 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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.

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.

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)	**Action Bladder Cancer UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Health-related quality of life data	**No**	This relates to the interpretation of Javelin trial data used to calculate health related quality of life years. Overall, we do not think the degree of uncertainty justifies an alternative interpretation from the submission.
Key issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)	**No**	We note that the difference is only a small variation in cost effectiveness.
Key issue 3: Definition of progression (BICR vs. INV)	**No**	We have nothing to add.
Key issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	**No**	We are not able to contribute to the committee's deliberation on this point, but note that the ERG accept the basis of the company's approach in the absence of further data.
Key issue 5: The proportion of patients receiving subsequent (post progression) treatment in the model	**No**	We are not able to contribute to the committee's deliberation on this point.

Key issue 6: The mix of subsequent (post progression) treatments included in the model	**No**	We have nothing to add.
Key issue 7: Uncertainty about whether end of life criteria are met	**No**	We urge the committee to accept that the criteria for end of life care has been met. From a patient perspective, we would draw attention to the quoted UK median of around 9.5 months, which perhaps more accurately reflects the experience of most patients in this group. We also suggest that most clinicians would agree that more than half of patients have a life expectancy of less than 12 months. We were surprised by the evidence research group's conclusion that 'on balance, (they) consider it plausible that criteria 1 is met'. We think it is met, based on published data, clinical judgement and patient experience. NICE has previously accepted that the end of life criteria is met when dealing with this specific group of patients.

Additional issues

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 (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Not applicable

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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 ICER

Not applicable

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Thank you for agreeing to comment on the 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 you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues is provided in the executive summary at the beginning of the ERG report.
- 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. In part 2 of this form we have included any of the issues raised by the ERG where we think having 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.

Please return this form by **5pm** on **Friday, 12th February 2021.**

NICE National Institute for Health and Care Excellence

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- Do not include medical information about yourself or another person that could identify you or the other person.
- 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. 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.

PART 1 – Treating a person with metastatic urothelial cancer after platinum-based chemotherapy, and current treatment options	
About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**
3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition?

	☐ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for this condition	

8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improvement in progression free survival, improvement in 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.)	Improvement in overall survival by 3 months with Hazard ratio of 0.70 or better favouring the experimental treatment. Treatment has to be well tolerated helping patients maintain good quality of life
10. In your view, is there an unmet need for patients and healthcare professionals in metastatic urothelial cancer after platinum-based chemotherapy?	The median survival in patients with metastatic urothelial cancer remains 14-15 months. 2nd line treatments in the form of Immune check point inhibitors has improved outcome and improved survival in a subset of patients. Avelumab as maintenance treatment post platinum treatment improved median survival significantly compared with best supportive care. (21.4 months versus 14.3 months favouring Avelumab HR 0.69, 95% confidence interval 0.56-0.86; p=0.001). This overall survival is measured from randomisation within the Avelumab maintenance trail. As patients were randomised after 4-6 cycles of first line chemotherapy, this will bring median survival for these patients from the start of their platinum based chemotherapy well over 2 years.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Patients are followed up with surveillance CT scans. At progression, patients receive 2nd line immune check point inhibitors.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Nice guidelines
• 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.)	The pathway is well defined. After first line chemotherapy patients undergo surveillance scans and on progression patients who are fit , are offered 2nd line immune check point inhibitors.
• What impact would the technology have on the current pathway of care?	The technology will bring the use of immune check point inhibitors to an earlier maintenance setting. In this way this will catch all patients responding to first line platinum-based chemotherapy with at least stable disease as the best response and will be offered Avelumab. Moving Avelumab to maintenance setting this will reduce number of patients receiving 2nd line immune check point inhibitors.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Immune check point inhibitors are used in 2nd line setting. This technology (Avelumab) will significantly improve the outcome for patients by bringing it to an earlier stage in maintenance setting.
• How does healthcare resource use differ between the technology and current care?	Patients will receive Avelumab post platinum based chemotherapy rather than having surveillance CT scans at 3 months intervals and receiving Atezolizumab or Pembrolizumab at the time of disease progression.
• In what clinical setting should the technology be used? (For example,	Should be used in Oncology clinics.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There are no additional investments required as immune check point inhibitors are routinely used in clinical practice in 2nd line setting. The introduction of this technology will bring the use of Immune check point inhibitor Avelumab to an earlier setting as maintenance treatment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This trial published in NEJM, September 2020 reported by Powles et al showed maintenance Avelumab plus best supportive care significantly prolonged overall survival compared to best supportive care alone, among patients with urothelial cancer who had disease that had not progressed on first line chemotherapy. JAVELIN Bladder 100 study was a large randomised trial, that recruited 700 patients. The improvement in progression free survival and overall survival was clinically and statistically significant and the benefit was seen across all groups of patients. There were no new safety signals of concern and the treatment was generally well tolerated. In view of that I expect the technology provides clinically meaningful benefits compared with current care.
• Do you expect the technology to increase length of life more than current care?	Yes. Trial reported median survival of 21.4 months v 14.3 months favouring technology
• Do you expect the technology to increase health-related quality of life more than current care?	By improving progression free survival and overall survival and with manageable toxicity reported with the technology this is likely to improve health related quality of life compared to current care.
14. Are there any groups of people for whom the technology would be more or less effective	The technology was found to be effective across different groups of patients (Hazard ration 0.69), though it was more effective in PDL positive population (Hazard ratio 0.56).

