Cost-effectiveness analysis of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy.

Thesis

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Abstract

Bladder cancer has high morbidity, mortality, and costs. It is the tenth most prevalent cancer in the United Kingdom (UK). 90% of all bladder cancers in Western Europe are urothelial cancers which often have a high programmed cell death ligand 1 (PD-L1) protein expression. Avelumab is an anti-PD-L1 antibody immunotherapy that showed significant prolonged overall survival (OS) as 1st line maintenance treatment in adult patients with locally advanced or metastatic urothelial carcinoma who did not progress after 1st line platinum-based chemotherapy compared to best supportive care (BSC) alone in the JAVELIN Bladder 100 trial. Based on this trial data avelumab received market authorization on the 21st of January 2021 for the trial population.

In this thesis, a cost-effectiveness analysis (CEA) of avelumab (+BSC) versus BSC was performed for adults with locally advanced or metastatic urothelial cancer without progression after 1st line platinum-based chemotherapy in the UK. Moreover, an additional CEA was performed for avelumab in the PD-L1 positive subgroup. These analyses were executed in accordance with the National Institute for Health and Care Excellence (NICE) guidelines.

For the CEA, a three-health state partitioned-survival model with a lifetime horizon of 40 years was developed in Excel. For this, the OS and progression-free survival (PFS) KM data from the JAVELIN Bladder 100 trial were extrapolated using the method of Hoyle and Henle to estimate the individual patient data (IPD). In addition, the utility values by health state and the relevant costs (drug acquisition, drug administration, premedication, monitoring and disease management, adverse events (AEs), terminal care and PD-L1 testing costs) were searched via a targeted literature review. Furthermore, a probability sensitivity analysis (PSA) and several scenario analyses were performed.

Over a lifetime horizon (40 years), avelumab showed an improvement in health benefits compared to BSC alone in the overall population (incremental life years (LYs): 1.07, incremental quality adjusted life years (QALYs): 0.78) and the PD-L1 subgroup (incremental LYs: 1.79, incremental QALYs: 1.17). The incremental cost per patient associated with avelumab versus BSC alone over a lifetime horizon was £114,483 in the overall population and £104,000 in the PD-L1 subgroup. The high acquisition cost of avelumab was the main reason for these high incremental costs. The incremental cost-effectiveness ratios (ICERs) amounted to £147,484.09 and £89,141 per QALY gained in the overall population and PD-L1 subgroup, respectively.

Despite the limitations of the study such as the absence of good data (e.g., specifics of subsequent therapies), the results of the study indicated that avelumab was not cost-effective for both considered populations according to the NICE threshold range and therefore should not be recommended to the National Health Service (NHS) as maintenance treatment for locally advanced or metastatic urothelial cancer for patients who did not progress after 1st line platinum-based chemotherapy. However, a market entry agreement (MEA) could be made to make the promising drug available for patients with the investigated indication and address the key uncertainties (implementation of a stopping-rule, the duration of the atezolizumab treatment and long-term effects).

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Abbreviations

AE: Adverse event
AIC: Akaike information criterion
BNF: British national formulary
BSC: Best supportive care
BSA: body surface area
CADTH: Canadian Agency for Drugs and Technologies in Health
CDF: Cancer drug fund
CEA: Cost-effectiveness analysis
CEAC: Cost Effectiveness Acceptability Curve
CHMP: Committee for Medicinal Products for Human Use
DNA: Deoxyribonucleic acid
eMIT: Electronic Market Information Tool
EQ-5D: Europol five-dimensions questionnaire
ERG: Evidence review group
HRQol: Health-related quality-of-life data
HTA: Health technology assessment
ICER: Cost-effectiveness ratio
KM: Kaplan-Meier
Lys: Life years
MEA: Market entry agreement
NHS: National Health Service
NHSCII: NHS Cost Inflation Indices
NICE: National Institute for Health and Care Excellence
OS: Overall survival
PD-L1: High programmed cell death ligand 1
PD: Progressed Disease
PF: Progression-Free
PFS: Progression-Free Survival
PROs: Patient-reported outcomes
PSA: Probabilistic sensitivity analysis
PSS: Personal Social Services
PSSRU: Personal Social Services Research Unit
QALYs: Quality adjusted life years
RCT: Randomized controlled trial
RECIST: Response Evaluation Criteria in Solid Tumors
Stdev: Standard deviation
SE: Standard error
SmPC: Summary of Product Characteristics
T: Stage
TA: Technology appraisal
TTD: Time to treatment discontinuation
UK: United Kingdom
WTP: Willingness to pay

1. Introduction

1.1. Urothelial cancer

Urothelial or transition cell cancer typically develops in the urothelial cells located in the transitional epithelium at the lumen side of the bladder, urethra, ureter, or renal pelvis (Figure 1-1). The cancer is predominantly situated in the bladder and about 90% of all bladder cancers diagnosed in Western Europe are urothelial cancers (1). At the time of diagnosis, bladder cancer is non-muscle-invasive in 75% of the patients (2). Two main non-invasive subtypes of urothelial cancer exist. The cancer can expand in the direction of the lumen, called papillary carcinoma, or can stay superficial in the urothelium, known as in situ or flat carcinoma. When the cancer penetrates into the deeper layers of the urinary wall it becomes invasive (3,4). Stages (T1 to T4) are used to describe the size and spread of the cancer (Figure 1-2). Stage 4 (T4) means that the cancer has spread to other organs (5). One speaks of locally advanced bladder cancer when the cancer only has spread to lymph nodes and into the nearby tissues (vagina, womb, ovaries, prostate, and back passage). Metastatic bladder cancer signifies that the cancer has spread to other organs such as the liver, lungs, and bones (6,7). Furthermore, urothelial cancer has multiple tumor features such as a high programmed cell death ligand 1 (PD-L1) protein expression, genomic instability, deoxyribonucleic acid (DNA) damage-response mutations, and a high tumor mutational burden by which the cancer cells try to survive and grow. Having more of these tumor features result into a worse prognosis (8–10).

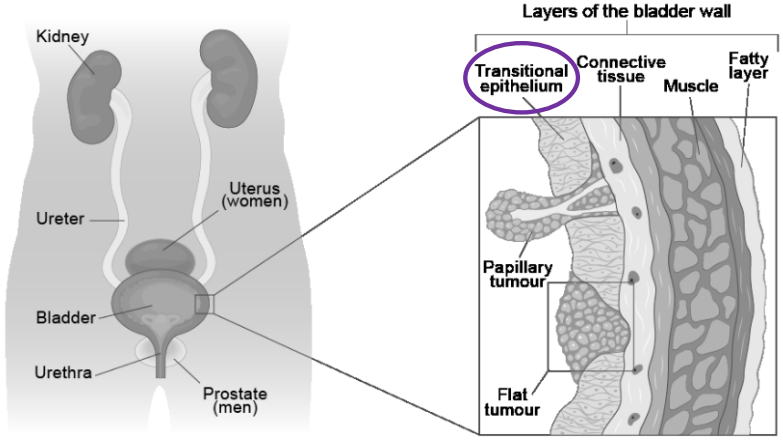

Figure 1-1: The anatomy of urothelial cancer, adapted from (11)

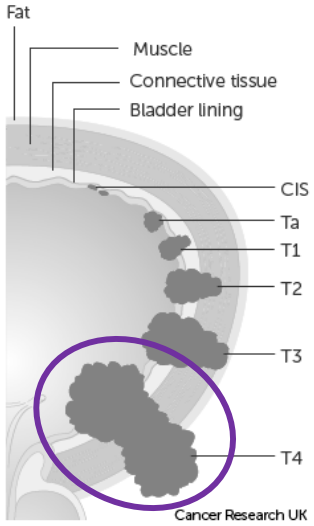

Figure 1-2: Stages bladder cancer, adapted from: (5)

Bladder cancer has high morbidity, mortality, and costs (2). Each year approximately 10,000 people in the United Kingdom (UK) are diagnosed with bladder cancer, making it the tenth most prevalent cancer in the UK (12). Bladder cancer is more common in older men. The age of diagnosis is 75 or higher in approximately 60% of the cases (13). The cancer can be cured at an early stage. However, UK data from 2014 showed that about 17-20% of patients are diagnosed at stage 4 presenting metastases resulting in a low chance of recovery (14). The one-year survival rate for patients diagnosed with stage 1 is about 95% but decreases to approximately 35% for patients diagnosed with stage 4. The 5-year survival for those diagnosed with stage 4 is about 9-11% (15). Because of the high prevalence in combination with the risk of recurrence and progression, bladder cancer has a major impact on healthcare (1). In 2001 in the UK, the total cost for bladder cancer treatment was estimated to be £55 million and was the costliest cancer based on the estimated cost per patient (£8349)(16).

1.2. Disease management

Nowadays, platinum-based chemotherapy is the standard 1st line treatment for advanced urothelial cancer for patients who are still sufficiently fit (17) (Figure 1-3). Regrettably, development of resistance against chemotherapy restrains progression free survival (PFS) and overall survival (OS). Therefore, patients with current disease management experience progression within about 9 months and have a median overall survival of approximately 14-15 months. Maintenance therapies after chemotherapies have proven to prolong PFS in various cancers (8,18). Today, 1st line maintenance treatment is not allowed in the UK for patients with advanced or metastatic urothelial cancer who respond to the chemotherapy. However, patients with the advanced or metastatic stage of urothelial cancer who experience progression with chemotherapy, are recommended atezolizumab as 2nd line treatment according to the guidelines of National Institute for Health and Care Excellence (NICE) (17,19).

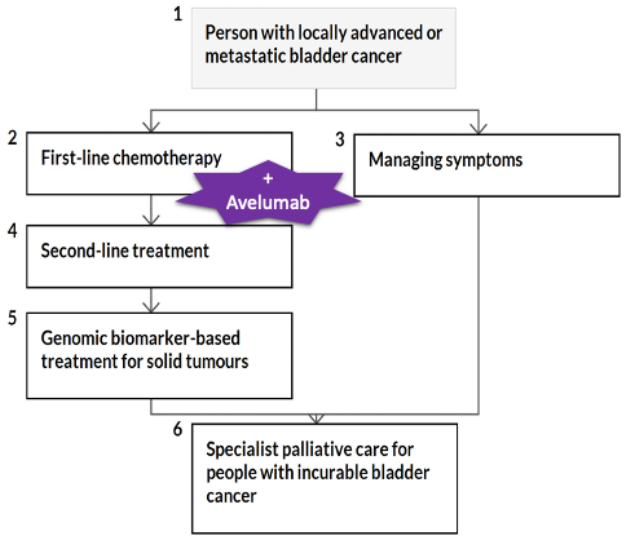

Figure 1-3: NICE pathway for managing locally advanced or metastatic bladder cancer, adapted from (17)

1.3. Avelumab in disease management

Avelumab (Bavencio®), developed and commercialized by Merck and Pfizer, could be used as maintenance treatment. Avelumab is an anti-PD-L1 human IgG1 lambda monoclonal antibody that binds to PD-L1 on cancer cells. Therefore PD-L1 is no longer available to bind to the receptors on T cells and antigen-presenting cells and consequently to perform its inhibitory effect on these cells. As a consequence natural killer cells retain their cytotoxic cell activity and the antigen-presenting cells activate immune responses (Figure 1-4) (20). Given that chemotherapy has several immune priming effects and reduces immunosuppressive cells, avelumab may reinforce the anti-cancer activity, and at the same time hindering potential interactions, cross-resistance, and cumulative toxicity. The JAVELIN Bladder 100 clinical trial, a phase III randomized controlled trial (RCT) of 700 patients with locally advanced or metastatic urothelial cancer who had not progressed with chemotherapy, showed a significantly prolonged survival when the platinum-based chemotherapy was followed by avelumab maintenance therapy plus best supportive care (BSC) compared to BSC alone after the chemotherapy (8).

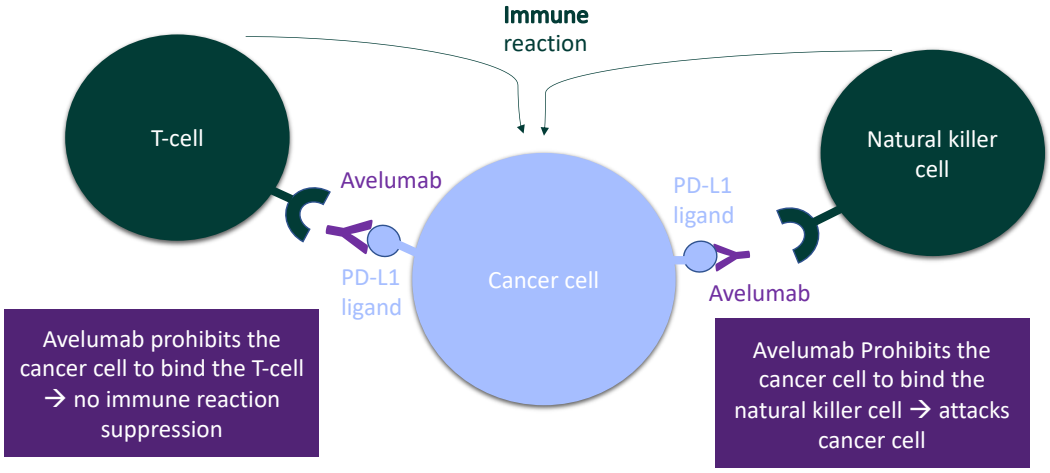

Figure 1-4: Working mechanism avelumab

1.4. Cost-effectiveness innovative cancer drugs

Many innovative cancer drugs, such as avelumab, developed for treating advanced or metastatic cancers are very costly while health care resources are limited. Therefore, discussions arise about the extent to which the drugs provide value. Multiple countries have their own national health technology assessment (HTA) agency to assess the cost-effective use of limited public resources by comparing two or more interventions or treatments based on both costs and benefits (21,22). In this thesis the cost-effectiveness of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy was assessed according to the guidelines of NICE, the HTA agency of England. NICE reviews clinical effectiveness and cost-effectiveness of new approved treatments and provides guidance for the National Health Service (NHS) to make reimbursement decisions (22).

1.5. Thesis objective

On the 10th of December 2020, avelumab obtained a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) to authorize the drug for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy in the UK (23). The positive opinion is based on the previously mentioned JAVELIN Bladder 100 clinical trial. On the 25th of January 2021, the European Commission approved avelumab for this indication. Given this recent approval by the European commission, the positive clinical data and the high prices of innovative cancer drugs, the aim of this study is to evaluate the costs and benefits of avelumab as a maintenance therapy that follows platinum-based chemotherapy compared to the chemotherapy followed by BSC alone among patients with locally advanced or metastatic urothelial cancer. To achieve this objective the following question needs to be answered:

What is the cost-effectiveness of avelumab as maintenance treatment after platinum-based chemotherapy compared to platinum-based chemotherapy followed by BSC alone among patients with locally advanced or metastatic urothelial cancer that has not progressed with the chemotherapy in the UK?

Furthermore, given that avelumab binds to PD-L1 a second objective was defined, namely, to assess the costs and benefits of avelumab for a subgroup of patients who tested positive for PD-L1 expression for which also data was measured in the JAVELIN Bladder 100 trial. This resulted in the following subquestion:

What is the comparative cost-effectiveness of avelumab as maintenance treatment after platinum-based chemotherapy compared to platinum-based chemotherapy followed by BSC alone among PD-L1 positive patients with locally advanced or metastatic urothelial cancer that has not progressed with the chemotherapy in the UK?

In the following chapter entitled 'theoretical framework' an overview of the relevant theory for a cost-effectiveness analysis (CEA) according to the NICE guidelines is given. Subsequential, in the method section the methodological considerations, model design, data inputs, and sensitivity analyses are discussed. In the results section, the outcomes of the model (base case analysis and sensitivity analyses) are described, namely the costs, quality adjusted life years (QALYS), life years (Lys), and cost-effectiveness ratio (ICER) for both considered populations. Lastly, in the discussion the results are discussed, the method is compared to similar CEAs, the assumptions and limitations are reviewed, and policy recommendations are considered.

2. Theoretical framework

2.1. Modelling

Mostly, the goal of a CEA is to understand the cost-effectiveness of an intervention over a lifetime because we aim to capture the full impact of an intervention and, if interventions extend life then a lifetime horizon is relevant (24). Therefore, long-term data on patient outcomes and costs need to be collected. However, clinical trials are often too short to obtain long-term data. In addition, not all relevant data such as costs may be found systematically in the trial and therefore various sources need to be combined. To overcome these limitations a decision model is required. To design a suitable model good knowledge of the natural history of the health condition is a necessity. Health conditions such as cancer have recurrent health events over time and health effects in the long run and patients are at continuous risk of events such as progression. Therefore, unidirectional models such as decision trees where patients only can move from the left to the right can become very complex for cancer treatments. In contrast, Markov models with cohort simulation can be kept less complex as these models contemplate different health states through which patients can transition over time. The health states of a Markov model must be chosen so that every patient is in one of the health states at every point in time. Patients remain in a certain health state for a predetermined period, known as a cycle. When a cycle has ended a patient can remain in their current health state or shift to another one. How and if patients will shift is predicted by transition probabilities (21,25).

When performing a CEA several methodological aspects, which set the boundaries of the analysis, need to be considered (24). As NICE is our audience, these considerations can be largely based on the NICE guidelines, that contain a reference case (24). NICE has to make recommendations for different interventions treating different diseases. To be consistent in their evaluations and recommendations, NICE developed the reference case which specifies several elements for an economic evaluation. An overview of these elements can be found in Table 2-1. A cost-utility analysis is the main method of economic evaluation preferred by NICE (15). Cost-utility analyses express benefits in QALYs. QALYs combine life years with an evaluation of the quality of these years measured via utility scores. A utility score is a preference-based value for a certain health state determined by patients or society (13).

Table 2-1 (a): summary of the reference case, taken from (24)

Element of health technology assessment	**Reference case**
Defining the decision problem	The scope developed by NICE
Comparator(s)	As listed in the scope developed by NICE
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers
Perspective on costs	NHS and Personal Social Services (PSS)
Type of economic evaluation	Cost–utility analysis with fully incremental analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Synthesis of evidence on health effects	Based on systematic review
Measuring and valuing health effects	Health effects should be expressed in QALYs. The European Quality of Life-5 Dimensions (EQ-5D) is the preferred measure of health- related quality of life in adults.

Table 2-1 (b): summary of the reference case, taken from (24)

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers
Source of preference data for valuation of changes in health- related quality of life	Representative sample of the UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)

After the economic evaluation is framed by the methodological considerations, Excel can be used to design and run a Markov model. A model synthesizes evidence on safety, effectiveness and costs of the intervention and comparator. These inputs can be collected via different forms of sources such as published scientific studies, relevant technology appraisals (TAs) by NICE, and routine data sources (21,24).

The costs and benefits of each cycle need to be summed up to obtain the total costs and QALYs for the intervention and the comparator over a lifetime horizon. Afterwards, the ICER, the dependent variable, is calculated. The ICER measures the extra costs per health benefit (e.g., QALY) gained by the new intervention compared to a comparator which is often the standard treatment of care (Formula 2-1). Graphically ICERs may be shown in a cost-effectiveness plane (Figure 2-1). The new intervention is cost-effective (lower costs and higher QALYS) when the ICER is presented in the southeast quadrant. In contrast, the new intervention is not cost-effective (higher costs and lower QALYs) when the ICER is located in the northwest quadrant. In the two remaining quadrants, the ICER must be compared to a cost-effectiveness threshold (λ) which represents the willingness to pay (WTP) per QALY. NICE uses a threshold range of £20,000 to £30,000 per QALY gained (24). When the ICER lies in the northeast quadrant, the new intervention (higher costs and higher QALYs) is cost-effective if the ICER is located below the threshold. The opposite is said for an ICER in the southwest quadrant where the new intervention (lower costs and lower QALYs) is cost-effective if the ICER is located above the threshold (21).

Formula 2-1: Calculation ICER

$$ICER = \frac{C_2 - C_1}{E_2 - E_1}$$

Where:
C_2= costs of new intervention
C_1= costs of comparator
E_2= health effects of new intervention
E_1= health effects of comparator

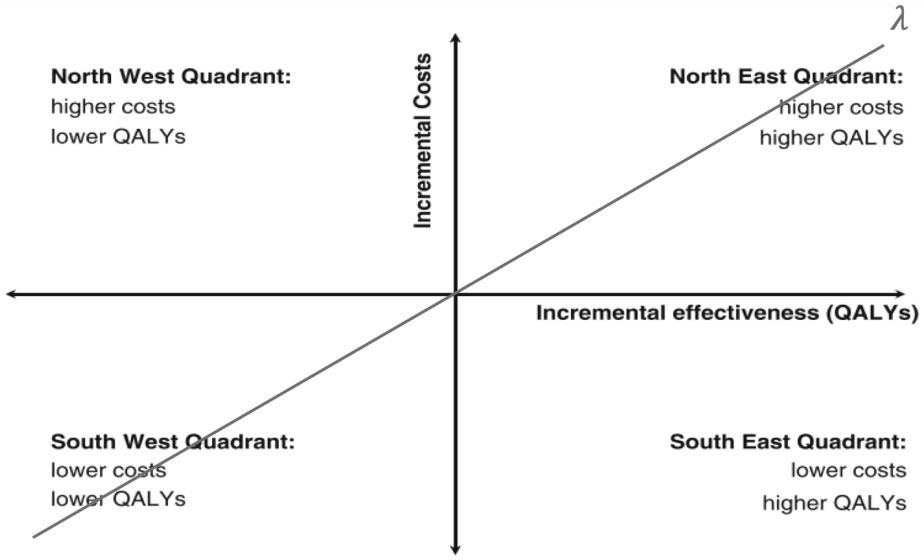

Figure 2-1: Example of a CE-plane, adapted from (21)

The NICE guidelines allow in certain circumstances positive recommendations when the ICER exceeds the upper limit of the threshold range applied by NICE (£30,000). Since 2009 the 'end-of-life' guidance by NICE exists which describes that higher weights to QALYs may be assigned to interventions that meet the end-of-life criteria. These criteria include: 1) the population of the CEA consists of patients with a short life expectancy (normally < 24 months), 2) enough evidence is available to substantiate life extension linked to the intervention (normally an average of at least 3 extra months compared to the current treatment), 3) The life extension estimates need to be robust and proven via PFS or OS, 4) the model assumptions applied in the reference case have to be plausible objective and robust (24,26). Often a threshold of £50,000 per QALY gained is permitted for these interventions (27).

