Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2359

# avelumab 20mg/mL concentrate for solution for infusion (Bavencio®)

Merck KGaA, Pfizer Ltd

09 July 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission assessed under the end of life and orphan equivalent process

**avelumab (Bavencio®)** is accepted for use within NHSScotland.

**Indication under review:** as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.

In a phase III study, maintenance treatment with avelumab plus best supportive care (BSC) significantly improved overall survival when compared with BSC alone.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

**Chairman**
**Scottish Medicines Consortium**

## Indication

Avelumab is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.[1]

## Dosing Information

The recommended dose of avelumab as monotherapy is 800mg administered intravenously over 60 minutes every 2 weeks. Patients have to be premedicated with an antihistamine and with paracetamol prior to the first four infusions of avelumab. If the fourth infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the physician.

Administration of avelumab should continue according to the recommended schedule until disease progression or unacceptable toxicity.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability; refer to the Summary of product characteristics (SPC). The SPC also includes guidelines for the management of immune-related adverse reactions.

Treatment should be initiated and supervised by a physician experienced in the treatment of cancer, see the SPC for further information.[1]

## Product availability date

March 2021 Avelumab meets SMC orphan equivalent and end of life criteria.
Avelumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 1 September 2020 for this indication (EAMS number 11648/0003).

## Summary of evidence on comparative efficacy

Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that binds to programmed death ligand 1 (PD-L1) and blocks its interaction with the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumour T-cell responses. Avelumab has also been shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).[1]

The key evidence supporting the efficacy and safety of avelumab comes from JAVELIN Bladder 100, an international, randomised, open-label, parallel group, phase III study. This study recruited adult patients with histologically confirmed, unresectable locally advanced or metastatic urothelial

carcinoma. Patients had documented stage IV disease at the start of first-line chemotherapy, which consisted of 4 to 6 cycles of gemcitabine plus cisplatin and/or gemcitabine plus carboplatin. Patients had no progressive disease as per RECIST v1.1 following completion of first-line chemotherapy. They had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤1.[2, 3]

Patients were randomised equally to receive avelumab (10mg/kg administered as 1-hour intravenous (IV) infusion once every 2 weeks) plus BSC (n=350) or BSC alone (n=350). Premedication, with an antihistamine and with paracetamol (or other regimens based on local practices, excluding systemic corticosteroids) to mitigate infusion-related reactions, was mandatory prior to the first four avelumab infusions. No dose modifications were permitted with avelumab, but an infusion could be omitted based on persisting toxicity. Treatment was to be continued until confirmed disease progression as assessed by blinded independent central review (BICR), unacceptable toxicity, patient withdrawal, loss to follow-up or study termination. Administration of avelumab was permitted beyond progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. [1, 2]

Randomisation was stratified according to best response to first-line chemotherapy (complete/partial response versus stable disease), and metastatic disease site (visceral versus non-visceral) at the time of initiating first-line chemotherapy.[2, 3]

The primary outcome was overall survival, which was defined as the time between date of randomisation and death due to any cause, in all the randomised patients and the PD-L1–positive population.

At data cut-off 21 October 2019, avelumab plus BSC was associated with a statistically significant improvement in overall survival compared with BSC alone. Secondary outcomes, including progression-free survival (PFS) and objective response (OR), showed consistency with the primary outcome analyses. Results for the primary and relevant secondary outcomes are shown in Table 1. Overall survival results were confirmed by an unplanned analysis with data cut off January 2020, which was requested by the European Medicines Agency (EMA).[2, 3]

**Table 1: Results of primary, secondary and exploratory outcomes of JAVELIN Bladder 100 (data cut-off date 21 October 2019).** [2, 3]

| | **All randomised patients** | | **Patients with PD-L1-positive tumours** | |
|---|---|---|---|---|
| | **Avelumab + BSC (n=350)** | **BSC (n=350)** | **Avelumab + BSC (n=189)** | **BSC (n=169)** |
| **Overall survival** | | | | |
| Median duration of follow-up, months | 19.6 | 19.2 | 18.3 | 20 |
| Number of events | 145 | 179 | 61 | 82 |
| Median overall survival, months | 21.4 | 14.3 | NE | 17.1 |

| | | | | |
|---|---|---|---|---|
| HR (95% CI) | 0.69 (0.56 to 0.86) | | 0.56 (0.40 to 0.79) | |
| p-value | p<0.001 | | p<0.001 | |
| KM estimate at 12 months | 0.71 | 0.58 | 0.79 | 0.60 |
| KM estimate at 24 months | 0.48 | 0.37 | 0.58 | 0.40 |
| **PFS assessed by BICR per RECIST v1.1.** | | | | |
| Patients with event | 225 | 260 | 109 | 130 |
| Median PFS, months | 3.7 | 2.0 | 5.7 | 2.1 |
| Stratified HR (95% CI) | 0.62 (0.52 to 0.75) | | 0.56 (0.43 to 0.73) | |
| KM estimate at 6 months | 41% | 22% | 48% | 23% |
| KM estimate at 12 months | 30% | 13% | 36% | 15% |
| **OR assessed by BICR per RECIST v1.1.** | | | | |
| OR, % | 9.7% | 1.4% | 14% | 1.2% |
| CR, % | 6.0% | 0.9% | 9.5% | 0.6% |
| PR, % | 3.7% | 0.6% | 4.2% | 0.6% |
| Abbreviations: BICR, blinded independent central review; BSC, best supportive care; CI, confidence interval; CR, complete response; HR, hazard ratio; KM, Kaplan Meier; NE, not evaluable; PD-L1, programmed death ligand-1; PFS progression-free survival; PR, partial response; OR, objective response. | | | | |