(or appropriate) than the general population?	
The use of the technology	
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.)	As 2nd line immune check point inhibitors are already in routine use, the technology approval will bring the use to an earlier stage. Therefore this will not lead to any additional requirements for treatment to be used across the country, or cause any difficulties in acceptance of this treatment. As this treatment is given at 2 weekly intervals this will increase resource utilisation in delivery of this treatment compared to 4 weekly or 6 weekly immune check point inhibitors given as 2nd line treatment.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The trial recruited patients and were treated with Avelumab till progression of disease or treatment was discontinued in view of treatment related toxicity. In the Avelumab arm reason for discontinuation was progressive disease in 189 patients (54%), adverse events in 39 patients (11.1%), withdrawal of consent in 16 (4.6%) and death in 5 (1.4%) patients. The median duration of treatment in Avelumab arm was 24.9 weeks (range 2.0-159.9 weeks). Patients can continue till disease progression based on the trial design, though as very few patients received treatment over 2

	years, a 2 years maximum use can be considered by the committee as with other immune check point inhibitors in 2nd line setting.
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?	Yes the use of technology will improve survival significantly.
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?	The standard of care is best supportive care with surveillance CT scans at 3 months intervals. This technology brings the use of immune check point inhibitors earlier in the disease pathway and brings substantial impact on health related benefits for this group of patients.
• Is the technology a 'step-change' in the management of the condition?	Yes, it is a step change in the management of this condition.
• Does the use of the technology address any particular unmet need of the patient population?	As above

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects encountered with immune check point inhibitors are treated with specific guidelines and protocols used by individual hospitals. Earlier identification of toxicities and earlier management has improved the outcome for these patients improving the quality of life.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes the clinical trial on technology reflect current UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	N-A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in robust end point of overall survival. Improvement in progression free survival
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Primary end point of overall survival was met.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Clinical trials reported toxicities usually seen with this class of drugs (immune check point inhibitors). There were no new safety signals.
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?	There is no reported real word data with Avelumab in this setting
Equality	
23. a) Are there any potential equality issues that should be taken into account when considering this treatment?	No
23. b) Consider whether these issues are different from issues with current care and why.	-

Topic-specific questions	
24. In current NHS practice, for people who would otherwise be considered for avelumab maintenance therapy: a) What is the typical life expectancy of a person in this indication? b) What proportion of people who would you expect to be alive after 5, 10 and 15 years?	14-15 MONTHS < 5% to be alive after 5 years <1% to be alive after 10 and 15 years
25. If avelumab maintenance therapy continued in NHS practice with no stopping rule, how many people would you expect to still be on treatment after 5 years?	< 1%

26. If avelumab maintenance therapy were stopped, how much longer would you expect the avelumab treatment effect to last?	There is no trial data to help answer this question in bladder cancer, in my view If Avelumab maintenance treatment is stopped, the treatment benefit may last for over 12 months
27. In current NHS practice, for people who would otherwise be considered for avelumab maintenance therapy: a) What proportion people would you expect to receive another active treatment after disease progression? b) Which subsequent therapies would be considered for these people? Please describe specific treatments, e.g. chemotherapies and immunotherapies.	About 20 % of patients may benefit from 3rd line treatment Clinical trials Weekly Paclitaxel chemotherapy.