2.2. Uncertainty

A CEA evaluates a treatment based on costs and benefits that will take place in the future. The future always includes an amount of uncertainty (e.g., uncertainty about the patient's response to the treatment)(28). Decision uncertainty is frequently used as a term to appoint the risk of making the wrong decision if the real cost-effectiveness of the technology could be determined. It is important to express the extent of uncertainty that a wrong decision will be made as the health care resources are limited (24). Especially for this study as it considered whether to implement or reimburse an expensive treatment on which a very costly wrong decision could be made.

Four main sources of uncertainty exist in CEA modeling, namely heterogeneity, structural uncertainty, methodological uncertainty, and parameter uncertainty (24,25). The impact of these uncertainties on a CEA is frequently shown by performing sensitivity analyses. Sensitivity analyses explore the sensitivity of model outputs to changes in input parameters. The probabilistic sensitivity analysis (PSA) is preferred by NICE for parameter uncertainty or precision (24). To perform a PSA, three steps must be followed. Firstly, the probability distribution of each input variable must be defined (figure 2-3). This probability distribution reflects the uncertainty of the input variable. Secondly, random values are drawn from each probability distribution and the related outputs (costs and benefits) are calculated. Thirdly, the second step is repeated many times. Consequently, probability distributions of the costs and benefits are obtained. Afterward, the ICER is calculated with the means of these output distributions. The uncertainty measured with a PSA can be presented by a scatter plot on the CE-plane and a cost-effectiveness acceptability curve (CEAC) (Figure 2-4). The scatter plot on the CE-plane gives

a visual representation of the uncertainty in the ICER by displaying the ICERs calculated for each random draw. Whereas a CEAC gives a more quantified representation of the decision uncertainty by presenting the probability that an intervention is cost-effective for a range of cost-effectiveness thresholds (21). To investigate the impact of alternative methods (e.g., extrapolation method), sources of evidence (e.g., different costs), and structural assumptions (e.g., health state categorization), scenario analyses may be performed. One speaks of a scenario analysis when the effect of an alternative method, input or assumption on the result is investigated for a specific given reason (29).

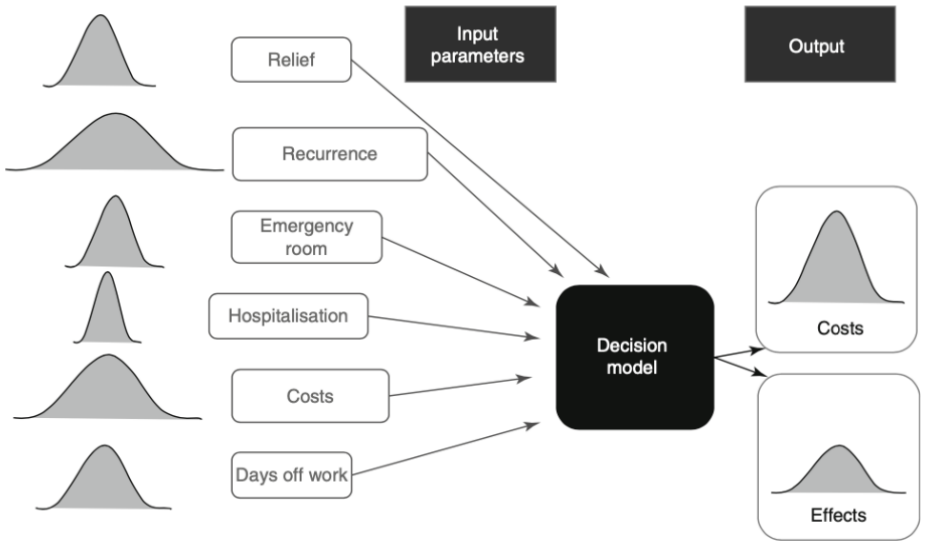

Figure 2-3: Parameter inputs for a CEA model for migraine, taken from (21)

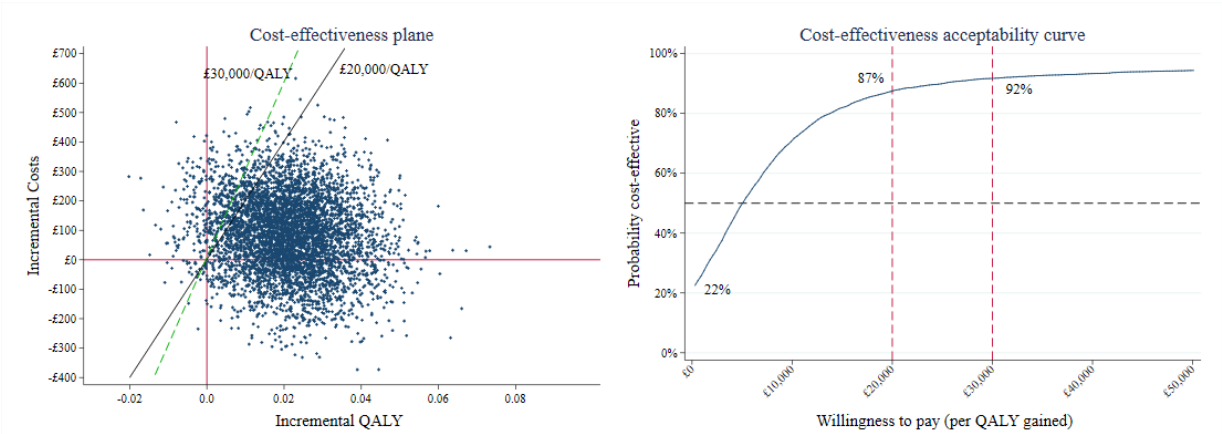

Figure 2-4: CE-plane (left) and CEAC (right) comparing the intervention to the comparator, taken from (30)

3. Methods

In this method section, the methodological considerations, model structure, data inputs (treatment effect, health outcomes and, costs), ad sensitivity analyses are discussed. As previously mentioned, the economic evaluation was performed according to the NICE guidelines (4).

3.1. Patient Population

The target patient population was the one of the JAVELIN Bladder 100 clinical trial, namely adults with locally advanced or metastatic urothelial cancer stage 4 whose disease did not progress during or after completion of 1st line platinum-based chemotherapy (8). This was also the population described in the scope by NICE (19).

As previously mentioned, avelumab binds to PD-L1 to inhibit the evasion of the immune system by tumor cells. Therefore, PD-L1 expression may be assumed predictive for the clinical outcomes of patients treated with avelumab. Consequentially, a targeted treatment approach may improve cost-effectiveness as QALYs are likely to be higher in these PD-L1 positive patients (31). Therefore, an additional evaluation was performed in the subgroup of patients with PD-L1 positive urothelial cancer for which also data was available in the clinical trial. In the trial a patient was considered PD-L1-positive if at least one of the following requirements was fulfilled: 1) minimum 25% of the tumor cells were found positive for PD-L1 expression, 2) minimum 25% of the immune cells were found positive for PD-L1 when at least 1% of the tumor tissue consisted of immune cells, 3) 100% of the immune cells were found positive for PD-L1 when no more than 1% of the tumor tissue consisted of immune cells (8).

3.2. Perspective

The healthcare perspective preferred by NICE was adopted. For the health outcomes, this perspective contemplated all the direct health benefits for the patient. The perspective on costs was the NHS, and PSS perspective. Hence, the costs included in the CEA consisted of drug acquisition costs, drug administration costs, premedication costs, monitoring and management of the disease costs, adverse events (AEs) costs, PD-L1 testing costs, and terminal care costs.

3.3. Intervention and comparator

The intervention of interest consisted of avelumab (800 mg intravenously administered). Avelumab was administered once every two weeks supplemented with BSC until progression as in the JAVELIN bladder 100 trial. This intervention was compared to BSC alone, which is the established clinical management for both considered populations. BSC was administered in the JAVELIN Bladder 100 trial in accordance with local practice based on clinical judgment and disease severity. BSC may consist of antibiotics, pain management, nutritional support, hydration, and palliative local radiotherapy for isolated lesions (8). BSC was also mentioned as comparator in the scope developed by NICE (19).

3.4. Model structure and settings

Microsoft Excel was used to design and run a cohort Markov model. The model consisted of three mutually exclusive health states, namely progression-free (PF) or stable disease (SD), progressed disease (PD), and death (Figure 3-1). This structure was based on structures used in other CEAs for locally advanced or metastatic urothelial cancer (32–35). The number of patients in the health states at each cycle was based on the area under the fitted curves to the trial OS and PFS Kaplan-Meier (KM) curves which were different for both treatment arms (Figure 3-2) (see 3.5.1.2.). The OS curve

determines the number of patients in the death state and the PFS curve determines the number of patients in the PF health state. The number of patients in the progressed state was determined by the difference between both curves. At the start, all patients were assumed to be in the PF health state where they received either avelumab plus BSC or BSC alone. They remained in this health state until progression or death. The patients that progressed could not return to the PF state. Both PF and progressed patients could move to the death state. Switching to other health states could only happen at the end of a cycle. However, to better represent the reality that patients can switch at any time, a half-cycle correction (HCC) was applied when costs and health outcomes accrued during the cycle length. Death is the end state from which patients cannot move.

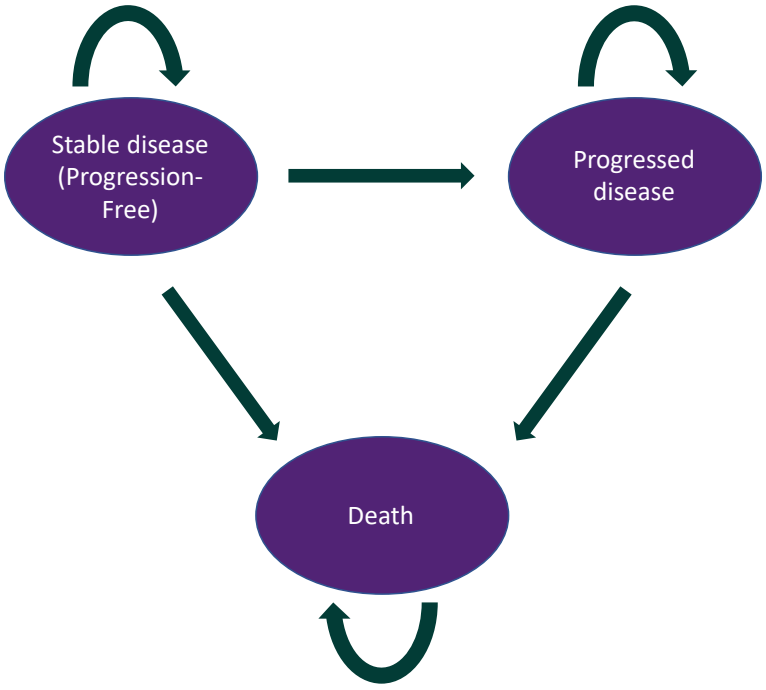

Figure 3-1: A Markov model, adapted from (32)

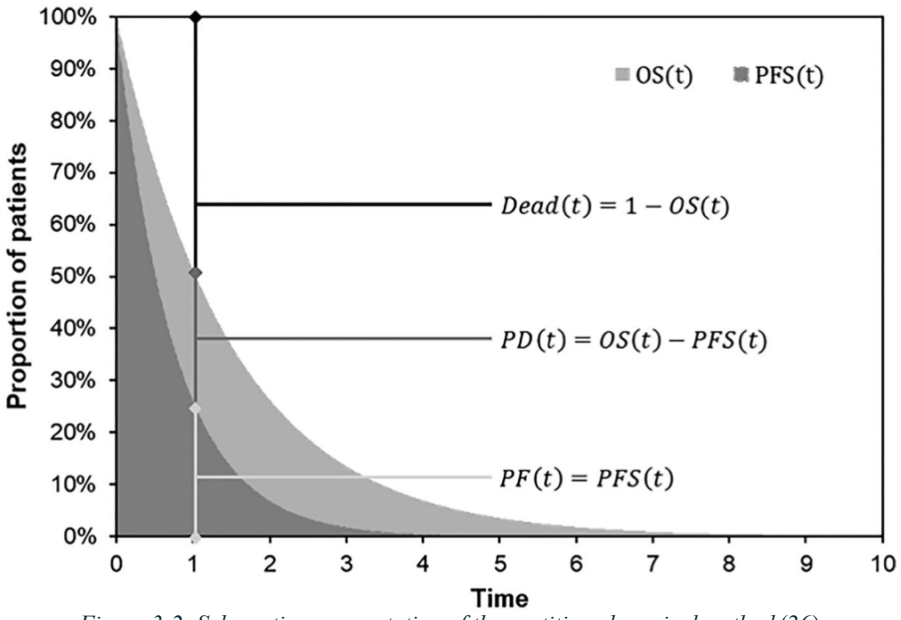

Figure 3-2: Schematic representation of the partitioned survival method (36)

The time horizon of the CEA had to be long enough to measure the relevant differences in costs and benefits between the two arms (24). A lifetime horizon was chosen as avelumab affects benefits (e.g., survival) and costs during the rest of the person's life. Moreover, a lifetime horizon is in accordance with the NICE guidelines. The lifetime horizon amounted to 40 years as at that timepoint less than 0,1% was alive in both arms. The cycle length was 28 days (4 weeks) like in the clinical trial. To compare costs and benefits at different time points, the NICE preferred discount rate of 3.5% was used (24).

3.5. Inputs

To run the model, multiple inputs were inserted in the model. The inputs such as OS, PFS, utility values, and costs were collected via different forms of sources such as published scientific studies, clinical trials, specific databases (e.g., British National Formulary (BNF)) and relevant TAs by NICE. To find scientific studies several search terms were often used (urothelial cancer, utility, costs and, economic evaluation) in search engines such Google Scholar, Embase, and sEURch. The same data for the overall population and PD-L1 subgroup were applied except from OS, PFS and the costs related to PD-L1 testing due to lack of specific data for the subgroup.

3.5.1. Treatment effect

3.5.1.1. JAVELIN Bladder 100

A randomized controlled phase 3 trial, named JAVELIN Bladder 100, investigated the clinical efficacy of avelumab as maintenance therapy in patients with stage 4 unresectable locally advanced or metastatic urothelial cancer who did not experience progression with platinum-based chemotherapy. For this, 700 patients, who had received four to six cycles of gemcitabine in combination with cisplatin or carboplatin from which the last dose was administered four to ten weeks prior to randomization, were assigned to BSC supplemented with avelumab or to BSC alone (Figure 3-3). Different endpoints were investigated (OS, PFS, safety and tolerability, and patient-reported outcomes (PROs)). OS and PFS were also investigated in a subgroup of PD-L1 positive patients (8).

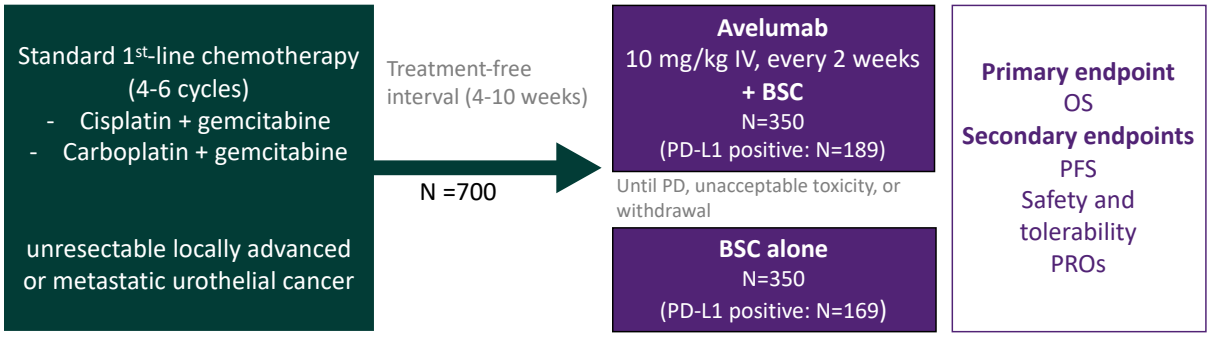

Figure 3-3: Schematic overview JAVELIN Bladder 100 trial

The trial outcomes were quite positive. In the total population, the OS at 1 year was 71.3% in the avelumab arm compared to 58.4% in the control arm. The median OS was prolonged by 7.1 months in the arm receiving avelumab compared to the control arm (median OS of 21.4 months vs. 14.3 months, HR: 0.69) (Figure 3-4). In the subgroup of PD-L1 positive patients, the OS at 1 year was also significantly increased, namely 79.1% in the avelumab arm compared to 60.4% in the control arm (Figure 3-5). Moreover, the median PFS was almost doubled in the treatment arm vs. the control arm of the overall population (median PFS 3.7 months vs. 2.0 months, HR: 0.62) and is even more than doubled in the treatment arm vs. the control arm of the PD-L1 subgroup (median PFS 5.7 months vs. 2.1 months, HR: 0.62) (Figure 3-4, 3-5)(8). Furthermore, avelumab showed an acceptable safety and tolerability profile

which was in line with earlier studies of avelumab monotherapy (37,38). More AEs were observed in the avelumab group compared to the control group. 47.7% Of the patients receiving avelumab experienced AEs of grade 3 or higher compared to only 25.5% of the patients receiving only BSC. However, all the grade 3 or higher AEs had an infrequent occurrence (< 5%) (Appendix A) (8). To conclude, the overall benefit/risk ratio was positive. Avelumab proved to be significantly effective for the life-threatening disease (38).