28. Compared with current NHS practice, if a person had been treated with avelumab maintenance therapy: a) Would you be more or less likely to consider subsequent therapies after disease progression? b) Would the specific subsequent treatments considered be different?	Depending on fitness we will anticipate approximately 20% of patients for further treatment based on fitness. More regular use of scans may help to find patients earlier with radiological disease progression bringing more fitter patients to receive further line of treatment. As patient would have already received immune check point inhibitors, subsequent therapies will include clinical trials, further use of chemotherapy.
29. Following disease progression with avelumab maintenance therapy, would you expect subsequent treatment with another immunotherapy to provide any clinical benefit?	There is no data to suggest the use of further immunotherapy after patient has progressed on Avelumab maintenance treatment.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your thoughts on the key issues below, but you do not have to respond to every issue. 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 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.	
Key issue 1: Health-related quality of life data	-
Key issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)	Significant benefit in median survival and progression free survival.
Key issue 3: Definition of progression (blinded	Benefit in progression free survival seen across all groups.

independent assessment vs. investigator assessment)	
Key issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	As discussed in my report above, please see answer to Q 16
Q	
Key issue 6: The mix of subsequent (post progression) treatments included in the model	-
Key issue 7: Uncertainty about whether end of life criteria are met	-

Are there any important issues that have been missed in ERG report?	The report covers it thoroughly.

PART 3 – Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Improvement in Median survival
- Improvement in progression free survival
- Benefits seen across all groups of patients
- No new safety signals
- Clinically and statistically significant results that are practice changing.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy lymphoma [ID3735]

ERG critique of the company's response to Technical Engagement

Produced by Aberdeen HTA Group

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This report provides the ERG's brief commentary and critique of the company's (Merck Serono/Pfizer Ltd) submitted response to technical engagement and in advance of the first AC meeting for this appraisal. The commentary/critique provided below should be read in conjunction with the company's submitted response to technical engagement. The commentary addresses each of the 7 key issues identified in the ERG report, and the company response to these at technical engagement. A confidential appendix to this report describes the impact of revised company and ERG analyses following technical engagement, applying a confidential patient access scheme (PAS) discount for post-progression treatment with atezolizumab.

Issue 1: Health Related quality of life data

The company submission (Document B, Section 2.6.1.5) noted that overall health status and health related quality of life (HRQoL) were similar between the avelumab + BSC and BSC alone arms of the JAVELIN Bladder 100 trial. However, utility data from the trial were not provided in the company submission (CS). In Table 1 of their response to technical engagement, the company have provided utility data for each arm of the study, split by pre-progression and post-progression states. The ERG notes that utilities for patient's pre-progression are slightly higher [redacted] in the avelumab + BSC arm compared to BSC alone, but are somewhat lower [redacted] for avelumab + BSC in the post-progression state compared to BSC. It is difficult to hypothesize why the utilities would be lower post progression in one group than another, but the ERG considers it relevant to raise this for the committee's consideration. The ERG notes that the ICER is not particularly sensitive to the post-progression utilities and, on balance, the ERG agrees with the company's view that it is appropriate to pool health state utilities across the treatment arms for use in the economic model.

Issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)

The ERG agrees with the company's statement that there is very little to distinguish between the generalised gamma and lognormal extrapolation curves for OS and accept the company's revision to their base case analysis to align with the ERG preferred extrapolation model.

Issue 3: Definition of progression (BICR vs. INV)

The ERG notes that there are advantages and disadvantages to both blinded independent review and investigator assessed progression. Blinded independent review will provide the most unbiased assessment of disease progression. However, the ERG's clinical expert view is that investigator's assessment of progression is more likely to drive treatment decision making in UK clinical practice and this has been further supported by the company's consultation with 8 UK clinical experts for the technical engagement response. The ERG therefore retains its preference for the use of investigator defined progression because this more accurately aligns with treatment allocation decisions in real world clinical practice. It was unclear from the company submission whether any decisions about patient care in the JAVELIN Bladder 100 trial were made based on investigator or blinded independent review.