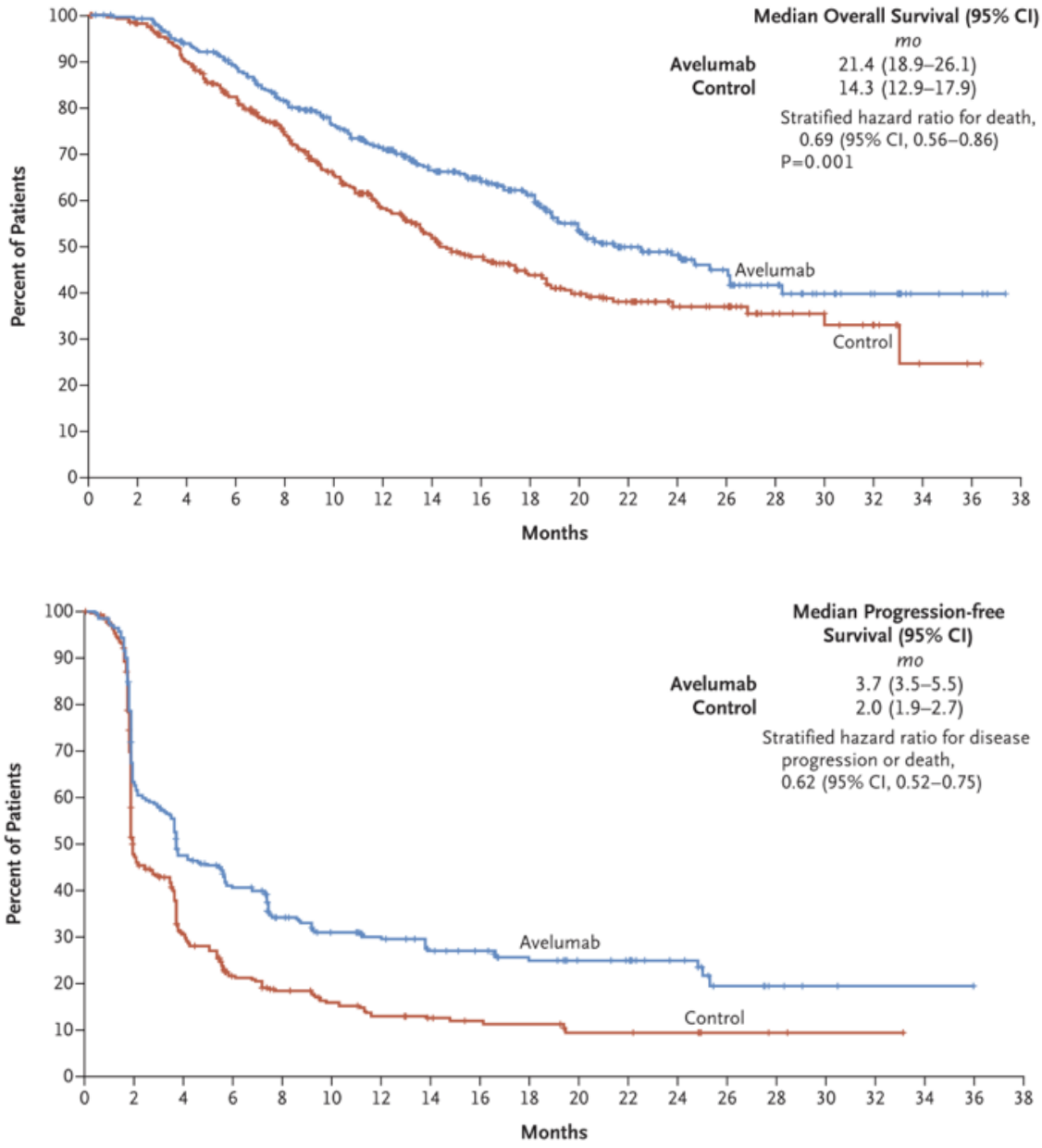

Figure 3-4: OS and PFS survival measured in the overall population of the JAVELIN Bladder 100 trial, taken from: (8)

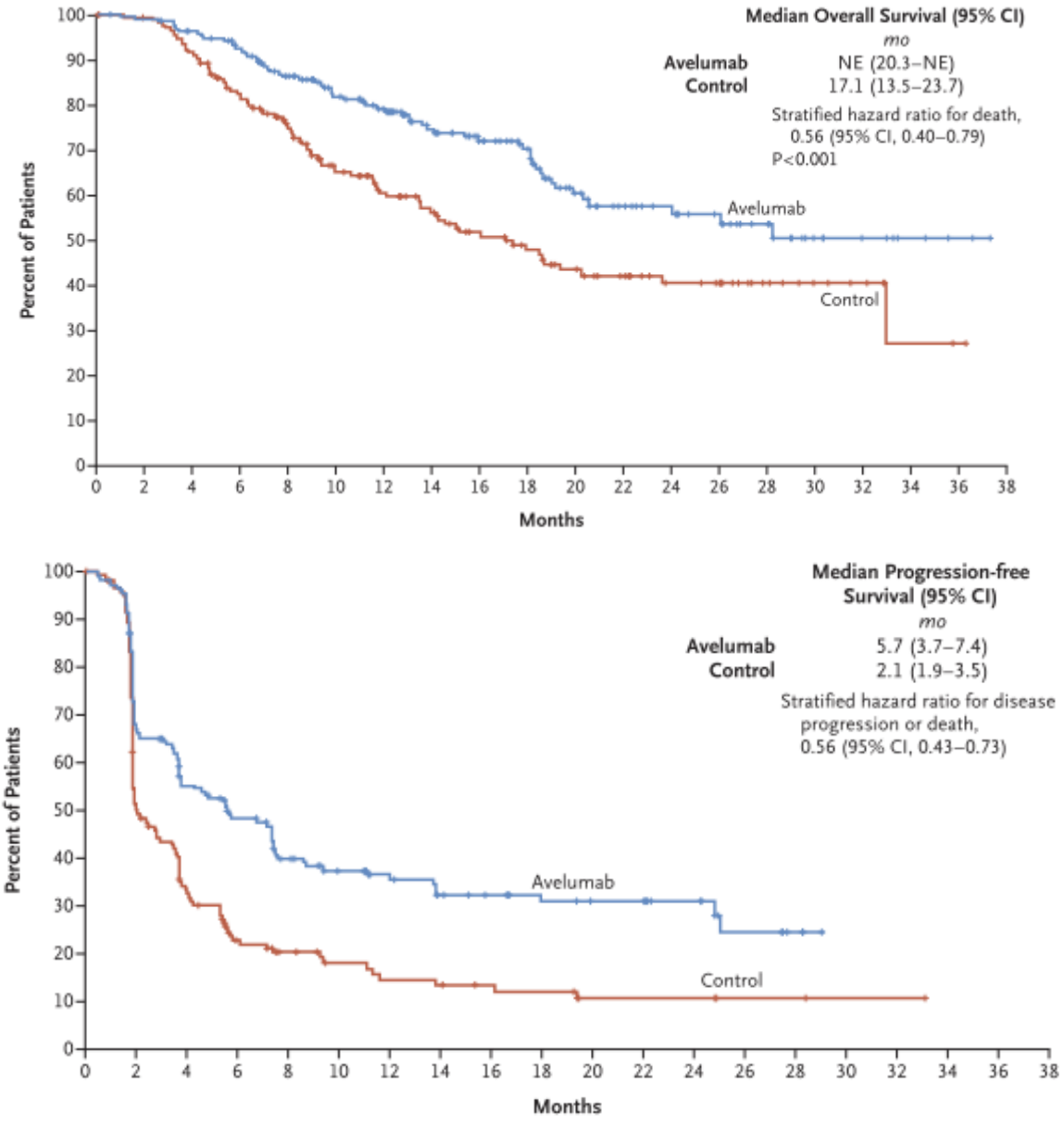

Figure 3-5: OS and PFS survival measured in the PD-L1 subgroup of the JAVELIN Bladder 100 trial, taken from: (8)

3.5.1.2. Modelling OS and PFS

Looking at the OS KM curves of the overall population and PD-L1 subgroup, not all patients died during the clinical trial (Figure 3-4, 3-5). Therefore, OS had to be extrapolated to estimate survival over the lifetime horizon required by the model. In addition, individual patient data (IPD) were not available (8). IPD is the occurrence of censorships or events for each patient. The method of Hoyle and Henley was used to estimate the IPD and to subsequently fit extrapolated curves to the OS KM curves to reflect a lifetime horizon (39). For this the x and y values were extracted from the KM curves, using the WebPlotDigitizer software version 4.4 (40). Thereafter, the 2 weekly IPD were estimated with the method of Hoyle and Henley based on these extracted x and y and the numbers of patients at risk (the number of patients who have not experienced the event or been censored). Subsequently, parametric distributions (exponential, Weibull, lognormal and, loglogistic) were fitted to the estimated IPD data using RStudio© (Version 1.4.1103, 2009-2021) (Figure 3-6, 3-8) (41). Lastly, the most appropriate parametric distributions were chosen based on best-fit (the lowest AIC (Akaike Information Criterion) value) and clinical plausibility. The same method was applied to the PFS curves of the overall population and the PD-L1 positive subgroup (Figure 3-7, 3-9).

Overall population

Based on the AIC values (Table 3-1) the lognormal distribution was found to be the best statistical fit for the OS KM curves of the overall population in the clinical trial. The 5-year survival for those diagnosed with stage 4, reported by Cancer Research UK, is about 9-11% (15). The lognormal distribution for BSC shows a 5-year OS of 10% and therefore appears clinical plausible. However, patients were still alive in the Markov trace after 40 years (0.61%) and given that the mean age in the trial was 67.44 (9.40)(42), this seemed to be unrealistic. The loglogistic distribution showed the same issue of patients living for an unrealistically long time. A Weibull distribution was also considered inappropriate as it showed a 5-year OS around 3% which did not reflect the 5-year OS of 9-11%. Therefore, an exponential distribution with a 5-year OS of 9% was applied for OS extrapolation despite it had the highest AIC score and does not fit the beginning and latter parts of the KM curve very well.

All the four extrapolations for PFS do not seem to fit the latter part. The lognormal distribution was chosen for the PFS curves as it had the lowest AIC value and no appropriate real-world data on PFS was found.

After applying the exponential and lognormal distribution for OS and PFS respectively, the OS and PFS rates from these distributions were used in the Markov trace. The distribution of the patients between the three health states was assumed to be clinical plausible. The determined lifetime horizon lasted 40 years as less than 0.01% of the patients considered in the model were alive in both arms after 40 years. This was assumed to be a good lifetime horizon given that TA519 (Pembrolizumab (2nd line) for Locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) had a lifetime horizon of 35 years for patients already receiving 2nd line treatment (34). In scenario analyses, the effect of all four distributions for both OS and PFS on the ICER was investigated as well as the effect of the life-time horizon by applying a shorter lifetime horizon of 20 years.

Table 3-1: AIC values of the fitted parametric curves for the OS and PFS of Avelumab + BSC and BSC alone for the overall population

Endpoint	Arm	Exponential	Weibull	Lognormal	Loglogistic
PFS	Avelumab + BSC	1815.228	1800.644	**1723.529**	1734.732
	BSC	1750.436	1751.324	1629.505	**1611.669**
OS	Avelumab + BSC	1524.525	1512.185	**1498.117**	1504.154
	BSC	1725.463	1714.435	**1691.036**	1695.973

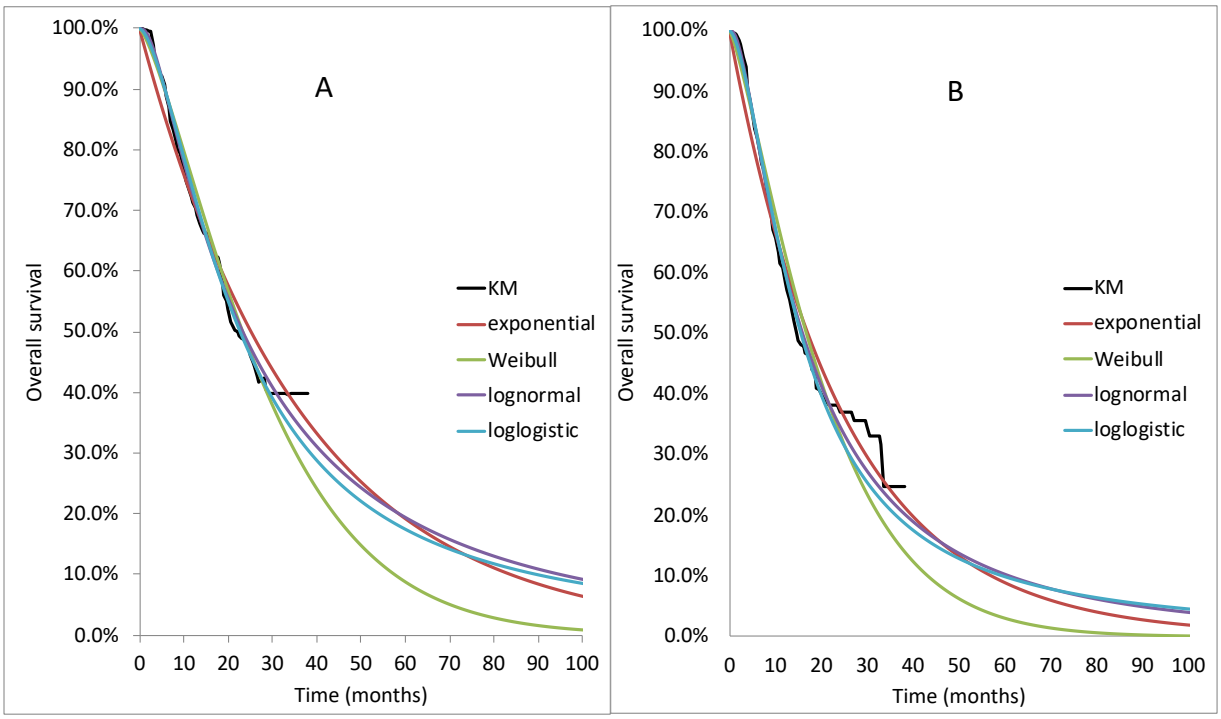

Figure 3-6: Fitted separate standard parametric curves for the OS of Avelumab + BSC (A) and BSC alone (B) in the overall population

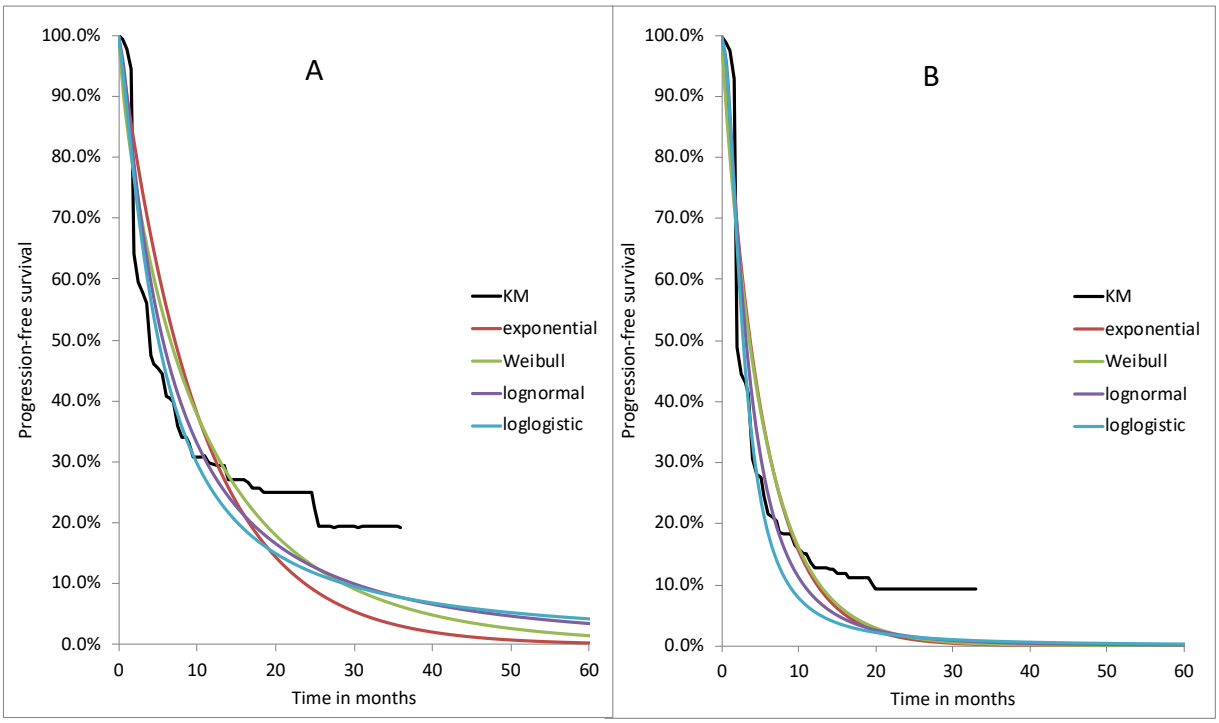

Figure 3-7: Fitted separate standard parametric curves for the PFS of Avelumab + BSC (A) and BSC alone (B) in the overall population

PD-L1 subgroup

Based on the AIC values for the PD-L1 subgroup (Table 3-2), the lognormal distribution was again found to be the best statistical fit for the OS KM curves. (15). The lognormal distribution for BSC shows a 5-year OS of 13% which is close to the range reported for the overall population by Cancer Research UK (9-11%). However, the PD-L1 subgroup has a worse prognosis than the overall population and therefore the 13% was assumed to be an overestimation. Furthermore, too many patients were still alive in the Markov trace after 40 years (1%). The latter was also the case when applying the loglogistic distribution. The Weibull showed a 5-year OS of 5% which was assumed to be too low as this is half as much as the range reported for the overall population by Cancer Research UK (9-11%) which also include the PD-L1 subgroup. Hence, the exponential distribution was also applied for OS of the PD-L1 subgroup, despite it had the highest AIC score and does not fit the beginning and latter parts of the KM curve very well.

The lognormal distribution was also chosen for the PFS curves as it had the lowest AIC value and no appropriate real-world statistics on PFS were found.

For the same reasoning as for the overall population, the lifetime horizon also lasted 40 years for the subgroup.

Table 3-2: AIC values of the fitted parametric curves for the OS and PFS of Avelumab + BSC and BSC alone for the PD-L1 subgroup

Endpoint	Arm	Exponential	Weibull	Lognormal	Loglogistic
PFS	Avelumab + BSC	*1102.444*	*1098.732*	***1061.053***	*1066.42*
	BSC	*929.1812*	*927.3867*	*874.1592*	***871.362***
OS	Avelumab + BSC	*683.7221*	*676.402*	***670.1034***	*673.1864*
	BSC	*835.2929*	*832.8879*	***817.4947***	*823.3443*

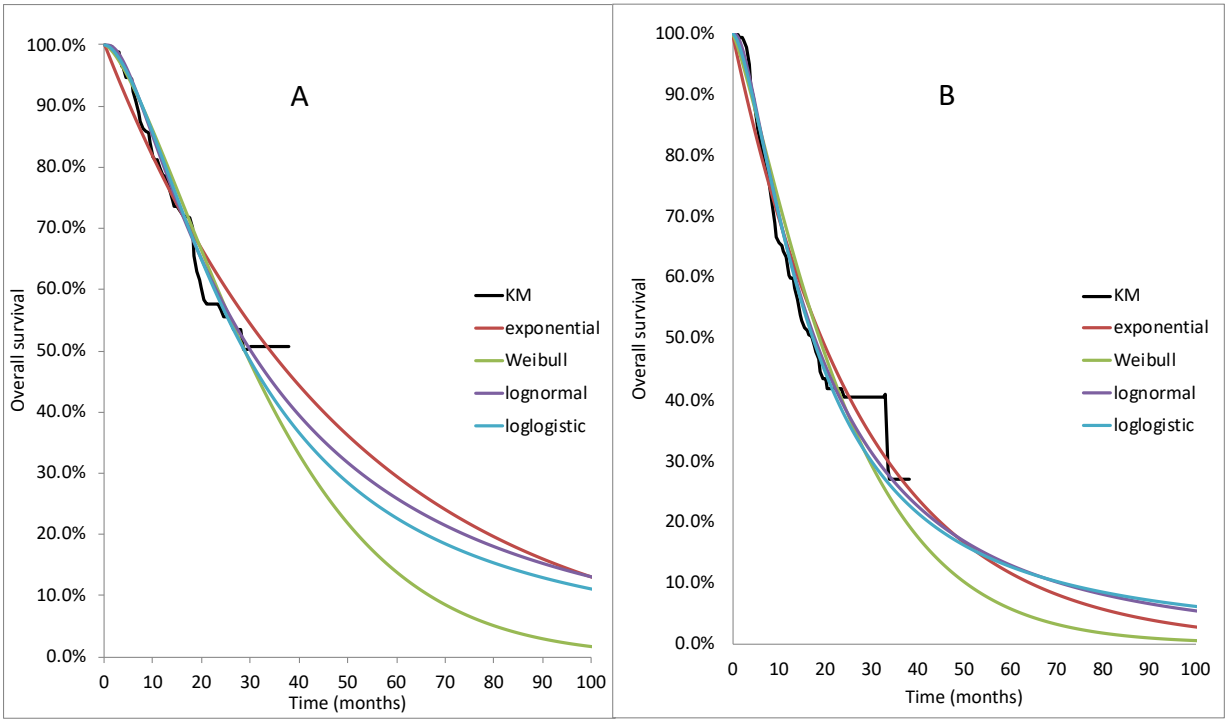

Figure 3-8: Fitted separate standard parametric curves for the OS of Avelumab + BSC (A) and BSC alone (B) in the PD-L1 subgroup

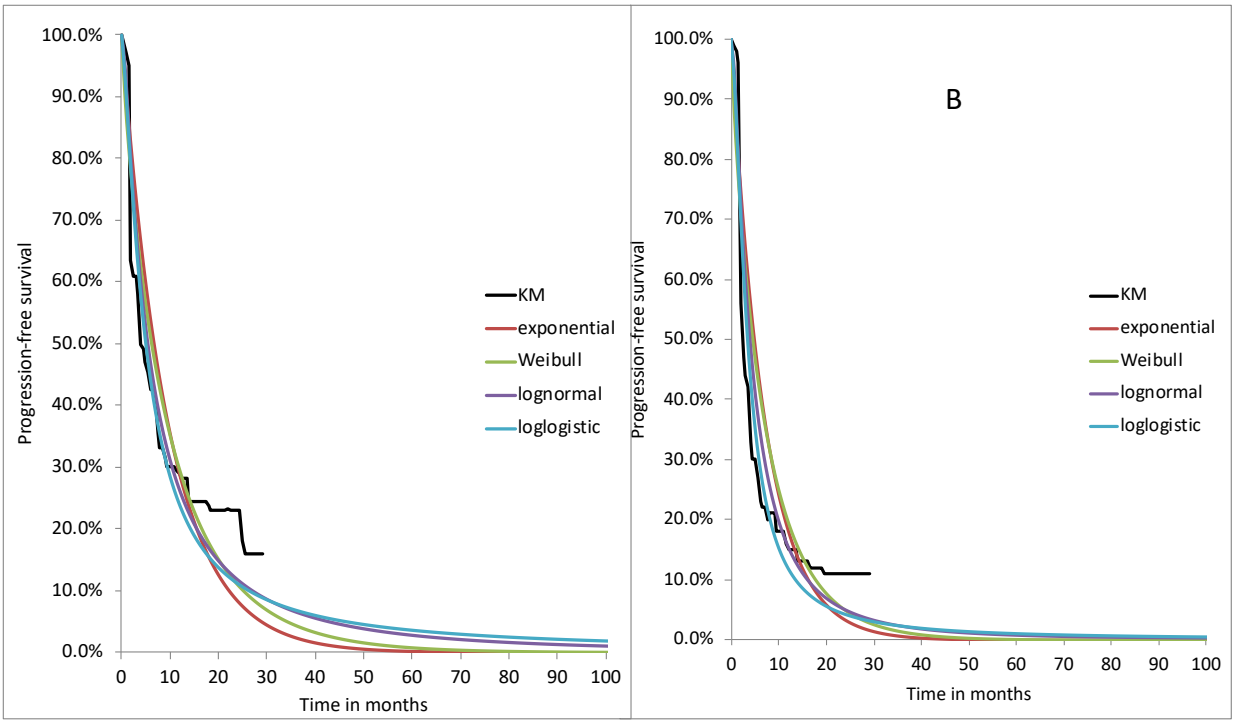

Figure 3-9: Fitted separate standard parametric curves for the PFS of Avelumab + BSC (A) and BSC alone (B) in the PD-L1 subgroup

3.5.1.3. Safety

AEs observed in the JAVELIN Bladder 100 trial are summarized in Appendix A (8). Often only grade ≥ 3 AEs with an incidence of at least 5% are considered in a model, but no AEs of grade ≥ 3 met this lower limit in the trial. To still include the impact of AEs, the incidence limit was lowered to 3%. The identified AEs with an incidence of at least 3% and a grade ≥ 3 observed in either treatment arm were urinary tract infection (UTI) and anemia (8). These AEs were assumed to have the biggest impact on the health outcomes and costs. The impact of these AEs on health outcomes (i.e., QALYs) and costs are discussed in section 3.5.2.2. and 3.5.3.5., respectively.

3.5.2. Health outcomes

3.5.2.1. Health state utilities (SD and PD)

To inform the CEA, utility values by progression status were searched in patients with locally advanced or metastatic urothelial cancer who did not experience progression after 1st line platinum-based chemotherapy. An overview of the utility values by progression status applied in the model are shown in Table 3-3. All health outcomes were half cycle corrected and discounted with a discount rate of 3.5%.

Table 3-3: Overview utility values by progression status

	Utility values value	**Source**
Progression-free	0.792	JAVELIN Bladder 100
Progressed	0.632	TA519 +TA530

Baseline utility scores were measured in the JAVELIN Bladder 100 clinical trial for both arms. They were measured with the EQ-5D-5L for which clinical trial participants had to score their problems (none, slight, moderate, severe, extreme/unable) in five categories (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). UK-specific valuation tariffs were used to determine a single global utility value (42).

The mean baseline utility values measured in the trial were 0.814 and 0.792 for patients receiving avelumab (+ BSC) and patients receiving only BSC, respectively (42). The difference in these baseline scores was probably due to random chance as patients in a RCT trial are supposed to be similar in both arms at the start of the study. To eliminate the difference in utility scores between the two arms the utility value of 0.792 measured for patients receiving BSC alone was applied to the SD state of both arms in the model. This value was chosen as it seemed to be more realistic given that the utility value for the average UK person aged 65-74 amounts to approximately 0.778 (43). The baseline value of 0.814 measured in the avelumab arm was applied in a scenario analysis. Differences between the two arms were captured with disutilities as the baseline values did not include any effect of AEs on the Health-related quality-of-life data (HRQOL) because the baseline values were measured before the treatments were started (section 3.5.2.2.).

No appropriate utility values were measured in the JAVELIN Bladder 100 trial for the PD state. Furthermore, no appropriate literature was observed and no CEAs for 1st line maintenance treatments for the given indication have previously been assessed in the UK (8). Therefore, the PD utility values used in TAs for 2nd line immunotherapies were considered, namely TA530 (nivolumab for treating patients with locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) and TA519 (pembrolizumab for treating patients with locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) (Table 3-4) (33,34). TA525 (atezolizumab (2nd line) for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) was not found to be suitable as it utility values were linked to on or off treatment instead of to the progression status (35). The utility values amounted to 0.623 and 0.641 in TA519 and TA530, respectively. These values were considered appropriate by the evidence review group (ERG) for the TAs. They were measured in the relevant trials (TA519: KEYNOTE-045, TA530: CheckMate 275) for the drug and indication with the EQ-5D-3L. The average of the two utility values was calculated and applied to the progressed state of both arms in the model.

Table 3-4: PD utility values

Progressed disease			
treatment	**Utility value**	**Standard Error**	**Source**
2L Nivolumab	0.623	N/A	TA530
2L Pembrolizumab	0.641	0.013	TA519
Average	**0.632**	**0.013**	

3.5.2.2. Adverse events (disutilities)

To account for the impact of AEs on the health outcomes during treatment with Avelumab (+BSC) and BSC alone, disutilities measured for the AEs (UTI and anemia) were considered. No disease-specific disutilities were available. Therefore, non-disease-specific disutilities found in scientific studies and applied in TAs with a similar population were used. Two relevant studies were found for the disutility value related to anemia. The study by Beusterien et al. measured a UK population preference disutility value of -0.09 with standard gamble in patients with chronic lymphocytic leukemia experiencing anemia (44). Chronic lymphocytic leukemia is more frequently observed in older men (median age at diagnosis is 72 years) (34). Furthermore, this disutility for anemia was applied previously in TA530

(nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy) (33). The other study, performed by Lloyd et al., measured a disutility for anemia with standard gamble interviews in members of the UK general public (46). The study measured a utility value of 0.583 in patients with severe anemia (patients with 7.0–8.0 g/dl, equal to grade 3 or higher) and 0.708 in patients without anemia, leading to a disutility of -0.125. This disutility value was used in TA391, an appraisal for prostate cancer (47). Prostate cancer is in 35% of the cases diagnosed in men older than 75 years (48). The applied disutility value for anemia in this study is an average of the utility values measured in the two mentioned studies, namely -0.11.

The applied disutility for UTI was based on three studies in adults (49–51) (Table 3-5). The studies were found in a systematic literature review of the quality of life in people with UTI performed by Bermingham et al. (52). None of the three studies investigated utility values in the population of this study regarding age, sex, and disease. Furthermore, they were performed in different countries (not in the UK), and they all used different measurement instruments. However, despite the differences between the three studies, the calculated disutilities are very similar. Therefore, the disutility of UTI was assumed to be robust to these differences. The average disutility of the three studies amounted to -0.094 which was applied in our model.

Table 3-5: Utility values UTI

Utility values for patients with a symptomatic UTI								
Study	Country	Population	Measure	Recall	No UTI	UTI	Severe UTI	Disutility
Maxwell et al.	USA + Canada	Older adults living in care homes N=514 Mean age = 80.5 (8.4) Male 28%	HUI2	1 week	n=496 0.49 (0.01)	n=18 0.40 (0.04)	-	-0.09
Zebracki et al.	USA + Canada	Adults with SCI N=415 Mean age = 30.9 (5.3) Male = 63%	Mapped EQ-5D	1 year	n=134 0.831 (0.01)	n=238 0.782 (0.01)	n=42 0.738 (0.03)	-0.093 (severe)
Haran et al.	Australia	Individuals with SCI predominantly living in N=305 Mean age = 44(14) Male = 83%	SF-36	6 months	n = 167 0.68 (0.01)	n = 138 0.58 (0.01)	-	-0.1
Average								**-0.094**

Both calculated disutilities for anemia and UTI were corrected for the incidence and duration of the AEs (Table 3-6). The applied incidences were the proportions of patients experiencing these AEs of a grade 3 or higher in the relevant arm in the JAVELIN Bladder 100 trial (8). The duration for anemia was taken from the TA391, while the duration for UTI was based on the maximum days of a long-course treatment duration (47,53). The total disutilities were applied as one-off events in the first cycle of the relevant arm in the model, as no further details about experiencing AEs were available, namely timing and frequency per individual.

Table 3-6: Overview of the adverse events with their disutility value, incidence, and duration + the total disutilities applied for both arms in the model

Adverse event (Grade ≥3)	Disutility		Standard error		Duration (days)	Incidence Avelumab + BSC (> 2%)	Incidence BSC (>2%)	Source disutility	Source duration	Source incidence
UTI	-0.09		0.01		14.00	4.40%	2.60%	Bermingham et al. (2012)	Lutters et al (2008)	JAVELIN bladder 100 clinical trial
Anemia	-0.13	-0.11	0.02	0.02	25.40	3.80%	2.90%	Lloyd et al (2008)	NICE TA391	
	-0.09		0.02					Beusterien et al (2010)		
Total disutility Avelumab +BSC					-0.0004					
Total disutility BSC					-0.0003					

3.5.3. Resource use and costs

The identified relevant costs were those related to the drug avelumab, BSC, subsequent interventions, drug administration, premedication, monitoring and management of the disease, adverse events, and terminal care. In the CEA for the PD-L1 positive subgroup costs related to diagnostic testing for the biological marker were considered. Data on resource use was collected via previous NICE TAs for avelumab or urothelial cancer, scientific studies, the JAVELIN Bladder 100 trial, and the Summary of Product Characteristics (SmPC) (8,54). An overview of the used NICE TAs can be found in appendix B. Costs were searched in the BNF 2021, NHS reference costs 2018-2019, Personal Social Services Research Unit (PSSRU) 2019, and the electronic Market Information Tool (eMIT) 2021 (55–58). All costs, except those taken from BNF 2021 and eMIT 2021, were when needed indexed to 2018-2019 using the NHS Cost Inflation Indices (NHSCII) from PSSRU 2019 (57). Furthermore, all costs were discounted with a discount rate of 3.5%.

3.5.3.1. Drug acquisition costs

Avelumab

Avelumab is on the market as a 200mg vial with a list price of £768 (Table 3-7)(59). In the JAVELIN Bladder 100 clinical trial, the intervention was administered intravenously once every 2 weeks at a dose of 10mg/kg body weight and supplemented with BSC (8). Despite the fact that the dosing was weight-based in the clinical trial, flat dosing of 800 mg per administration was used in the CEA, as a flat dose usage is mentioned in the SmPC of avelumab (54). In addition, Novakovic et al. showed similar benefits (efficacy and safety) between weight-based dosing and flat dosing of avelumab in patients with metastatic Merkel cell carcinoma and platinum-treated urothelial carcinoma (60). Hence, the same efficacy and safety results of the trial could be used. Furthermore, the difference in costs between the two dosing strategies will probably not differ. To achieve the flat dosing of 800 mg per administration, four vials should be used, which results in a total drug acquisition cost of £3,072 per administration for avelumab. When applying weight-based dosing, 757.6 mg would need to be administered for an average weighted person (75.76 kg) (35). The average weight was taken from TA525 (atezolizumab for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) as no weights measured in the JAVELIN Bladder 100 trial were made public. When wastage costs would be assumed also 4 vials would have been needed on average for weight-based dosing resulting in the same total drug acquisition cost of £3,072 per administration.

Avelumab was administered two times per cycle to patients in the PF health state until progression. In a scenario analysis the effect of a stopping-rule of 3 years on the result was investigated (Section 4.6.2.). An HCC was applied to the second administration.

Table 3-7: Drug acquisition cost avelumab

Drug Acquisition Related Cost Avelumab								
	Dose (mg)	Vial size (mg)	Vial (ml)	Cost/Vial (£)	Number of vials/patient	Times per cycle	Cost/Cycle (£)	Reference
Avelumab	800	200	10	768.00	4	2	**6144.00**	BNF 2021

BSC

As previously mentioned BSC may consist of antibiotics, pain management, nutritional support, hydration, and palliative local radiotherapy for isolated lesions according to the trial and scope (8,19). However, no detailed data on the exact BSC treatment was provided. Therefore, the drugs considered for BSC in TA530 (nivolumab (2nd line) for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) were used in the model (Table 3-8)(33). The cheapest unit cost for each drug was searched in eMIT2021 (58). The total cost per cycle amounted to £14.37. This cost estimate was applied to the PF patients in both treatment arms and to those who progressed and did not receive 2nd line treatment. As BSC was not costly and given in both arms no large impact of assumptions related to BSC content and cost on the result was expected.

Table 3-8: Drug acquisition cost BSC

Drug Acquisition Related Costs BSC												
	Dosage (mg)	Frequency	Times per cycle	Cost per pack	dose per unit (mg)	Pack size	Unit cost	Cost/ Cycle	Quantity	Standard deviation pack	Source costs	source medication use
Prednisolone	10.00	Every day	14	£2.93	20.00	28	£0.10	**£1.47**	22783	£21.49	eMIT 2021	TA530
Morphine	40.00	Every day	56	£10.26	20.00	56	£0.18	**£10.26**	1082	£0.27		
Gabapentin	300.00	Every day	28	£1.98	300.00	100	£0.02	**£0.55**	65784	£0.54		
Alendronic acid	10.00	Every day	28	£2.10	10.00	28	£0.07	**£2.10**	754	£0.69		
Total cost per cycle								**£14.37**				

Subsequent therapies

During treatment with avelumab as maintenance therapy or BSC alone, patients may progress and receive subsequent therapies. There is no established standard 2nd line therapy after failure of 1st line platinum-based chemotherapy. 42.3% of the patients who received avelumab in the clinical trial, received subsequent therapy of which 6.3% immunotherapy (anti-PD or anti-PD-L1 treatment), 2.60% fibroblast growth factor receptor and 40% other 2nd line therapy. In the arm of patients who received only BSC, 61.7% received 2nd line therapy of which 43.7% immunotherapy, 2.30% fibroblast growth factor receptor and 34% other 2nd line therapy. Some patients may receive multiple subsequent therapies (Figure 3-10)(8). The drug acquisition costs related to these subsequent therapies were applied as one-off costs to all the newly progressed patients. An overview of the drug acquisition costs for the considered subsequent therapies in the model can be found in Table 3-9.

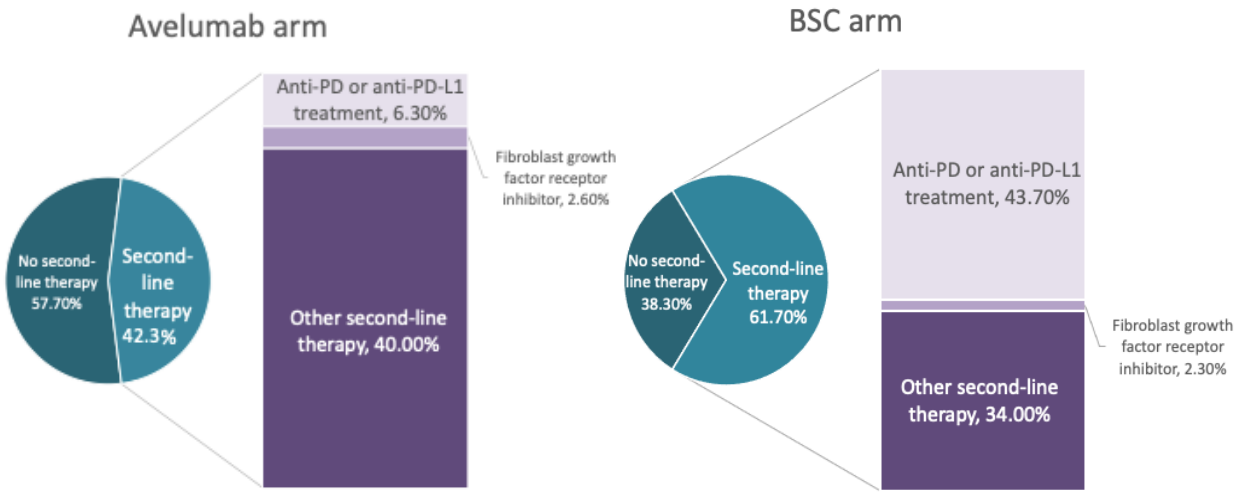

Figure 3-10: Subsequent anticancer therapies and their incidences based on the JAVELIN Bladder 100 trial patients

Three anti-PD or anti-PD-L1 immunotherapies are mentioned in the NICE guidelines for diagnosis and management of bladder cancer as 2nd line therapy for advanced or metastatic bladder cancer, namely atezolizumab, pembrolizumab and, nivolumab. However, pembrolizumab and nivolumab are no longer recommended, within their marketing authorization, as a treatment option (17). Therefore, only atezolizumab was considered as immunotherapy in our base case analyses. Atezolizumab was administered every 3 weeks, at a fixed dose of 1200 mg for which only one vial with a list price of £3807.69 was necessary (61). This immunotherapy is allowed for a maximum of two years. As the maximum allowed duration of treatment is not always reached and given that atezolizumab has a big impact on the ICER because of its high drug costs, a shorter duration was applied in the base case analysis, namely a duration of 3 months. This treatment duration was determined based on the time when 50% of the patients had the probability to be on treatment in the IMvigor 210 trial, a study of atezolizumab in participants with locally advanced or metastatic urothelial bladder cancer. The time to treatment discontinuation (TTD) curve is shown in appendix C (35). A scenario analysis was performed with the maximum treatment duration (24 cycles). Furthermore, a scenario analysis with pembrolizumab was performed as it only recently was withdrawn from the market in the UK (28 April 2021) and therefore probably still administered in the trial as 2nd line treatment. Before pembrolizumab was withdrawn, it was funded by the cancer drug fund (CDF). Pembrolizumab was administered every three weeks at a flat dose of 200 mg (62). Therefore, 2 vials of 100 mg with a list price of £2630.00 were consumed per administration. The average treatment duration per patient of 6.84 months mentioned in TA629 (A CDF review of TA519: pembrolizumab for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) was used for the duration of the pembrolizumab treatment. This duration included follow-up of pembrolizumab administration when it was sourced from the CDF (63).

Other 2nd line treatments described in the NICE guidelines for diagnosis and management of bladder cancer are four different chemotherapy regimens: gemcitabine plus cisplatin, accelerated MVAC (methotrexate, vinblastine, doxorubicin and, cisplatin) in combination with a Granulocyte colony-stimulating factor (G-CSF), and carboplatin or gemcitabine plus paclitaxel (17). A survey of the UK practice in 2014 identified seven different regimes that were preferred as 2nd line chemotherapy (MVAC, paclitaxel, vinflunine, docetaxel, gemcitabine/cisplatin, gemcitabine/carboplatin, single agent gemcitabine). MVAC, gemcitabine/cisplatin, gemcitabine/carboplatin and, paclitaxel were preferred the most (Appendix D) (64). However, a recent study (January 2003 - March 2017) of the chemotherapy practice of patients with locally advanced or metastatic urothelial cancer from the Leeds Cancer Centre showed that single-agent paclitaxel was most often (43.4%) used as 2nd line chemotherapy after 1st line platinum-based chemotherapy (65). Given the limit of further details of the UK practice, only single-agent paclitaxel therapy was considered in the model as 2nd line treatment for the patients receiving

'other 2nd line therapy' even though this treatment is not mentioned in the NICE guidelines. Furthermore, it is likely that platinum-based chemotherapies (such as gemcitabine plus cisplatin) are less used as 2nd line treatment as they are already administered as 1st line treatment in the patients of the study. Paclitaxel (80 mg/m^2) was administered intravenously over 60 minutes, three times every 28-day cycle for a maximum of 6 cycles. As paclitaxel is generically available, the price (£7.22 per vial) was searched in eMIT, which provides the average prices paid by NHS hospitals (58). The average body surface area (BSA) value of the patients enrolled in the JAVELIN bladder 100 clinical trial was not available. Therefore, the BSA value of 1.90 m2 was taken from TA519 (pembrolizumab (2nd line) for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) which was assumed to be appropriate as this appraisal investigated a 2nd line treatment for the indication of interest. TA519 took the value from the European sites of KEYNOTE-045, a trial of pembrolizumab as 2nd line therapy for advanced urothelial carcinoma (34). Wastage costs were assumed for paclitaxel.

2nd Line therapy with a fibroblast growth receptor inhibitor was not considered in the model for the following reasons: 1) the therapy was not mentioned in the NICE guidelines for bladder cancer, 2) the incidences of trial patients receiving this 2nd line therapy was low (avelumab arm: 2.60%, control arm: 2.30%) 3) the difference in the incidences between both arms was relatively small and therefore this treatment was assumed to have a limited effect on the ICER.

Table 3-9: Drug acquisition related costs subsequent therapies

Drug Acquisition Related Costs subsequent therapies	Immunotherapy (anti-PD or anti-PD-L1 treatment)		Other second-line therapy
Drug	**Pembrolizumab (scenario)**	**Atezolizumab**	**Paclitaxel**
Dose	200 mg	1,200 mg	80 mg/m2
Vial (mg)	100	1200	100
Vial (ml)	4	20	16.7
Price/Vial	£2,630.00	£3,807.69	£7.22
SE pack			47.08292945
Packsize			1
Quantity			42701.66632
SE unit			£0.23
Number of vials/patient	2	1	2
Frequency	every 3 weeks	every 3 weeks	3 times per cycle
Cost / Cycle (£)	**£7,013.33**	**£5,076.92**	**£43.31**
Max cycles	24	24	6
Average cycles	6.84	3	
References	TA517, BNF (2020)	TA525, BNF (2020)	TA530, eMIT (2020)

3.5.3.2. Administration costs

Administration costs were applied to the patients who were intravenously administered avelumab in the stable disease state and 2nd line chemo- or immunotherapy in the PD state. Therefore, patients who received only BSC did not experience any cost of administration. The unit costs for administration have been sourced from the NHS reference costs 2018-2019 (56). The intravenous administration is assumed to occur in an outpatient setting. As the time for administration is 60 minutes or less, the Healthcare Resource Groups (HRG) code SB12Z: Deliver simple parenteral chemotherapy at first attendance was applied (Table 3-10) (56). This code was also used in related TAs (33–35,66). To be

consistent with these appraisals no pharmacy costs were considered. An HCC was again applied to the second administration of avelumab in each cycle in the stable disease state.