The ERG notes that INV assessed progression reduces the company's original preferred base case ICER by £2,086 compared to BICR assessment.

Issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit

Time to treatment discontinuation

The ERG and company preferred base case analyses are aligned in that 95% of patients will discontinue treatment at 2 years. Applying treatment discontinuation assumptions at 2 years is consistent with previous technology appraisals for Urothelial cancer as noted by the company. The ERG and the company preferred approaches are also aligned in terms of preferring the use of the same extrapolation curve for the time period up to 2 years and for the time period between years 2 and 5 for the 5% of patients who are assumed to remain on treatment at 2 years. The ERG and company preferred analyses diverge about the most appropriate extrapolation curve to fit to the data (a) up to two years and (b) between years 2 and 5 for the 5% of patients who were modelled to remain on treatment at year 2. The ERG considers the gamma extrapolation curve to be more appropriate because (1) it is a better visual fit to all stages of the KM curves and has the best statistical fit (lowest AIC and BIC) to the observed KM data up to two years. The company argue that the LN is more appropriate because when fitted to the KM data (without reducing the proportion remaining on treatment to 5% at 2 years) it gives the lowest proportion on treatment at 5 years. The ERG does not consider this rationale to be robust, given that the survival curves are already heavily adjusted to reduce the proportion on treatment to 5%. When applying the proportion remaining on treatment to 5% at 2 years, fitting the gamma (ERG preferred) and LN (company preferred) extrapolations, lead to similar proportions remaining on treatment at 5 years [redacted]% and [redacted]% respectively). The ERG considers the greatest divergence between the company and ERG preferred approaches to occur at the tail of the KM curve up to year 2 (between years 1 and 2).

Treatment effect capping beyond avelumab treatment discontinuation

The company preferred base case analysis assumed that 95% of patients discontinued treatment at 2 years, and that all patients would stop treatment by 5 years. The implication of these assumptions is an instant drop in the proportion of patients on treatment at 2 years from [redacted]%, [redacted]% and [redacted]% for the company preferred log normal survival curve, ERG

preferred generalised gamma survival curve and KM data from the trial respectively. The ERG agrees with the company that discontinuation assumptions are appropriate, and clinically relevant. However, the ERG considers the company preferred base case analyses to provide an optimistic estimate of the ICER because the economic model assumes that reductions in treatment acquisition costs can be achieved without any negative impact on QALYS. That is because the extrapolated OS or PFS benefit of avelumab is extrapolated over the full model time horizon without adjustment for the treatment discontinuation assumptions applied.

The ERG accepts that there is substantial uncertainty in the duration of continued treatment benefits over time, beyond treatment discontinuation. In the absence of robust data to generate an alternative assumption, the ERG retained the company assumptions for the base case analysis, choosing instead to explore the combinations of treatment discontinuation and treatment effect (OS and PFS) capping in scenario analyses. As noted in the company's response to technical engagement, the ERG and the company now agree, post technical engagement discussion, that the most appropriate way to implement scenario analyses around treatment effect capping is to set the hazards on the avelumab arm equal to the WW arm beyond the chosen treatment capping time point. The ERG agree that the company's methodology is appropriate and is consistent with previous technology appraisals in urothelial cancer. The company have provided several additional scenario analyses to explore the impact of setting the hazards of OS and PFS for avelumab equal to watchful waiting (i.e. HR = 1) beyond year 5, year 6, year 7 and year 8 (See Table 1 in the appendix of the company's response to technical engagement). The company consider it inappropriate to apply a treatment waning effect from year 2 because patients can remain on treatment in the model up to year 5. The ERG note however that this argument only applies to the 5% of patients that remain on treatment.

The company have also provided scenario analyses that explore the application of a gradual treatment waning effect over time. These scenarios assume that the hazard ratio of OS and PFS for avelumab vs. watchful waiting gradually approaches one beyond the treatment effect capping time point, rather than instantaneously dropping to one. Several different durations of gradual reduction are explored. The impact of different scenarios applied to the company's original base case, ERG preferred base case and company revised base case analysis can be found in Tables 2, 3 and 4 of the appendix to the company's response to

technical engagement. The ERG prefers scenario analyses where the hazard ratio is set to one at the treatment benefit capping time point, as this more closely aligns with the company's assumptions about instantaneous discontinuation from treatment at years 2 and 5.

Issue 5: The proportion of patients receiving subsequent (post progression) treatment in the model

The ERG's report highlights concerns raised by the ERG's clinical expert advisor that the proportion of patients receiving treatment post progression in both arms of the JAVELIN Bladder 100 trial (Avelumab + BSC: [redacted]%; BSC: [redacted]%) was likely to be higher than what would be expected in UK clinical practice. In response to a clarification question, the company provided additional information from the Systematic Anti-Cancer Therapy (SACT) dataset, which showed that, in UK clinical practice, 41.9% of patients receive a second-line therapy following progression on first-line platinum-based chemotherapy. The company provided a scenario analysis taking the average of the proportions observed in each arm of the trial and the 41.9% observed in the SACT dataset. This analysis formed part of the ERG preferred base case, leading to [redacted]% and [redacted]% of patients receiving subsequent post-progression treatments in the avelumab and WW arms of the model respectively. The company have raised concerns in response to technical engagement that the ERG preferred analysis is arbitrarily chosen and that the proportions observed in the trials should be used for the base case assumptions. The company also notes responses from UK clinical experts consulted to inform the technical engagement response who note that the SACT dataset is not reflective of the population of interest, and that the proportion of patients who receive subsequent treatments would range from 60% to 85% in practice. However, the company have not provided any further elaboration from those clinical experts with regards to how generalisable the differences in the proportion receiving post-progression treatment between the trial arms would be to UK clinical practice.

The ERG has further reviewed our preferred assumptions with our clinical expert advisor in light of the company response. The ERG retains the view that the proportion of patients on treatment post-progression in the JAVELIN Bladder 100 trial likely over-estimates real world clinical practice use of post-progression therapies. There three main reasons for this:

- As noted by the company, the cohort entering the JAVELIN Bladder 100 trial will likely have had a better response to first line treatment than the entire group of metastatic patients. They are therefore likely to respond better to treatment, and a higher proportion will likely be treated with additional treatments post progression than in real world clinical practice. The ERG's clinical expert explains that patients who have progressed following platinum doublet chemotherapy or 2nd line IOs have few evidenced based treatment options available. Whilst some patients will receive further chemotherapy, there is weak evidence regarding survival benefits. The ERG's clinical expert view is that, on balance, the proportion of patients receiving further chemotherapy in the JAVELIN bladder 100 trial post progression is likely an over-estimate of real-world clinical practice.

- The ERG accepts that between 2013 and 2018 (dates for the SACT dataset), subsequent treatment would have been limited to further chemotherapies and may largely exclude subsequent IOs such as atezolizumab. The ERG accepts that there is a lack of evidence to inform the proportion of patients receiving treatment post-progression, especially since the introduction of IOs, but it is unlikely that IOs would be used post-progression in addition to further chemotherapies (2nd line), but rather as a replacement for them. The ERG considers it appropriate to apply expert opinion and judgement in the absence of robust data, but also accepts that there is likely to be some heterogeneity in clinical practice across the UK and therefore disagree that the decision is arbitrary. The ERG considers it likely that the true usage of post progression therapies is likely somewhere between that reported in the SACT dataset, and in the clinical trial, hence the decision to take an average of the two data sources.

- The application of an average of the proportion receiving post-progression therapy across the trial arms and the SACT dataset may even be considered to provide an optimistic estimate of the ICER for avelumab. As noted in response to issue 1 above, the utility of patients in the avelumab arm post progression is lower than in the BSC arm. One reason for this is likely to be that the proportion of patients receiving post-progression treatments is also lower in the avelumab arm. The fact that more people receive post-progression therapy in the WW arm post progression may be a contributing factor to the higher utilities post progression in the WW arm compared to the avelumab arm.

For the reasons outlined, the ERG retains our original preference for the proportion of patients receiving post progression treatments in the model.