Table 3-10: Administration costs

Chemotherapy Administration Costs	Unit Cost (£)	Frequency	Source unit cost
Deliver Simple Parenteral Chemotherapy at First Attendance	£254.00	Every two weeks	NHS reference cost (2018-2019), SB12Z

3.5.3.3. Premedication costs

In the JAVELIN Bladder 100 clinical trial an antihistamine and paracetamol were administered about 30 to 60 minutes before the first four infusions of avelumab to mitigate infusion-related hypersensitivity reactions (8). The same premedication usage is mentioned in the SmPC of avelumab (54). The SmPC adds that when the fourth infusion was administered without infusion-related reaction, continuation with premedication should be judged by the physician. In the trial 10.20% experienced an infusion-related reaction of any grade. However, given the lack of data availability on further use of premedication after the fourth infusion, no costs of premedication were considered after the second model cycle (fourth treatment cycle). No information about the dosing of the drugs and which antihistamine were provided. Therefore, the same histamine drug and dosage as in TA391 (cabazitaxel for treating hormone relapsed metastatic prostate cancer after a docetaxel-containing regimen) were considered and the cheapest option for paracetamol was chosen (Table 3-11) (47). The unit costs were searched in eMIT (58). No wastage costs were considered for premedication as these were tablets taken orally. For simplicity and consistency with other TAs, no premedication costs were considered for the subsequent therapies.

Table 3-11: Premedication costs

Premedication Costs (before the first 4 infusions of Avelumab)	Dosage	Cost per pack	Pack size	Unit cost	Quantity	Standard deviation pack	Incidence	Source costs	source incidence
Antihistamine (Chlorphenamine)	1x 4 mg tablet before	£1.50	28	£0.05	152600	£0.62	100%	eMIT 2021	Bladder 100 clinical trial
Paracetamol 500mg tablets / Packsize 100	1 X 500 mg tablet before chemo	£0.41	100	£0.00	966596	£0.61	100%		
total costs/ infusion avelumab									**£0.06**

3.5.3.4. Health-state unit costs and resource use

Patients on treatment are regularly clinically and radiologically monitored. No specific UK data about health care resource use by patients treated for locally advanced or metastatic urothelial cancer were identified during a literature review. Therefore, TA530 (nivolumab for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) was assumed to have the most detailed and correct health care use data of all TAs for locally advanced or metastatic urothelial cancer as it considered specific diagnostic tests and linked monitoring frequencies to the drug administration frequencies. These data from TA530 were also in line with TA517 (avelumab for Merkel cell carcinoma)

(33,66). The data includes several diagnostic tests and follow-up visits during 1st line and 2nd line treatments. The different monitoring tests and follow-up visits together with their frequencies and costs per treatment are summarized in Table 3-12. Thyroid tests were not required for 2nd line chemotherapies. The frequencies are related to the administration cycles and the costs were searched in the NHS reference costs 2018-2019 (56). Health care resource use related to BSC was also taken from TA530 (nivolumab for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) (Table 3-13).

Table 3-12: Healthcare resource use costs avelumab and 2nd line treatments

Healthcare Resource Use Costs									
Resource use	unit cost (£)	1L avelumab		2L immunotherapy		2L chemotherapy		sources	
	unit cost (£)	Frequency per month	Cost/cycle (£)	Frequency per month	Cost/cycle (£)	Frequency per month	Cost/cycle (£)	frequency	unit cost
Monitoring – oncologist	£197.70	2	£395.41	1.33	£263.61	3	£593.11	TA530, TA517	NHS reference costs 2018-19 outpatient attendances, consultant led, service code 370
Follow-up	£194	2	£388.34	1.33	£258.89	3	£582.51		NHS reference costs 2018-19, consultant led, non-admitted face to face attendance, follow-up, oncology, currency code: WF01A
CT scan	£105	0.33	£34.84	0.33	£34.50	0.33	£34.50		NHS reference costs 2018-19, diagnostic imaging, computerised tomography scan of two areas, with contrast, outpatient, currency code: RD24Z
Blood count	£3	2.00	£6.00	1.33	£4.00	3	£9.00		NHS reference costs 2018-19, Directly accessed pathology services, Haematology, currency code: DAPS05
Biochemical tests (thyroid, liver, renal test)	£1	6	£6.00	4	£4.00	6	£6.00		NHS reference costs 2018-19, Directly accessed pathology services, Clinical biochemistry, currency code: DAPS04
Total costs/cycle			**£830.59**		**£564.99**		**£1,225.12**		

Table 3-13: Healthcare resource use costs BSC

Best supportive care cost and resource use						
Item	Incidence	Frequency per month	Unit cost	Total cost	Reference cost	Reference Incidence + frequency
GP home visit	50%	2	£39.23	£39.23	Curtis, Lesley A. and Burns, Amanda (2019); cost er patient contact lasting 9.22 minutes (including carbon emissions (6 KgCO2e)2(carbon costs less than £1)	TA530
Community nurse specialist visist	50%	2	£98.74	£98.74	NHS reference costs 2018-19, Specialist Nursing, Cancer Related, Adult, Face to face	
blood transfusions	10%	1.00	£180.45	£18.05	NICE guidelines NG24, Costing guidance, 2015 (indexed to 2019)	
Total cost per cycle				**£156.02**		

3.5.3.5. Adverse events costs

As previously mentioned, only AEs with a grade ≥ 3 and a prevalence of at least 3% in either treatment arm in the JAVELIN Bladder 100 trial were considered, namely urinary tract infection and anemia (Section 3.5.3.1.). The unit costs related to these AEs were searched in the NHS reference costs 2018-2019 (Table 3-14) (56). No information was provided about the treatment setting of the adverse events for which the total costs provided in the tab: TOTAL Healthcare Resource Group (HRG) were used (Appendix E). After that the costs were adjusted for the incidences, they were incorporated as a one-off cost in the first cycle of the Markov trace of the relevant arm. This approach was considered as no further details about experiencing the AEs were available such as the timing of the AEs and the frequency per patient. The total costs for AEs were £99.02 and £63.42 for the avelumab and comparator arm, respectively.

Table 3-14: Costs adverse events

Adverse event costs **Grade 3 or higher adverse events**	**Costs (£)**	**Incidence Avelumab + BSC (> 3%)**	**Incidence BSC alone (> 3%)**	**Source**
Urinary tract infection	£1,602.37	4.40%	2.60%	NHS Reference costs 2018/2019: weighted average of: LA04H-R; total
Anaemia	£750.30	3.80%	2.90%	NHS Reference costs 2018/2019: weighted average of: SA01G-K, SA03G-H, SA04G-L, SA05G-J; total
Total Costs Avelumab	**£99.02**			
Total Costs BSC	**£63.42**			

3.5.3.6. Cost of terminal care

To keep the consistency with previous TAs for urothelial cancer and given the limited data in literature, the terminal care estimated cost of TA519 (Pembrolizumab (2nd line) for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) was considered (Appendix F) (34). The estimate was based on brown et al., which provides terminal care costs that are related to cancer in general, so not to a specific type of cancer. Furthermore, the cost estimate included costs related to radiotherapy as there exists a predisposition of bleeding in patients with urothelial cancer. The cost was indexed to 2018-2019 and amounted to £ 7,692.40. This value was applied as a one-off cost to all patients entering the death health state.

3.5.3.7. Costs of PD-L1 testing

As previously explained, PD-L1 positive patients were expected to have better results (OS and PFS) and therefore the treatment may be more cost-effective in this subgroup. However, also the costs for the PD-L1 tests have to be considered. In the trial PD-L1 expression was assessed using the Ventana PD-L1 assay (SP263, Ventana Medical Systems). 51.1% of the trial patients were tested positive for PD-L1 positive tumors according to the requirements earlier discussed (Section 3.1.). Hence, to identify one positive person 1.96 persons should be tested. The costs for a PD-L1 test (£40.50) was taken from TA428 (pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy) (67). The total cost per person was £79.26 (Table 3-15). This cost was applied as a one-off cost to all the patients of the avelumab arm in the model.

Table 3-15: Costs of PD-L1 testing

% Of patients with PD-L1 positive tumors	51.1%
PD-L1 test cost	£40.50
Total PD-L1 costs per patient	£79.26

3.6. Sensitivity analyses

4.6.1 PSA

A PSA of 1000 simulations with 1000 patients was run for which random values were drawn from the individual distributions of the inputs with uncertainty. Different distribution types were applied for different parameters (Table 3-16). The distributions were determined by standard errors (SE) (Appendix G). When no SE was available, they were mostly calculated as a 20% percentage of the mean. For BSA a smaller percentage, namely 10% was applied to have a more realistic interval. In eMIT, standard deviations (Stdevs) and quantities were available. The Stdevs for costs searched in eMIT were converted to SEs with following formula:

$$SE\ (cost\ eMIT) = SD\ (eMIT)/sqrt(quantity)$$

Table 3-16: Distribution types for parameters with uncertainty + reasoning

Parameter	Distribution	Reason
Probabilities subsequent therapies	Dirichlet	Sum values has to add up to 1
(Dis)utilities	Beta	Values between 0 and 1
Other probabilities/ incidences		
Duration, frequencies, costs, patient characteristics	Gamma	Positive values
OS and PFS curves	Bivariate normal distribution	Intercept and log(scale) are correlated parameters

4.6.2. Scenario analyses

Furthermore, scenario analyses were performed for several parameters as previously mentioned in the relevant sections above to investigate the impact of certain assumptions on the results. A summary of all the applied scenario analyses can be found in Table 3-17. These scenarios were considered important for following reasons: 1) a life-time horizon of 20 years was applied in a scenario as 40 years still seemed somewhat unrealistic as the mean age in the trial was 67.44, 2) the effect of considering other distributions for OS on the result wat tested as the exponential applied in the base case analysis had the worst fit, 3) also all the considered distributions were applied for PFS in scenario analyses as no appropriate real-world data was found and therefore the lognormal distribution in the base case analyses was only chosen based on the best AIC value, 4) A scenario analysis with the baseline utility value measured in avelumab arm of the trial was performed to see how big the impact was on the result in comparison with using the utility value of the BSC arm in the base case analysis, 5) as related TAs often did not consider BSC costs, it was interesting to see the difference in the result with and without BSC costs (34,35,68) 6) A scenario analysis with pembrolizumab was performed as it was only recently withdrawn from the market 7) A scenario analysis with the maximum allowed cycles for the expensive atezolizumab was performed to investigate the impact of the difference in duration on the result, and 8) a stopping rule of 3 years was applied in a scenario analysis as the clinical trial only was

executed for 3 years and no maintenance treatment is currently on the market in the UK for the indication.

Table 3-17: Summary of scenario analyses

#	Component	Parameter	Base-case	Scenario
1	Model settings	Life-time horizon	40 years	20 years
2	Survival curve extrapolation	OS	Exponential	Weibull, lognormal, loglogistic
3		PFS	Lognormal	exponential, Weibull, loglogistic
4	Utilities	PF utility	0.792	0.814
5	Resource use and costs	BSC costs	Acquisition: £14.37 Resource use: £156.01	Acquisition: £0 Resource use: £0
6		2nd Line immunotherapies	Atezolizumab	Pembrolizumab
7		Duration atezolizumab treatment	6.84 months	2 years
8		Duration avelumab treatment	Until disease progression	Until disease progression or max 3 years (stopping rule)

4. Results

4.1. Overall population

Avelumab showed higher costs and higher benefits than BSC alone over a lifetime horizon (40 years). The incremental cost amounted to £114,483 and the QALYs and LYs were improved by 0.78 QALYs and 1.05 LYs, respectively (Table 4-1). The ICER for avelumab (+BSC) vs. BSC alone was £147,484 per QALY gained. This result suggested that avelumab cannot be considered cost-effective for the overall population at the NICE WTP threshold range of £20,000 to £30,000 per QALY gained. A discount of at least 95% needs to be applied to consider avelumab cost-effective at the £30,000 upper limit of the NICE WTP threshold range.

As discussed in the theoretical framework a higher threshold could be considered when an intervention meets the end-of-life criteria: : 1) the population of the CEA consists of patients with a short life expectancy (normally < 24 months), 2) Enough evidence is available to substantiate life extension linked to the intervention (normally an average of at least 3 extra months compared to the current treatment), 3) The life extension estimates need to be robust and proven via PFS or OS, 4) the model assumptions applied in the reference case have to be plausible objective and robust (24,26). Avelumab extended OS by more than 3 months. In the JAVELIN Bladder 100 trial, the median OS was improved by 7.1 months compared to BSC alone and in our model the mean OS was improved by 12.6 months for avelumab compared to BSC alone. In addition, in our model only around 37% of the patients survived after 24 months. However, the mean LYs for the BSC arms (this would be the current life expectancy of the population without the new treatment) is over 2 years, namely 2.49. Therefore, we could conclude that the end-of-life criteria were not met. Subsequently, the threshold should not be elevated to £50,000 per QALY gained as is allowed by NICE for a 'life-extending treatment at the end of life'.

Table 4-1: Base case results for overall population (40-year time horizon)

	QALYs	LYs	Costs	ICER
Avelumab + BSC	2.44	3.54	£136,198	**£147,484**
BSC	1.66	2.49	£21,715	
Increment	**0.78**	**1.05**	**£114,483**	

The average QALYs and LYs per patient (discounted and half-cycle corrected) for both treatment arms per health state are shown in Tables 4-2 and 4-3, respectively. Over a 40-year time horizon, patients treated with avelumab lived around 70% longer than patients who only received BSC (3.54 years vs. 2.49 years). The biggest LYs increment was observed in the SD state (SD: 1.32 vs PD: 0.53). Hence, patients' lives were mostly enlarged in the SD state.

Table 4-2: Average QALYs per patient in the base case analysis for overall population (40-year time horizon)

QALYs	Avelumab + BSC	BSC	Increment
Stable disease	1.03	0.43	**0.61**
Progressed disease	1.40	1.23	**0.17**
TOTAL	2.44	1.66	**0.77**

Table 4-3: Average LYs per patient in the base case analysis for overall population (40-year time horizon)

LYs	Avelumab + BSC	BSC	Increment
Stable disease	1.32	0.53	**0.78**
Progressed disease	2.22	1.95	**0.27**
TOTAL	3.54	2.49	**1.05**

The average costs per patient (discounted and half-cycle corrected when needed) for each cost type in each treatment arm in both SD and PD health state over a 40-year time horizon in the base case analysis for the overall population are shown in Table 4-4. The greatest difference in costs between the avelumab and BSC arm originated from the SD costs and more specific from the drug acquisition costs of avelumab (avelumab arm: £97,176 vs BSC arm: £0). These high acquisition costs of avelumab result from the high drug price of avelumab (£768/vial) in combination with the number of vials per administration (four), the frequency (every two weeks), and treatment duration (until progression). The total drug acquisition costs of avelumab accounted for more than 70% of the total costs for the avelumab arm. The total costs in the progressed disease were higher for the BSC arm as a higher proportion received subsequent therapies (Avelumab arm: 46% vs BSC arm: 61.7%). Furthermore, most of the patients in the BSC arm received expensive immunotherapy (atezolizumab) as 2nd line therapy whereas in the avelumab the major part of the patients received the less expensive chemotherapy (paclitaxel) (Figure 3-10).

Table 4-4: average costs per patient in the base case analysis for overall population (40-year time horizon)

Cost type	Avelumab + BSC	BSC	Increment
Stable disease			
Drug acquisition costs avelumab	£97,176	£0.00	**£97,176**
Drug acquisition costs BSC	£230	£100	**£130**
Chemotherapy administration costs	£8,045	£0.00	**£8,045**
Premedication costs	£0.05	£0.00	**£0.05**
HC resource use costs	£15,787	£1,091	**£14,696**
AE costs	£99	£63	**£35**
TOTAL	**£121,339**	**£1,255**	**£120,084**
Progressed disease			
Drug acquisition costs subsequent therapies	£969	£6,610	**-£5,640**
Drug acquisition costs BSC	£239	£140	**£99**
Chemotherapy administration costs	£1,725	£1,958	**-£233**
Health-state unit costs and resource use	£5,378	£4,710	**£668**
End of life costs	£6,744	£7,040	**-£296**
TOTAL	**£15,057**	**£20,459**	**-£5,402**
Stable disease + progressed disease			
TOTAL	£136,198	£21,715	**£114,483**

The results from the PSA for the overall population are presented in Table 4-5. The probabilistic ICER, calculated with the mean costs and mean QALYs, equaled on average to £145,209 per QALY gained which is very similar to the deterministic ICER of £147,484 per QALY gained. Almost all the results from the runs of the PSA fell in the northeast quadrant of the CE plane (Figure 4-1), reflecting that avelumab (+ BSC) is a more expensive and more effective intervention than BSC alone. The CE Plane shows a broad variation in differences in QALYs between the two arms. This variation could be partially explained by the large SE (0.2013) of the utility value applied in the SD health state. The difference in costs looked rather stable.

Table 4-5; Results PSA for overall population (40-year time horizon)

	Costs avelumab	Costs BSC	LYs avelumab	LYs BSC	QALYs avelumab	QALYs BSC
Mean	£132,355	£19,092	3.54	2.49	2.44	1.66
Min	£99,360	£12,605	2.74	1.98	1.30	1.13
Max	£179,795	£27,184	4.60	3.00	3.17	2.03
Stdev	£13,745	£2,183	0.26	0.17	0.32	0.16
2.5th percentile	£109,013	£15,159	3.08	2.18	1.68	1.31
97.5th percentile	£161,178	£23,581	4.10	2.82	2.94	1.94

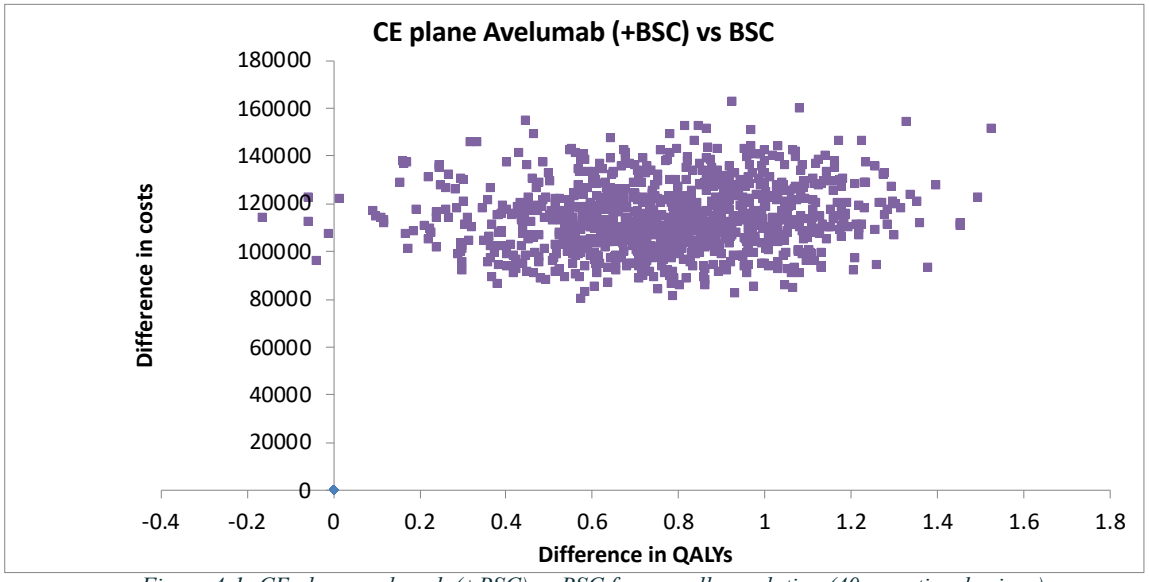

Figure 4-1: CE plane avelumab (+BSC) vs BSC for overall population (40-year time horizon)

The CEAC (Figure 4-2) shows that the probability of avelumab (+BSC) to be cost-effective compared to BSC alone was 0% when the threshold limit of £30.000 per QALY gained was considered. Starting from a threshold of approximately £70.000 per QALY, the curve started rising. At a threshold of £ 140.000 per QALY there is a 50% probability for both treatments to be cost-effective.

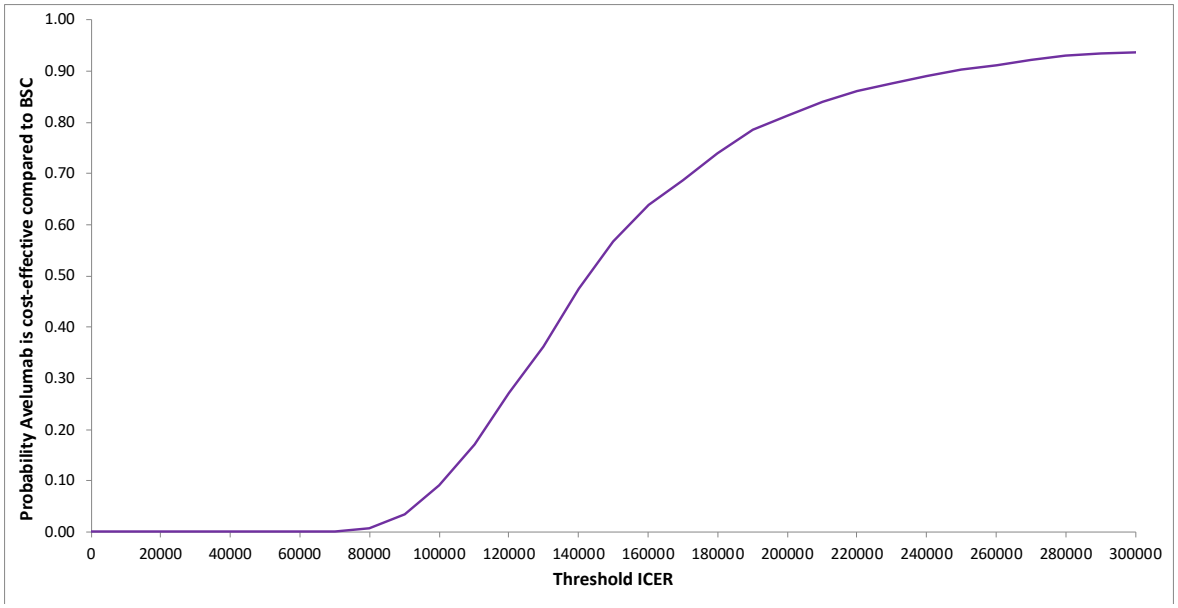

Figure 4-2: CEAC for overall population (40-year time horizon)

The results of the scenario analyses performed in the overall population are shown in Table 4-6. Considering the Weibull distribution for OS, implementing a stopping rule of 3 years and applying the maximum allowed cycles for atezolizumab had a big impact on the ICER. Considering the Weibull distribution for OS had mainly reduced the incremental QALYs (0.57 in the scenario compared to 0.78 in the base case). This resulted in an ICER of £194,283 per QALY gained which is about 30% higher than the base case result (£147,484 per QALY gained). In contrast, implementing the stopping rule for avelumab and applying the maximum allowed cycles for atezolizumab resulted in lower ICERs than the ICER of the base case analysis, namely £112,481 (24% lower) and £87,454 (40% lower), respectively. These lower ICERs could be explained by lower incremental costs as the incremental QALYs did not differ from the incremental QALYs of the base case analysis. All the other considered scenario analyses showed a relative difference smaller than 15% compared to the base case result.

Table 4-6: Results of scenario analyses (red ICER: relative difference with base case analysis > 15%; green: relative difference with base case analysis < 15%) for overall population (40-year time horizon)

Parameter	Base-case	Scenario	Incremental costs	Incremental QALYs	ICER
Lifetime horizon	40 years	20 years	£114,468	0.78	£147,364
OS	Exponential	Weibull	£110,577	0.57	£194,283
		lognormal	£148,767	0.77	£148,766
		loglogistic	£114,332	0.69	£165,998
PFS	Lognormal	exponential	£95,089	0.74	£128,989
		Weibull	£106,711	0.76	£141,285
		loglogistic	£114,905	0.79	£146,312
PF utility	0.792	0.814	£114,483	0.79	£144,335
Duration avelumab treatment	Until disease progression	Until disease progression or max 3 years (stopping rule)	£70,888	0.78	£112,481
BSC costs	Acquisition: £14.37 Resource use: £156.01	Acquisition: £0 Resource use: £0	£87,312	0.78	£143,993
2nd Line immunotherapies	Atezolizumab	Pembrolizumab	£102,107	0.78	£131,540
Duration atezolizumab treatment	6.84 months	3 years	£67,885	0.78	£87,454

4.2. PD-L1 subgroup

In the PD-L1 subgroup both the incremental health outcomes and costs were more favorable than in the overall population. The incremental QALYS amounted to 1.17 in the subgroup compared to 0.78 in the overall population and the incremental LYs amounted to 1.79 in the subgroup compared to 1.05 in the overall population (Table 4-8, 4-9). The total incremental cost was £104,003 in the subgroup compared to £114,483 in the overall population (Table 4-10). The ICER for the PD-L1 subgroup amounted to £89,175 per QALY gained which is about 40% lower than the ICER for the overall population (Table 4-7). However, the ICER is still higher than the WTP threshold limit of £30,000 per QALY gained. Also, in the PD-L1 subgroup, the end-of-life criteria were not met as the mean LYs in the BSC arm were again higher than 2 years, namely 2.79, and therefore no higher threshold could be applied. The PSA provided a mean ICER of £88,509 per QALY gained which is again very similar to the base case result (Table 4-11). All the results of the PSA lay in the northeast quadrant (Figure 4-3). The CEAC showed a probability of 0% for avelumab to be cost-effective compared to BSC alone at a

threshold of £30,000 (Figure 4-4). Therefore, avelumab was also not suggested cost-effective in the PD-L1 subgroup. All the data inputs used in the CEA of the overall population were kept the same in the CEA of the PD-L1 subgroup except the KM data and inclusion of PD-L1 testing costs. The costs related to PD-L1 testing (increment: £79.26) had almost a negligible effect on the ICER (Table 4-10). The acquisition cost of avelumab should be reduced by at least 79% for avelumab to be cost-effective at the NICE threshold limit of £ 30.000 in the PD-L1 subgroup.

Table 4-7: Base case results for PD-L1 subgroup (40-year time horizon)

	QALYs	LYs	Costs	ICER
Avelumab + BSC	3.05	4.58	£126,143	**£89,175**
BSC	1.88	2.79	£22,101	
Increment	**1.17**	**1.79**	**£104,003**	

Table 4-8: Average QALYs per patient in the base case analysis for PD-L1 subgroup (40-year time horizon)

QALYs	Avelumab + BSC	BSC	Increment
Stable disease	1.03	0.43	**0.61**
Progressed disease	1.40	1.23	**0.17**
TOTAL	**3.05**	**1.88**	**1.17**

Table 4-9: Average LYs per patient in the base case analysis for PD-L1 subgroup (40-year time horizon)

LYs	Avelumab + BSC	BSC	Increment
Stable disease	1.20	0.76	**0.44**
Progressed disease	3.38	2.03	**1.35**
TOTAL	**4.58**	**2.79**	**1.79**

Table 4-10: Average costs per patient in the base case analysis for PD-L1 subgroup (40-year time horizon)

Cost type	Avelumab + BSC	BSC	Increment
Stable disease			
costs PD-L1 testing	£79	£0	**£79**
Drug acquisition costs avelumab	£88,174	£0	**£88,174**
Drug acquisition costs BSC	£210	£142	**£67**
Chemotherapy administration costs	£7,300	£0	**£7,300**
Premedication costs	£0.05	£0.00	**£0.05**
HC resource use costs	£14,385	£1,543	**£12,842**
AE costs	£99	£63	**£36**
TOTAL	**£110,247**	**£1,749**	**£108,498**
Progressed disease			
Drug acquisition costs subsequent therapies	£975	£6,559	**-£5,584**
Drug acquisition costs BSC	£360	£145	**£214**
Chemotherapy administration costs	£1,734	£1,944	**-£209**
Health-state unit costs and resource use	£6,697	£4,743	**£1,954**
End of life costs	£6,466	£6,962	**-£496**
TOTAL	**£16,231**	**£20,352**	**-£4,121**
Stable disease + progressed disease			
TOTAL	£126,104	£22,100	**£104,003**

Table 4-11: Results PSA for PD-L1 subgroup (40-year time horizon)

	Costs avelumab	Costs BSC	LYs avelumab	LYs BSC	QALYs avelumab	QALYs BSC
Mean	£123,282	£19,726	4.60	2.80	3.05	1.88
Min	£79,655	£13,623	3.30	2.07	1.67	1.10
Max	£186,776	£28,014	6.45	3.70	4.14	2.53
Stdev	£15,429	£2,273	0.50	0.27	0.38	0.24
2.5th percentile	£96,277	£15,649	3.64	2.33	2.26	1.38
97.5th percentile	£154,014	£24,748	5.63	3.38	3.75	2.34

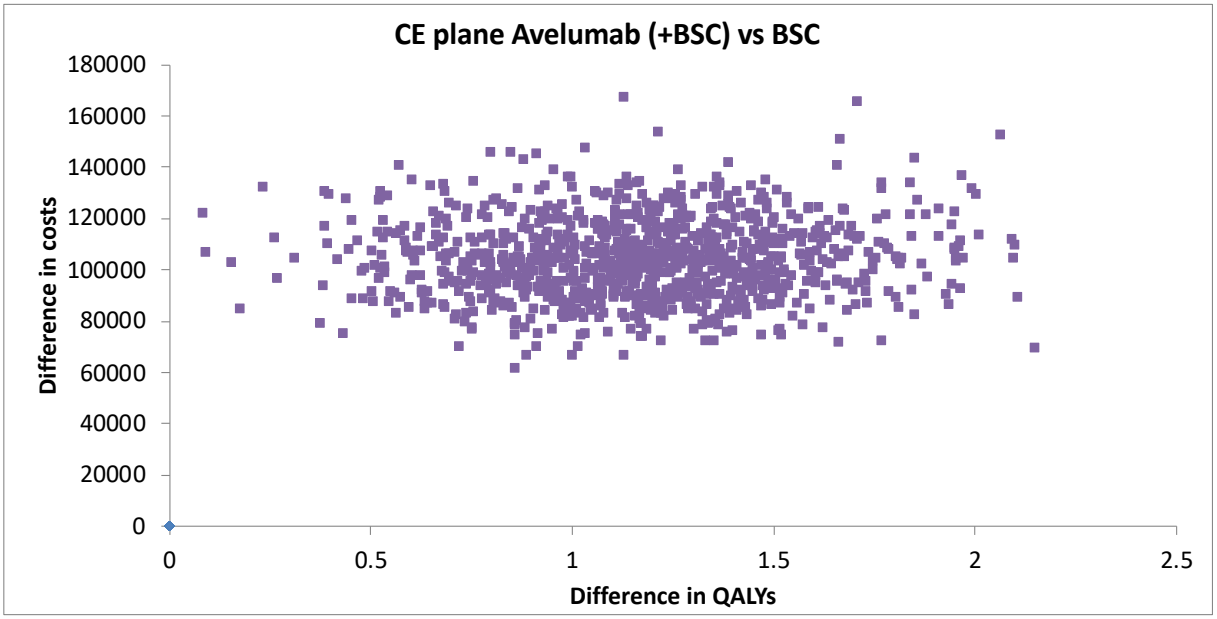

Figure 4-3: CE plane avelumab (+BSC) vs BSC for the PD-L1 subgroup (40-year time horizon)

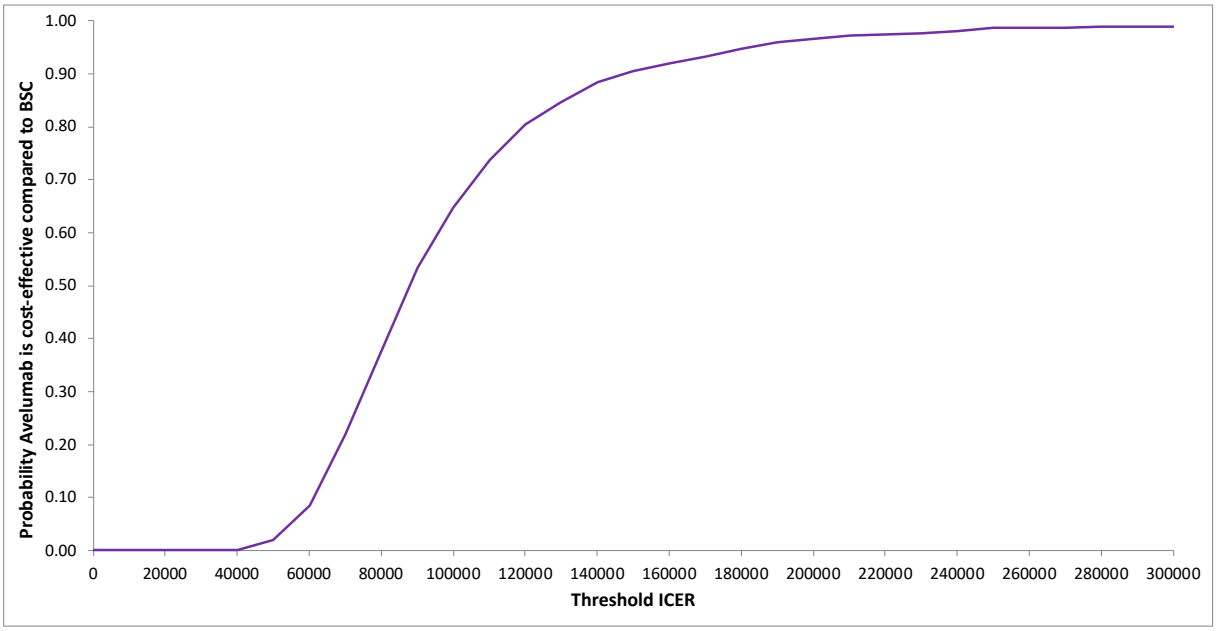

Figure 4-4:: CEAC PD-L1 subgroup (40-year time horizon)

The same scenarios performed for the overall population were performed for the PD-L1 subgroup and almost the same conclusions could be made as for the overall population, namely considering the Weibull distribution for OS, implementing a stopping-rule of 3 years, and applying the maximum allowed cycles for atezolizumab had a big impact on the ICER (Table 4-12). Furthermore, also the other distributions (lognormal and exponential) for OS resulted in a relative difference higher than 15% compared to the base case result with the exponential distribution. Applying the Weibull, lognormal, and loglogistic for OS resulted in an ICER approximately 60%, 20%, and 46% higher than the base case result. The implementation of the stopping rule for avelumab and the application of the maximum allowed cycles for atezolizumab lowered the ICER by approximately 34% and 45%.

Table 4-12: Results of scenario analyses (red ICER: relative difference with base case analysis > 15%; green: relative difference with base case analysis < 15%) for the PD-L1 subgroup (40-year time horizon)

Parameter	Base-case	Scenario	Incremental costs	Incremental QALYs	ICER
Lifetime horizon	40 years	20 years	£104,051	1.17	£89,070
OS	Exponential	Weibull	£102,030	0.67	£151,189
		lognormal	£103,741	0.97	£106,835
		loglogistic	£103,502	0.79	£130,625
PFS	Lognormal	exponential	£88,672	1.14	£77,713
		Weibull	£95,025	1.15	£82,859
		loglogistic	£107,786	1.18	£91,286
PF utility	0.792	0.814	£104,042	1.18	£88,449
Duration avelumab treatment	Until disease progression	Until disease progression or max 3 years (stopping rule)	£68,446	1.17	£58,665
BSC costs	Acquisition: £14.37 Resource use: £156.01	Acquisition: £0 Resource use: £0	£100,708	1.17	£86,317
2nd Line immunotherapies	Atezolizumab	Pembrolizumab	£90,740	1.17	£77,774
Duration atezolizumab treatment	6.84 months	3 years	£57,902	1.17	£49,628

5. Discussion

5.1. Results

The model determined a deterministic ICER of £147,484 per QALY gained for the overall population and a deterministic ICER of £89,175 per QALY gained for its PD-L1 subgroup for avelumab compared to BSC alone. These ICERs demonstrated that avelumab was 100% not cost-effective as maintenance treatment for the patients in both the overall population and PD-L1 subgroup with locally advanced or metastatic urothelial cancer who did not experience progression with 1st line platinum-based chemotherapy at the NICE threshold limit of £30.000 per QALY gained. Although avelumab (+BSC) showed higher benefits than BSC alone (higher QALYs and LYs), the drug acquisition cost of avelumab was too high to be cost-effective. The acquisition cost of avelumab should be reduced by at least 95% and 79% to be cost-effective at the NICE threshold limit of £30.000 per QALY gained in the overall population and PD-L1 subgroup, respectively.

The deterministic ICERs were very similar to the probabilistic ICERs for both the populations. Hence, the results are robust to the PSAs. Furthermore, most scenario analyses in the overall population showed a relative difference smaller than 15% compared to the base case result. Only the Weibull distribution for OS, applying a stopping rule for avelumab, and using the maximum allowed cycles for atezolizumab demonstrated a big influence on the result for the overall population. For the PD-L1 also the lognormal and loglogistic distribution for OS had a large impact on the result. Only, the stopping rule and allowing the maximum allowed cycles for atezolizumab improved the cost-effectiveness substantially in both the populations. It might be realistic to implement a stopping rule in practice as the trial only provided data for three years and no other maintenance treatments are nowadays administered in the UK. For the treatment duration of atezolizumab only a few patients will be able to reach the maximum allowed cycles of atezolizumab in practice due to progression, AEs, or death and therefore using these maximum allowed cycles is not very representative to the real world.

5.2. Similar studies

To validate our study, similar CEAs were searched. Two CEAs of avelumab for maintenance treatment of patients with locally advanced or metastatic urothelial cancer who did not progress during or after 1st line platinum-based chemotherapy were found via a targeted literature review at the time writing this study, namely one published by the Canadian Agency for Drugs and Technologies in Health (CADTH) and one published by NICE (68–70). A comparison of our study and the two similar published studies based on the evidence that was made available can be found in Appendix H.

The CADTH supports the Canadian health care decision-makers with making decisions about the use of medicines and medical devices in the Canadian health care system by providing evidence-based information (71). The CADTH CEA, published on the 23rd of March 2021, calculated an ICER of $278,373 (£162,065) per QALY gained for avelumab compared to BSC alone. Therefore, CADTH concluded that avelumab had a 100% probability of being not cost-effective when a threshold of $50,000 per QALY gained was applied. The CADTH stated that the price should be reduced with a minimum of 83% so that avelumab (+BSC) is cost-effective at this threshold (68). The result of the study performed is difficult to compare with our result as some methodological considerations may differ as they do not apply the NICE guidelines. Furthermore, it does not use UK-specific data and their costs are expressed in Canadian dollars. However, it was still useful to validate our model by comparing some methodological assumptions. In general, most methodological assumptions were similar. The differences based on the available data of the published study included: 1) dosing method of avelumab

2) the length of the time horizon, 3) the impact of AEs on health outcomes and costs, and 4) BSC costs. The effects of these differences on the result are discussed in section 5.3.

More interesting was to compare our CEA with the company (Merck Serono) submission to NICE as it normally also uses UK data inputs and applies the NICE guidelines and is therefore probably very similar. On the 6th of May 2021, NICE published the company submission of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy (70). Some values were still confidential such as the ICER, but assumptions could be compared. More details about the comparisons can also be found further in the discussion.

5.3. Modelling and data assumptions

As for all CEAs, there were some considerable challenges that may restrict the use of the study results. Therefore, it was important to be transparent and reflect on the strengths and limitations of the methodological considerations, model structure, data, and assumptions. An overview of the key assumptions made can be found in appendix I. In addition, there are always general limitations of a CEA with modelling. Firstly, the model may be too simplistic when the model neglects aspects that experts feel as requirements (72). Furthermore, the cost-effectiveness result will only be suitable for the UK or very similar countries in resource utilization and costs patterns (73). However, the used methods and model design can be used in other countries and some other similar indications.

5.3.1. Methodological considerations

The methodological considerations described in the method section defined the framework of this CEA and set boundaries to the economic evaluation. The boundaries were mainly set by the NICE guidelines and its reference case.

The two populations (overall population + PD-L1 subgroup) considered were assumed to be appropriate for the CEA to make a recommendation by NICE to the NHS. The overall population of patients with locally advanced or metastatic urothelial cancer without progression during or after platinum-based chemotherapy was described as the population in the scope by NICE (19). Furthermore, a strength of this study is that this population is the same as the total ITT population of the JAVELIN bladder 100 trial from which many data were used. Moreover, it was also useful to consider its subgroup of patients who tested positive for the PD-L1 mutation as it resulted in a lower ICER for avelumab (PD-L1 antibody). Also, data for the PD-L1 subgroup was measured in the JAVELIN Bladder 100 trial (8,74).

One of the most influential boundaries set by the NICE guidelines on the outcome is the perspective for costs. The reference case from NICE only considers costs related to the NHS and PSS. In exceptional cases, a broader perspective may be adopted and the impact on costs for other governmental bodies may be considered (24). However, no specific reasons were noticed to expand the perspective. In contrast, a good reason was observed to apply the narrow perspective by NICE namely, bladder cancer is most common diagnosed in men aged 75+ who therefore can gain a limited amount of years (75). Hence, costs such as productivity costs, informal caregiver's costs and, medical costs non-related to urothelial cancer will only have a small impact on the ICER. Moreover, the difference in OS between the avelumab arm and BSC arm is so small that even if the total costs for both treatments increase with a broader perspective, the ICER is unlikely to be significantly affected.

Urothelial cancer and the treatment options may have spill-over effects, impact on the HRQoL and, health care use for people other than the patient (e.g., family members, carers) (7). NICE allows to include these health benefits for these people. However, given that 1) the condition of investigation

has limited impact for these 'others' compared to diseases such as dementia, 2) the difficulty to quantify the benefits for these 'others' and, 3) the difference in spill-over effects between the avelumab arm and BSC arm were assumed to be small, only the direct health benefits to the patient were considered (5,8).

BSC is the current standard of care for patients with locally advanced or metastatic urothelial cancer without experiencing progression after 1st line platinum-based chemotherapy (8). Therefore, it was used as a comparator in our models. Furthermore, it was the comparator described in the relevant scope by NICE (19). The similar CEAs discussed previously also used BSC as a comparator. However, the company submission to NICE used the term 'watchful waiting' based on clinical advice because subsequent therapies may be provided when the disease progresses (70).

5.3.1. Model structure

A 3-state partitioned survival Markov model (PF, PD, death) was chosen based on available CEAs for locally advanced or metastatic urothelial cancer. It was assumed to be appropriate as this model was also applied in the two similar CEA studies (68,70). Furthermore, the model made it possible to implement intuitively the clinical trial endpoints like OS, PFS, HRQoL and, safety.