Issue 6: The mix of subsequent (post progression) treatments included in the model

The ERG notes that the company have contacted 8 UK-based clinicians who validate the ERG's clinical expert opinion that a subsequent immunotherapy would not be provided to patients who had progressed following avelumab. The company also note that the expert advice sought from their clinicians aligns with the ERG's clinical expert view that no further benefit would be gained in terms of patient outcomes from treating with two immunotherapies in succession. The ERG and company now therefore agree that immunotherapies should be removed from the post-progression basket of treatment following progression in the avelumab arm and that those treatments should be re-distributed to the subsequent chemotherapies included in the model.

Issue 7: Uncertainty about whether end of life criteria are met

The ERG agrees with the company that the end of life criterion of extending life by at least 3 months has been clearly met based on the data provided by the company in the original submission, in the economic model projections and in the additional information provided at technical engagement. The ERG noted that the second criterion, where expected overall survival should be less than 24 months in the absence of avelumab was less clear, with the economic model projecting mean OS on the WW arm of the model greater than 24 months and median OS of less than 24 months. The ERG's report states that further data from the JAVELIN Bladder 100 trial or from the literature reporting mean OS in the patient group most likely to receive avelumab in clinical practice, would help reduce uncertainty for decision making. In response to technical engagement, the company have provided evidence from several studies reporting median OS ranging from 9.3 to 18.5 months. However, mean data from these studies were not included within the company response to technical engagement. It is unclear from the response document mean data would have been available from the quoted studies. The ERG retains the view that the end of life criterion for life extension is clearly met. The evidence provided by the company in response to technical engagement supports the case that median OS for BSC is <24 months, but the ERG notes that

some uncertainty remains with regards to whether mean OS without avelumab (i.e. BSC) is above or below 24 months.

Summary.

In summary, the ERG and company preferred base case analyses are now aligned on all but two of the issues raised for technical engagement. The remaining issues of disagreement, which require a judgement call from the committee to resolve, are:

Issue 4: Whether TTD should be modelled using a generalised gamma (ERG preferred) or Log Normal (company preferred) extrapolation model. Also, what is the most appropriate assumption about the duration of continued treatment benefit beyond treatment discontinuation? The ERG and company base cases both assume continued treatment benefit over the lifetime horizon of the model, given the absence of robust data about when a treatment cap should be imposed. However, this likely leads to an optimistic estimate of the ICER.

Issue 5: Whether the subsequent therapies included in the JAVELIN Bladder 100 trial are appropriate for application to UK clinical practice. The ERG's clinical expert opinion is that the proportions are higher than what would be expected in UK clinical practice, but the company clinical expert opinion is that they are appropriate.

Table 1 below outlines the impact on the ICER of applying the ERG preferred assumptions to the company's revised base case analysis. The ERG preferred base case analysis remains the same as that reported in the ERG report. However, a plausible alternative scenario, exploring the impact on the ICER of using blinded independent review definition of progression, in combination with the company preferred proportion of patients requiring post-progression treatment (based on the JAVELIN Bladder 100 trial) is provided for the committee's information.

Table 1: Comparison of company and ERG preferred ICERs

Analysis No.	Description	Incremental Cost	Incremental QALY	ICER
1	Company original base case	[redacted]	[redacted]	£29,245
2 (Issue 2)	Apply LN to OS extrapolation for both arms	[redacted]	[redacted]	£30,629
3 (Issue 3)	INV assessed progression (3-knot hazard and 3-knot odds for avelumab and WW respectively)	[redacted]	[redacted]	£27,159
4 (Issue 6)	Remove IOs from post progression therapy in avelumab arm	[redacted]	[redacted]	£25,822
5	**Company revised base case post technical engagement (1-4 combined)**	[redacted]	[redacted]	**£24,721**
6	ERG preferred generalised gamma extrapolation of TTD between years 2 and 5	[redacted]	[redacted]	£25,790
7	ERG preferred proportion on post-progression treatment	[redacted]	[redacted]	£33,733
8	**ERG preferred base case analysis (5,6,7 combined)**	[redacted]	[redacted]	**£34,802**
Scenario analyses				
9	8 + treatment waning effect applied at 5 years (i.e. HR of OS and PFS = 1 beyond 5 years)	[redacted]	[redacted]	£39,231

These results are reproduced in a confidential appendix to this report, considering the confidential comparator PAS price for atezolizumab.