A cycle lasted 4 weeks, which is in line with the trial cycle length (8). The CEA by CADTH applied the same cycle length, but the company submission published by NICE used a shorter cycle length of seven days to reflect the frequency of clinical events and to be in line with the administration frequency of avelumab (2-weekly). However, the 4 weeks duration was assumed to be suitable given that in our model HCC was applied for the second avelumab administration in each cycle and for the health outcomes.

As preferred by NICE, a lifetime horizon was applied to the model. Based on the extrapolations of the KM curves this amounted 40 years for both considered populations. This was assumed to be reasonable as the TA519 for pembrolizumab, which is a 2nd line treatment for the indication, applied a lifetime horizon of 35 years for patients who already were progressed. However, the two similar studies both applied a shorter lifetime horizon (CADTH: 15 years, company submission to NICE: 25 years). A scenario analysis was executed with a lifetime horizon of 20 years for the overall population and PD-L1 subgroup which resulted in a result with a relative difference smaller than 10% in comparison with the base case result because most patients already died in the first years. Less than 10% was alive after 15 years in the avelumab arm of the models.

5.3.2. Clinical evidence

Data from the robust, multicenter RCT JAVELIN bladder 100 was used to estimate PFS and OS rates for the models of the two populations. The trial was started in 2016, the primary completion date was October 2019, and June 2022 is the estimated study completion date. Hence, the data are very recent. Furthermore, the study also used the appropriate comparator, namely BSC (8,24). Moreover, 4 trial sites were in the UK which enrolled representative patients for those who will get the treatment in the UK practice (70). However, no further details were available on what proportion were UK patients or which sites in the UK. A limitation of the trial could have been the lack of blinding as the comparator group only received BSC and was not administered a placebo intravenously. However, progression was assessed by a Blinded Independent Central Review. It evaluated objectively tumor growth, lesions, and burden using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (42). Overall, it was assumed that the study was of good quality, and its results were appropriate for the CEAs.

As with many RCTs for cancers, survival data were incomplete to reflect a lifetime horizon. Hence, extrapolation of the OS and PFS data was necessary. Furthermore, the actual OS and PFS data of the JAVELIN bladder 100 were not available. Therefore, the method of Hoyle and Henley was used to recreate IPD from the PFS and OS KM curves from Powles et al. and to subsequently extrapolate the survival curves (8,39). The method of Hoyle and Henley uses the number of patients at risk which improve the accuracy of the extrapolations. However, despite this method is considered the best for estimating OS and PFS data it still entails an amount of uncertainty. The best extrapolation curves were chosen based on clinical plausibility and the AIC values which is in accordance with the NICE guidelines (24). Only the exponential, Weibull, lognormal and, loglogistic parametric distributions were fitted to the IPD data while other distributions also could have been considered such as the Gompertz and generalized gamma which was done in the company submission published by NICE (70). This company submission chose the generalized gamma for OS. However, the CADTH also applied an exponential distribution for OS as we did. Extrapolations make the results sensitive to distributional assumptions. Therefore, future real-world data is needed to validate the extrapolation results. Scenario analyses were performed to investigate the sensitivity to the distributional assumptions. Most scenarios had a result with a relative difference smaller than 15% compared to the base case analysis. The biggest change in ICER was observed when the Weibull distribution was applied for OS. This was also the only distribution that did not reflect the 5-year survival for stage 4 bladder cancer reported by Cancer Research UK. Applying the Weibull distribution for OS resulted in a 30% and 60% higher ICER compared to the base case ICER for the overall population and PD-L1 subgroup, respectively.

5.3.3. Utility values

Several assumptions had to be made for the utility values (Section 3.5.2.2.). In the JAVELIN bladder 100, values gathered at baseline and day 1 of cycle 6 in both treatment arms with the EQ-5D-5L measure instrument were made available (42). UK-specific valuation tariffs were used to determine a single global utility value, which was assumed to be appropriate to support a NICE recommendation for the NHS in England and Wales. The EQ-5D is the measurement preferred by NICE (76). However, NICE does not recommend the EQ-5D with 5 levels because of quality and reliability concerns of the EQ-5D-5L value set for England (77). Therefore, the EQ-5D-5L should be mapped to the EQ-5D-3L but this was not possible given the lack of information on the collected data with the EQ-5D-5L.

The baseline values (avelumab arm: 0.814, control arm: 0.792) were considered for the PF health state as all patients were PF at the start of the trial. These values had a large standard deviation (avelumab arm: 0.1794, control arm: 0.2013) which reflects a high variability in responses of the patients to the EQ-5D-5L questionnaire. This high variability may explain the random difference of 0.22 observed between both treatment arms. However, the higher baseline value measured in the avelumab arm may also suggest that patients in the avelumab arm were on average somewhat healthier and therefore more likely to have better outcomes outside of the fact that they received the theoretically better treatment. If this was the case, the difference in OS and PFS between the two arms was overestimated resulting in an underestimated ICER.

To eliminate the difference in utilities at baseline in our model the baseline value of 0.792 measured in the trial for the BSC arm was used for the PF health state in the base case analyses for the populations as this value approximates the best the utility value measured for an average UK person aged 65-74. However, it might still have been an overestimation as the utility value for an average UK person aged 65-74 amounts to 0.778 and the average UK person is not considered to have a life-threatening disease such as advanced urothelial cancer (43). Furthermore, the company submission that mapped the EQ-5D-5L data to EQ-5D-3L data applied a lower PF utility value of 0.772 compared to 0.792 in this study (70). A lower PF utility value results in a higher ICER. A scenario analysis was performed with the baseline value of 0.814 measured in the avelumab arm of the trial. Using this value

showed a result with a relative difference smaller than 10% compared to the result of the base case analysis in both considered populations.

The utility values measured at day 1 of cycle 6 in both arms could not be used in our model that applied utility values by health state as these values measured at day 1 of cycle 6 were measured in both PF and progressed patients. At cycle 6 in the Markov traces of both treatment arms of the overall population, there were many patients in both the PF and PD health states (> 30%).

As no suitable utilities for the PD health state were available from the trial or found in literature, the average (0.632) of PD utility values used in TAs for 2nd line therapies for locally advanced or metastatic urothelial cancer was applied. Although these utility values applied for 2nd line therapies were measured in the relevant trials with the EQ-5D-3L, they may underestimate the PD utility values of this study as they are measured in patients who are initially in a further progressed state. Furthermore, the company submission, which had PD data available from the trial, applied a higher PD utility value (0.698)(70). This higher PD utility value results in a slightly lower ICER in the overall population, namely £144,247.

No disease-specific disutilities were available. Therefore, disutilities used in other TAs and found in scientific studies were applied (Section 3.5.2.2.). The values found for anemia were measured or used in similar UK populations of mainly older men with cancer. In contrast, the disutility values found for UTI originated from studies performed in different countries with different measurement instruments and with different patient populations such as adults with SCI aged around 30 years and elderly around 80 years old living in care homes (Table 3-5). However, these disutility values measured for UTI were very similar in all these very different populations and therefore the average of these values was assumed to be appropriate to use in our model. Furthermore, differences in disutilities will not significantly change the ICER given the correction of the disutilities for the duration and infrequent occurrence. The incidences were taken from the JAVELIN bladder 100 trial. The company submission published by NICE considered much more AEs by using an incidence lower limit of 1% compared to our 3% whereas the study by the CADTH did not consider the impact of any AE on the health outcomes. But as previously mentioned, considering AEs are not expected to have a large impact on the results due to the very low incidences and the correction for the duration.

5.3.4. Resource use and costs

Also, for several costs and healthcare resource use data, choices and assumptions had to be made. First, flat dosing was chosen for avelumab instead of weight-based dosing, although the dosing was weight-based in the trial (Section 3.5.3.1.). The choice was justified by the SmPC which recommended flat dosing (54). In addition, flat dosing has several advantages over weight-based dosing such as 1) reduction of preparation time, 2) less drug wastage, 3) less chance of dosing errors, 4) Reduction of inter-subject variability in drug exposure, and 5) the use of the drug for another patient when last-minute cancelations occur (78). Moreover, a scientific study proved similar efficacy and safety between weight-based and flat dosing of avelumab in patients with locally advanced or metastatic urothelial cancer. Hence, the efficacy and safety results from the JAVELIN Bladder 100 were assumed to be appropriate for the models with flat dosing. Furthermore, the same number of vials are used for the two dosing strategies by an average weighted person, assuming drug wastage. The proven similarity in efficacy, safety, and vial usage between both dosing manners together with the practical advantages of flat dosing and the SmPC recommendation made us assume that flat dosing was the best choice. Also, the company CEA published by NICE applied flat dosing.

In our model, it was assumed that all patients in the PF health state received avelumab every two weeks until progression, as described in the trial protocol and the SmPC (8,54). However, some

patients may have had delayed or reduced doses due to for example AEs but because of lacking data, we could not take these aspects into account. Therefore, the avelumab use was probably overestimated in our model. Lower use of avelumab means a lower ICER. Furthermore, no active maintenance treatment is yet recommended for patients who received 1st line chemotherapy and did not experience progression. Hence uncertainty exists about how long patients may continue the treatment. Given that only data from the first 3 years of the trial was available a scenario analysis was performed in which the costs related to avelumab (acquisition, administration, HC resource use) only were considered for the cycles during the first 3 years. This had a big impact on the ICER. It was namely 24% and 34% lowered for the overall population and the PD-L1 subgroup, respectively. Therefore, it may be a good strategy to make the drug cost-effective. Unfortunately, the effect of this stopping rule on the long-term health outcomes was still unknown. Therefore, the ICER will probably be higher when implementing this stopping rule in practice because the health outcomes used in the model beyond the three years are based on an extrapolation of trial data where no stopping-rule was performed. Given that a stopping-rule was one of the key drivers of the CEA results for both populations further investigation on the effect of the stopping rule on the health outcomes and ICERs should be performed in the future.

Specific data on medication and resource use related to BSC was not provided in the trial and NICE guidelines. Therefore, the drugs and resource use applied for BSC in TA530 (Nivolumab, a 2nd line treatment for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) were considered (Section 3.5.3.1.). However, it may be good to collect real-world data on medication and resource use related to BSC after 1st line chemotherapy before progression in the future. Patients in the avelumab arm experienced progression later than patients in the BSC arm, and a higher percentage in the avelumab arm received only BSC as subsequent therapy than in the BSC arm (avelumab arm: 57,70%, BSC arm: 38.8%), therefore patients receiving avelumab have more costs related to BSC. So higher BSC costs result in a higher ICER. (33). However, the considered BSC was not very costly and BSC was given to both arms for which no large impact of BSC on the result was observed. A scenario analysis where no costs related to BSC were considered resulted in a relative difference of less than 15% compared to the base case result in both considered populations. The CADTH omitted BSC costs and the company submission to NICE only captured BSC costs via health-state resource use associated with the management of locally advanced or metastatic urothelial cancer (68,70).

Also, few specifics on the subsequent therapies were provided by the available trial data (Section 3.5.3.1.). Only Incidences for receiving 2nd line immunotherapies (anti-PD or anti-PD-L1), fibroblast growth factor receptor and, other 2nd line therapies per treatment arm of the overall population were found in the trial article by Powles et al., but no further specifics on which drugs were provided (8). Therefore, several assumptions had to be made. This was done by consulting the NICE guidelines and scientific studies of the UK practice. Only one immunotherapy mentioned in the NICE guidelines for locally advanced or metastatic urothelial cancer was still recommended, namely atezolizumab. Atezolizumab was reimbursed via the CDF. A scenario analysis was performed with pembrolizumab which showed a slight reduction in the ICER because 1) it was costlier than atezolizumab, 2) administered for more cycles than atezolizumab and, 3) 2nd line immunotherapies were more administered to patients in the BSC arm (avelumab arm: 6.30% vs BSC arm: 43,7%). The other 2nd line therapies mentioned in these NICE guidelines were chemotherapies A study of the UK practice showed that mainly single-drug paclitaxel was administered as 2nd line chemotherapy. Hence, this was the only therapy considered as 'other 2nd line therapy' because of the lack of more detailed data on UK-specific use of subsequent therapies (65). Also, the company submission to NICE only considered atezolizumab as 2nd line immunotherapy but considered more options as 2nd line chemotherapy. The company had more information available and therefore considered cisplatin, carboplatin, gemcitabine, docetaxel, paclitaxel and, pemetrexed as 2nd line chemotherapies. However, their information on the related incidences was redacted in their submission and therefore the effect of considering these other 2nd

line chemotherapies on the ICER could not be judged but if the costs of the drugs with high incidences tend to be higher than paclitaxel, it could be assumed that 2nd line chemotherapy costs would increase. Higher costs related to 2nd line chemotherapies result in a higher ICER as a higher percentage in the avelumab arm received 2nd line chemotherapy (Avelumab arm: 40% vs BSC arm: 34%).

A previously discussed assumption and investigated by a scenario analysis was the number of cycles for atezolizumab. Not all patients are able to receive the maximum allowed number of cycles (24 model cycles, 2 years) for the 2nd line immunotherapy. We tried to be as realistic as possible in the base case analysis by applying the duration when there was a 50% probability to be on treatment (section 3.5.3.1.). As atezolizumab was more often administered to patients in the BSC arm, the ICER decreases when the treatment duration increases. The scenario analysis with the maximum treatment duration allowed, resulted in an ICER that was only 60% of the base case result for both the considered populations. In the future real-world data on the treatment duration of atezolizumab should be collected given its large influence on the result.

In the SD state, only the costs related to grade 3 or higher AEs with an incidence of at least 3% were considered (section 3.5.3.5.). Given the low incidence, no high AEs costs were observed. No adverse events of 2nd line chemotherapies were considered in the PD state for simplicity. Furthermore, given that only 56% receives a 2nd line treatment and the 2nd line therapies do not seem to cause extreme adverse events with high incidences, the effect of the adverse events of the 2nd line chemotherapies on the ICER was assumed to be minimal.

The other considered costs were assumed to be appropriate. Firstly, the administration costs were in line with related TAs and the company submission to NICE (section 3.5.3.2.). Secondly, premedication costs were very low and therefore had a negligible effect on the results (section 3.5.3.3.). The company submission published by NICE did not even consider premedication costs. Furthermore, no premedication costs for the subsequent therapies were applied for simplicity. Thirdly, the health-state unit and resource use costs were also in line with a previous TA for the indication (TA530: nivolumab, 2nd line) (Section 3.5.3.4.). However, it may be a good idea to get validation by clinical experts in the future to see if these data are also relevant for patients without progression after 1st line chemotherapy. Fourthly, costs related to PD-L1 test were considered in the same way as was done in a previous TA (section 3.5.3.7.). And lastly, the terminal care estimate was applied in a related TA (TA519, pembrolizumab) and based on a scientific study often used in TAs for cancers (section 3.5.3.6.) (34).

The best available UK data from the BNF, NHS reference costs 2018-2019, PSSRU 2019, eMIT, and related TAs were used for the cost calculations. Some unit costs dated from 2018-2019 as no more recent data was available or no later NHS Cost Inflation index was available. However, given that the drug costs including the expensive drug price of avelumab and atezolizumab are 2021 values and much higher than the other considered costs, the ICER may be not significantly affected when 2021 prices were available for all costs.

5.4. Sensitivity analyses

The uncertainty intervals used for the PSA were, when possible, based on available data. However, for some values which were not provided with standard errors, percentages of the mean were assumed. Mostly 20% was considered to address a wide variety of uncertainty. Only for the patient characteristic, BSA, a lower percentage of 10% was chosen to achieve a realistic 95% confidence interval.

5.5. UK policy recommendations

Several key uncertainties had a large influence on the result and therefore should be resolved in the future to have more reliable CEAs result and subsequently to make a more justified recommendation for both populations. First, the implementation of a stopping rule should be investigated and more specifically the effect of a stopping rule on the health outcomes. This could be done by an extra clinical trial, or a performance-based market entry agreement (MEA) during which real-world data is collected from patients receiving avelumab with a stopping rule. Secondly, robust real-world data should be gathered on the duration of 2nd line atezolizumab treatment as this showed to have a large impact on the ICER. Thirdly, extrapolations of OS and PFS always entail uncertainty and in the PD-L1 subgroup a relatively big impact of the different distributions for OS on the result was observed. Therefore, it is always good to have long-term real-world data to validate the extrapolation. Furthermore, it might be good to have our CEA validated by clinical experts.

Based on the study results a policy recommendation is proposed under the previously discussed assumptions and key uncertainties of our CEAs. Although Avelumab (+BSC) showed substantial higher benefits (QALYS and LYs) compared to BSC alone, it was not cost-effective as maintenance treatment for patients (overall population + PD-L1 subgroup) with locally advanced or metastatic urothelial cancer who are PF after platinum-based chemotherapy at a WTP threshold of £30,000 per QALY gained. Therefore, we would not recommend avelumab with the current list price within its marketing authorization for the considered indication to the NHS because it would not contribute to health maximization as it would probably crowd out more effective interventions.

Avelumab was more cost-effective in the PD-L1 subgroup as the ICER (£89,175 per QALY gained) was about 40% lower than the ICER of the overall population (£147,484 per QALY gained). Therefore, it may be more successful for the company to focus on reimbursement of avelumab for this subgroup. However, this ICER is still about three times as high as the WTP threshold of £30,000 per QALY gained and even the result from the scenario analysis with the lowest ICER (£49,628 per QALY gained) is still £20,000 per QALY gained higher than this threshold. The same data from the overall population was used for the subgroup except the OS and PFS data and costs related to PD-L1 testing. However, utility values and the use of subsequent therapies may differ for the subgroup as well. Therefore, it may be useful to perform efforts to collect these data via trials or in real world and recalculate the result.

No budget impact analysis was performed in this study. However, a simple calculation of multiplying the incremental cost (overall population: £114,483) with the patients currently eligible for the treatment (circa 750) resulted in a total cost of around £85 million (79). In 2019, the UK spent around £225.2 billion to health care (80). Hence, reimbursement of avelumab as maintenance treatment for bladder cancer would take around 0.04% of the UK health care budget. This can be considered as a large impact on the health care budget and for sure would crowd out other health care interventions.

In conclusion, as the clinical data are positive but there exist financial (high ICER and budget impact) and clinical (long-term effects) uncertainties a MEA can be considered in the future to make the promising intervention available for the patients and to address the key uncertainties (stopping-rule, duration atezolizumab treatment and long-term effects). The MEA should include a commercial agreement (e.g., a discount) for which the ICER is lowered and a collection plan to gather real world evidence to address these key uncertainties. The company submission to NICE also applied a discount, which is confidential.

6. Conclusion

Despite the limitations of our study, we showed that avelumab (+BSC) showed an increment in health outcomes, but also higher costs compared to BSC alone. Based on the ICERs we concluded that avelumab was not cost-effective as maintenance treatment for patients (overall population or PD-L1 subgroup) with locally advanced or metastatic urothelial cancer who did not progress with 1st line platinum-based chemotherapy at a WTP threshold of £30,000. Therefore, we suggested to give a recommendation to the NHS to not reimburse the drug at the current price of avelumab as it would crowd out other health care interventions. However, a MEA could be considered to address financial and clinical uncertainties.

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8. Appendices

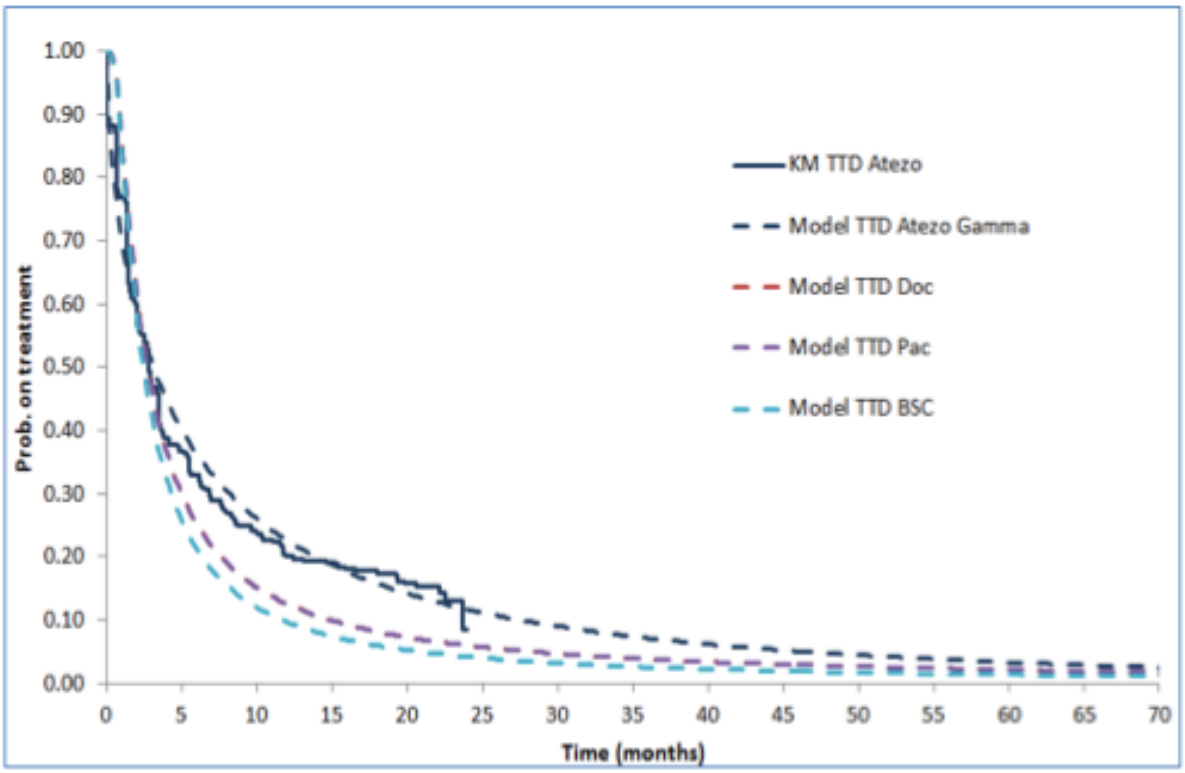
Appendix A: Adverse events in Bladder 100 clinical trial

Event	Avelumab Group (N=344)		Control Group (N=345)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	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
Urinary tract infection	59 (17.2)	15 (4.4)	36 (10.4)	9 (2.6)
Diarrhea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0
Asthenia	56 (16.3)	0	19 (5.5)	4 (1.2)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	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
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
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0
Rash	40 (11.6)	1 (0.3)	4 (1.2)	0
Anemia	39 (11.3)	13 (3.8)	23 (6.7)	10 (2.9)
Hematuria	36 (10.5)	6 (1.7)	37 (10.7)	5 (1.4)
Infusion-related reaction	35 (10.2)	3 (0.9)	0	0

Appendix B: Related TAs used in this study

TA number	Indication	Drug
TA391 (review of TA255) (47)	Hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen	Cabazitaxel
TA428 (67)	PD-L1-positive non-small-cell lung cancer after platinum- based chemotherapy	Pembrolizumab
TA517 (66)	Metastatic Merkel cell carcinoma	Avelumab
TA519 (34)	Locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy	Pembrolizumab
TA525 (35)		Atezolizumab
TA530 (33)		Nivolumab
TA692 (CDF review TA519) (63)		Pembrolizumab

Appendix C: TA525-KM and extrapolated time to treatment discontinuation (TTD)



Appendix D: Responses to multiple-choice question regarding favored 2nd line chemotherapy, taken from Lamb et al. (64)

Option	After prior neoadjuvant/adjuvant		In palliative setting	
	n	%	*n*	%
MVAC	7	21.2	4	12.1
Gemcitabine/cisplatin	6	18.2	1	3.0
Gemcitabine/carboplatin	6	18.2	7	21.2
Paclitaxel	5	15.2	6	18.2
Vinflunine	3	9.1	5	15.2
Docetaxol	2	6.1	5	15.2
Gemcitabine/cisplatin (split dose)	1	3.0	1	3.0
Single-agent gemcitabine	0	0.0	1	3.0

Appendix E: Weighted average cost anemia and UTI

AEs anaemia	activity	unit cost	weighted costs	source
Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	1,876	£2,833.36	£51.91	NHS Reference costs 2018/2019: weighted average of: SA01G-K, SA03G-H, SA04G-L, SA05G-J; total
Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 5-7	1,308	£1,559.40	£19.92	
Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 2-4	1,960	£1,042.64	£19.96	
Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 0-1	1,758	£634.36	£10.89	
Haemolytic Anaemia with CC Score 3+	2,143	£1,724.82	£36.10	
Haemolytic Anaemia with CC Score 0-2	1,892	£578.29	£10.69	
Iron Deficiency Anaemia with CC Score 14+	4,736	£2,279.83	£105.45	
Iron Deficiency Anaemia with CC Score 10-13	7,867	£1,287.24	£98.91	
Iron Deficiency Anaemia with CC Score 6-9	16,440	£776.38	£124.66	
Iron Deficiency Anaemia with CC Score 2-5	31,231	£483.58	£147.50	
Iron Deficiency Anaemia with CC Score 0-1	29,254	£341.86	£97.68	
Megaloblastic Anaemia with CC Score 8+	1,231	£1,860.93	£22.37	
Megaloblastic Anaemia with CC Score 0-3	692	£629.87	£4.26	
Weighted average			**£750.30**	

AE costs Urinary tract infection	activity	unit cost	weighted costs	Source
Kidney or Urinary Tract Infections, with Interventions, with CC Score 12+	2,145	£6,014.13	£49.34	NHS Reference costs F442018/2019: weighted average of: LA04H-R; total
Kidney or Urinary Tract Infections, with Interventions, with CC Score 9-11	3,042	£4,667.63	£54.30	
Kidney or Urinary Tract Infections, with Interventions, with CC Score 6-8	4,411	£3,835.56	£64.70	
Kidney or Urinary Tract Infections, with Interventions, with CC Score 3-5	4,105	£3,000.17	£47.10	
Kidney or Urinary Tract Infections, with Interventions, with CC Score 0-2	2,261	£2,474.83	£21.40	
Kidney or Urinary Tract Infections, without Interventions, with CC Score 13+	8,560	£3,051.23	£99.89	
Kidney or Urinary Tract Infections, without Interventions, with CC Score 8-12	45,706	£2,209.98	£386.30	
Kidney or Urinary Tract Infections, without Interventions, with CC Score 4-7	89,469	£1,535.93	£525.53	
Kidney or Urinary Tract Infections, without Interventions, with CC Score 2-3	51,153	£1,077.93	£210.87	
Kidney or Urinary Tract Infections, without Interventions, with CC Score 0-1	50,630	£738.21	£142.94	
weighted average			**£1,602.37**	

Resource	Number of consumption	Unit cost	% of patients in each setting	Total cost	Reference (resource use)	Reference (unit cost)
Community nurse specialist visit (per hour)	28 hours	£76	27%	£1,447.25	Appendix 1 of NICE guideline CG81,[113], Marie curie report[114]	Per patient contact lasting 11.4 minutes per home visit + 12-minutes travel time per visit (PSSRU 2015), £3.30 per minute of patient contact (PSSRU 2016).
GP Home visit	7.00 visits	£91.26	27%		Marie Curie Report[114]	Cost per hour of patient-related work (PSSRU 2015), Inflated to 2016 using the HCHS index 2015/2016.
Macmillan nurse	50.00 hours	£50.69	27%		Marie Curie report[114]	Macmillan nurse: 66.7% of community nurse cost (assumption as per Brown et al).
Drugs and equipment	As required	-	27%		Marie Curie report[114]	-
Terminal care in hospital	1 episode (9.66 days)	£3,345	56%	£1,866.51	Marie Curie report[114]	National Schedule of Reference Costs Year: 2015-16 - All NHS trusts and NHS foundation trusts. Non-elective long-stay. Ureteric or Bladder Disorders, without Interventions, with CC Score 5+. LB19E (average length of stay)
Terminal care in hospice	1 episode	£4,181.25	17%	£706.53	Marie Curie report[114] Assumption 25% increase on hospital IP care	National Schedule of Reference Costs Year: 2015-16 - All NHS trusts and NHS foundation trusts. Non-elective long-stay. Ureteric or Bladder Disorders, without Interventions, with CC Score 5+. LB19E (average length of stay) 25% increase on hospital inpatient care. Assumption as per Brown et al.
Radiotherapy	5.88	£550.20	100%	£3232.43	NICE TA272[51]	NHS Reference costs Year: 2015-16 - SC46Z and SC22Z - Outpatient
Total cost	**£7252.82**					

* GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HCHS, Hospital and Community Health Service; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups

Appendix G: Overview parameter values + SE + distribution + source (1L: 1st line, 2L: 2nd line)

Parameter name	Value	Standard error	Distribution	Source
Patient characteristics				
Body surface area	1.90	0.19	gamma	TA519
Utilities				
Utility value stable disease	0.79	0.20	beta	JAVELIN Bladder 100 clinical trial
Utility value progressed disease	0.63	0.01	beta	NICE TA519 + TA530
Adverse events				
Disutilities				
Disutility urinary tract infection	0.09	0.01	beta	Bermingham et al. (2012)
Disutility anemia	0.11	0.02	beta	Lloyd et al (2008), Beusterien et al (2010)
Incidences				
Avelumab +BSC				
Probability receiving urinary tract infection with avelumab	4.40%	-	beta	JAVELIN Bladder 100 clinical trial
Probability receiving anemia with avelumab	3.80%	-	beta	JAVELIN Bladder 100 clinical trial
BSC				
Probability receiving urinary tract infection with best standard of care	2.60%	-	beta	JAVELIN Bladder 100 clinical trial
Probability receiving anemia with best standard of care	2.90%	-	beta	JAVELIN Bladder 100 clinical trial
Duration				
Duration urinary tract infection	14.00	2.80	gamma	Lutters et al (2008)
Duration anemia	25.40	5.08	gamma	NICE TA391
total disutilities				
Total disutilities with avelumab	0.00044	-	-	-
Total disutilities with BSC	0.00031	-	-	-
Costs				
Drug costs				
Drug acquisition costs				
acquisition cost avelumab	768.00	-	-	British national formulary
acquisition cost pembrolizumab	2630.00	-	-	British national formulary
acquisition cost atezolizumab	3807.69	-	-	British national formulary
acquisition cost paclitaxel	7.22	0.23	gamma	eMIT 2021
acquisition cost prednisolone	0.10	0.14	gamma	eMIT 2021
acquisition cost morphine	0.18	0.01	gamma	eMIT 2021
acquisition cost gabapentin	0.02	0.00	gamma	eMIT 2021
acquisition cost alendronic acid	0.07	0.03	gamma	eMIT 2021
dosage (mg/m2)				
Dosage of paclitaxel	80.00	-	-	TA530
weight vial (mg)				
weight of vial paclitaxel	100.00	-	-	eMIT
number of vials per cycle				
Number of vials avelumab per cycle	4.00	-	-	-
Number of vials pembrolizumab per cycle	2.00	-	-	TA519
Number of vials atezolizumab per cycle	1.00	-	-	TA525
Frequency administration per cycle				
Number of administrations of second-line immunotherapy per cycle	1.33	0.23	gamma	SmPC
Number of administrations of second-line chemotherapy per cycle	3.00	0.23	gamma	SmPC
Number of administrations of prednisolone per cycle	14.00	0.23	gamma	TA530
Number of administrations of morphine per cycle	56.00	0.23	gamma	TA530
Number of administrations of gabapentin per cycle	28.00	0.23	gamma	TA530
Number of administrations of alendronic acid per cycle	28.00	0.23	gamma	TA531
Incidence after Avelumab (+BSC)				
Proportion of patients in the avelumab arm receiving second-line immunotherapy	0.06	-	Dirichlet	JAVELIN Bladder 100 clinical trial
Proportion of patients in the avelumab arm receiving second-line chemotherapy	0.40	-	Dirichlet	JAVELIN Bladder 100 clinical trial
Proportion of patients in the avelumab arm receiving no second-line therapy	0.58	-	Dirichlet	JAVELIN Bladder 100 clinical trial
Incidence after BSC				
Proportion of patients in the BSC arm receiving second-line immunotherapy	0.44	-	Dirichlet	JAVELIN Bladder 100 clinical trial
Proportion of patients in the BSC arm receiving second-line chemotherapy	0.34	-	Dirichlet	JAVELIN Bladder 100 clinical trial
Proportion of patients in the BSC arm receiving no second-line therapy	0.38	-	Dirichlet	JAVELIN Bladder 100 clinical trial
Cycles				
Number of cycles receiving second-line immunotherapy	3.00	-	-	TA519
Number of cycles receiving second-line chemotherapy	6.00	-	-	TA519
Total drug costs				
Total acquisition costs avelumab in stable disease	3072.00	-	-	-
Total acquisition costs BSC in stable disease	14.37	-	-	-
Total acquisition costs avelumab arm in progressed disease	1063.48	-	-	-
Total acquisition costs BSC arm in progressed disease	6744.19	-	-	-

Administration costs				
Administration cost avelumab/immunotherapy/chemotherapy	254.00	50.80	gamma	NHS reference costs 2018-2019
Premedication costs (only first 4 infusions)				
Unit cost antihistamine (Chlorphenamine) (1x 4 mg tablet before chemo)	0.05	0.00	gamma	eMIT 2020
Unit cost paracetamol (1 X 500 mg tablet before chemo)	0.00	0.00	gamma	eMIT 2021
HC resource use				
HC resource unit costs				
Unit cost Monitoring – oncologist	197.70	39.54	gamma	NHS 2018-2019
Unit cost Follow-up	194.17	38.83	gamma	NHS 2018-2019
Unit cost CT scan	104.53	20.91	gamma	NHS 2018-2019
Unit cost Blood count	3.00	0.60	gamma	NHS 2018-2019
Unit cost Biochemical tests (thyroid, liver, renal test)	1.00	0.20	gamma	NHS 2018-2019
unit cost GP home visit	39.23	7.85	gamma	Curtis, Lesley A. and Burns, Amanda (2019);
unit cost community nurse specialist visit	98.74	19.75	gamma	NHS 2018-2019
unit cost blood transfusions	180.45	36.09	gamma	NICE guidelines NG24
1L Avelumab +BSC				
Frequency monitoring – oncologist per cycle during treatment with avelumab	2.00	0.40	gamma	TA517 +TA530
Frequency follow-up per cycle during treatment with avelumab	2.00	0.40	gamma	TA517 +TA530
Frequency CT scan per cycle during treatment with avelumab	0.33	0.07	gamma	TA517 +TA530
Frequency blood count per cycle during treatment with avelumab	2.00	0.40	gamma	TA517 +TA530
Frequency biochemical tests (thyroid, liver, renal test) per cycle during treatment with avelumab	6.00	1.20	gamma	TA517 +TA530
2L immunotherapy				
Frequency monitoring – oncologist per cycle during treatment with 2L immunotherapy	1.33	0.27	gamma	TA517 +TA530
Frequency follow-up per cycle during treatment withv2L immunotherapy	1.33	0.27	gamma	TA517 +TA530
Frequency CT scan per cycle during treatment with 2L immunotherapy	0.33	0.07	gamma	TA517 +TA530
Frequency blood count per cycle during treatment with 2L immunotherapy	1.33	0.27	gamma	TA517 +TA530
Frequency biochemical tests (thyroid, liver, renal test) per cycle during treatment with 2L immunotherapy	4.00	0.80	gamma	TA517 +TA530
2L Chemotherapy				
Frequency monitoring – oncologist per cycle during treatment with 2L chemotherapy	3.00	0.60	gamma	TA517 +TA530
Frequency follow-up per cycle during treatment with 2L chemotherapy	3.00	0.60	gamma	TA517 +TA530
Frequency CT scan per cycle during treatment with 2L chemotherapy	0.33	0.07	gamma	TA517 +TA530
Frequency blood count per cycle during treatment with 2L chemotherapy	3.00	0.60	gamma	TA517 +TA530
Frequency biochemical tests (thyroid, liver, renal test) per cycle during treatment with 2L chemotherapy	6.00	1.20	gamma	TA517 +TA530
BSC				
frequency				
Frequency GP home visit per cycle when receiving BSC	2.00	0.40	gamma	TA530
Frequency Community nurse's specialist visit per cycle when receiving BSC	2.00	0.40	gamma	TA530
Frequency blood transfusions per cycle when receiving BSC	1.00	0.20	gamma	TA530
Incidence				
Probability of GP home visit when receiving BSC	0.50	0.10	beta	TA530
Probability of community nurse specialist visit when receiving BSC	0.50	0.10	beta	TA530
Probability of blood transfusions when receiving BSC	0.10	0.02	beta	TA530
Total costs HC resource use				
Total costs HC resource use per cycle when treated with avelumab	830.59	-	-	-
Total costs HC resource use per cycle when receiving BSC	156.01	-	-	-
Total costs HC resource use per cycle when treated with 2L immunotherapy	565.34	-	-	-
Total costs HC resource use per cycle when treated with 2L chemotherapy	1225.47	-	-	-
Adverse events costs				
costs AEs				
cost related to treatment of UTI	1602.37	320.47	gamma	NHS Reference costs 2018/2019
cost related to treatment of anemia	750.30	150.06	gamma	NHS Reference costs 2018/2019
Total costs AEs				
Total costs of the adverse events related to avelumab	99.02	-	-	-
Total costs of the adverse events related to best standard of care	63.42	-	-	-
Costs of terminal care				
Total cost estimate terminal care	**7692.40**	1538.48	gamma	TA519
PD-L1 testing				
Proportion of patients with PD-L1 positive tumors	0.51	0.10	beta	JAVELIN Bladder 100 clinical trial
PD-L1 test cost	40.50	8.10	gamma	TA428
Total PD-L1 costs per patient	79.26			-

Appendix H: Comparison of similar studies with this study

	This study (NICE guidelines)	**CADTH** (68,69)	**Merck submission (NICE guidelines**(70)
Type economic evaluation	Cost-utility analysis	Cost-utility analysis	Cost-utility analysis
Population	patients with locally advanced or metastatic urothelial cancer who did not progress during or after 1st line platinum-based chemotherapy + PD-L1 subgroup	patients with locally advanced or metastatic urothelial cancer who did not progress during or after 1st line platinum-based chemotherapy	patients with locally advanced or metastatic urothelial cancer who did not progress during or after 1st line platinum-based chemotherapy
Intervention	Avelumab + BSC (flat dosing)	Avelumab + BSC (weight-based dosing)	Avelumab + BSC (weight-based dosing)
Comparator	BSC	BSC	BSC = watchful waiting
Perspective	NHS and PSS	Canadian publicly funded health care payer	NHS and PSS
Model design	3-State partitioned survival analysis (PF, PD, death)	3-State partitioned survival analysis (PF, PD, death)	3-State partitioned survival analysis (PF, PD, death)
Time horizon	40 years	15 years	25 years
Cycle length	4 weeks	4 weeks	1 week
Discount rate	3.5%	?	3.5%
Time in health states	Modelling OS and PFS curves OS: exponential PFS: lognormal	Modelling OS and PFS curves OS: exponential PFS:?	Modelling OS and PFS curves OS: Generalized gamma PFS: 3-knot normal spline-based models fitted to each treatment arm
AEs	Grade 3 or higher Incidence 3% or higher	No AEs	Grade 3 or higher Incidence 1% or higher
Source utility values	JAVELIN bladder 100 + other TAs + external data for AEs PF: 0.792 (EQ-5D-5L) PD: 0.632	? No disutilities applied	JAVELIN bladder 100 + external data for AEs PF: 0.772 (EQ-5D-3L) PD: 0.698
Price avelumab per vial	£768	$1,325 (=£773.68)	£768 + patient access scheme
Types + incidences subsequent therapies	JAVELIN bladder 100	JAVELIN bladder 100	JAVELIN bladder 100 (more detail available)
Costs	Acquisition costs Administration Resource use and monitoring costs Terminal care costs AEs	BSC + AEs costs neglected Others?	Acquisition costs (no BSC costs) Administration Resource use and monitoring costs Terminal care costs AEs

Appendix I: Overview key model assumptions

Assumption	Justification (with supporting literature)
A 3-state partitioned survival model (PF, PD, death) was designed.	This model design was also used in other CEA for the same indication (33,35,63,70).
The model cycle length lasted 4 weeks.	The treatment cycle in the trial lasted 4 weeks (8). Furthermore, HCC was applied for interventions and clinical events during a cycle.
A lifetime horizon lasted 40 years.	After 40 years less than 0.1% was alive. A lifetime horizon is preferred by NICE for treatments that affect survival or benefits for the resting life years (24). In TA519 (Pembrolizumab) a lifetime horizon lasted 35 years for a 2nd line treatment (63).A scenario analysis was performed with a lifetime horizon of 20 years.
The exponential and lognormal distribution were applied for OS and PFS extrapolation, respectively.	The best extrapolations were identified based on statistical fit (internal validity) and clinical plausibility (external validity, if real-world data was available). This way of identification is preferred by NICE (24). Furthermore, scenario analyses were performed with the other considered extrapolations.
The baseline utility measured in the BSC arm was chosen as PF utility value for both treatment arms in the base case CEAs.	It approximated the utility value of 0.778 measured in the average UK person aged 65-74 the most (43). A scenario analysis was performed with the baseline value measured in the avelumab arm
The average of PD utilities from two TAs for 2nd line immunotherapies was applied	Best values available.
Non-disease specific disutilities were applied.	No disease specific disutilities were available. Non-disease specific disutilities for anemia were applied in similar TAs (33,47). UTI disutilities were assumed to be robust to differences in countries, populations and, measurement instruments (52).
Flat dosing was applied instead of weight-based dosing.	1. Flat-dosing was recommended in the SmPC of avelumab (54) 2. Flat and weight-based dosing have similar efficacy and safety (60) 3. Flat-dosing has more practical advantages (78)
The considered 2nd line immunotherapy was atezolizumab.	Atezolizumab was the only 2nd line immunotherapy recommended in the NICE guidelines (17).
Only single dose paclitaxel was considered as other 2nd line therapy.	This was the most common used 2nd line chemotherapy in a UK observational study (65). Furthermore, it is less likely to receive platinum-based chemotherapies as 2nd line -treatment in patients who already received platinum-based chemotherapy as 1st line therapy.
No stopping-rule was implemented for avelumab in the base case analysis	No stopping rule was mentioned in the SmPC or applied in the trial (8,54). Furthermore, the effect of a stopping-rule on the health outcomes could not be predicted. A scenario analysis was performed with a stopping rule of 3 years as only the trial data of the first 3 years was available.
Atezolizumab was only administered for three cycles in the base case analysis	Given the big impact of the number of cycles of atezolizumab on the ICER, we tried to be realistic as possible by applying the median duration until treatment discontinuation (81). A scenario analysis was performed with maximum number of cycles allowed (2 years, 24 cycles)