Health Related Quality of Life (HRQoL) was descriptively assessed using the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy (NCCN-FACT) Bladder Symptom Index (FBlSI-18) and the EuroQol 5 dimensions 5 levels (EQ-5D-5L). Overall, changes from baseline in FBISI-18 total scores and in EQ-5D-5L index scores appeared to be similar between the two treatment groups.[2, 4]

As of data cut-off 21 October 2019, the median duration of treatment in the avelumab group was 24.9 weeks (range, 2.0 to 159.9) and in the control group was 13.1 weeks (range 0.1 to 155.6). In avelumab group, the mean number of infusions received was 18.4 (range, 1.0 to 80.00) and the median number of infusions received after progression was 3.0.[2]

## Summary of evidence on comparative safety

According to the EMA, overall, the safety profile of avelumab in the key study was similar, regardless of PD-L1-status, to the previously reported safety profile of avelumab monotherapy in other solid tumours. No new safety concerns were raised, and the safety profile was considered manageable.[2]

In the JAVELIN Bladder 100 study at data cut-off 21 October 2019, any treatment-emergent adverse event (AE) was reported by 98% (337/344) of patients in the avelumab group and 78% (268/345) in the control group and these were considered treatment-related in 77% and 1.2% respectively. In the avelumab and control groups respectively, patients reporting a grade 3 or

higher treatment-emergent AE were 47% versus 25%, patients reporting a grade 3 or higher treatment-related AE were 17% versus 0%, patients with a serious treatment-emergent AE were 28% versus 20%, patients with a serious treatment-related AE were 9.0% versus 0% and patients having a dose reduction of avelumab due to treatment-emergent AEs were 0.3%. The proportion of AEs that led to dose interruption of avelumab was 41% and patients discontinuing therapy due to an AE was 12% versus 0%.[3]

The most frequently reported treatment-related AEs of any grade with an incidence >5% in the avelumab group versus the control group were: pruritus (14% versus 0%), hypothyroidism (10% versus 0%), diarrhoea (10% versus 0%), infusion-related reaction (10% versus 0%), asthenia (9.9% versus 0%), fatigue (9.6% versus 0%), rash (7.3% versus 0%), chills (7.0% versus 0%), nausea (7.0% versus 0%), arthralgia (6.7% versus 0%), pyrexia (6.7% versus 0%), hyperthyroidism (6.1% versus 0%), dry skin (5.2% versus 0%). [3]

Two deaths were assessed as being related to avelumab toxicity by the investigator (sepsis after a urinary tract infection and possible central venous catheter infection; another with ischemic stroke).[3]

## Summary of clinical effectiveness issues

Patients with locally advanced or metastatic urothelial carcinoma, if eligible, will receive platinum-based combination chemotherapy first-line, which results in median overall survival ranging from 9-14 months. For patients progressing during, or after, platinum-based chemotherapy, the use of the PD-1 inhibitor pembrolizumab (or another checkpoint inhibitor) is recommended. Other second line options include chemotherapy, best supportive care (BSC) or entry into a clinical trial.[2, 5, 6] Pembrolizumab use within NHS Scotland is restricted in adults who have received prior platinum-containing chemotherapy, and its use is subject to a two-year clinical stopping rule. Clinical experts consulted by SMC considered that avelumab fills an unmet need, namely in the first-line maintenance setting where survival is poor and no other medicine is available. Avelumab meets SMC orphan equivalent and end of life criteria.

In JAVELIN Bladder 100, treatment with avelumab plus BSC was associated with a statistically significant improvement in overall survival with a median gain of 7.1 months over BSC alone in all randomised patients, and a statistically significant reduction in the risk of dying (hazard ratio [HR]: 0.56) in the population of patients with PD-L1 positive tumours. These improvements were considered clinically relevant by the EMA. Secondary outcomes were supportive, including OR and PFS, both by BICR and by investigator.[2, 3]

The predefined efficacy boundaries were crossed at the interim analysis, thus the interim analysis constituted the primary overall survival analysis. Some uncertainty may have been introduced by the interim nature of the analysis. Long-term survival, beyond the study duration, for both avelumab with BSC and BSC alone is uncertain.

The study was limited by its open-label design, which may have introduced bias for certain outcomes, including HRQoL. Another design limitation was the lack of adjustment for multiplicity for secondary outcomes.[2, 3]

At baseline, there were some differences between the treatment groups, including that a greater proportion of patients in the avelumab group had a PD-L1 positive status compared with the control group (54% versus 48%), and fewer patients had an unknown PD-L1 status in the avelumab group (6.3% versus 14%). As noted by the EMA, the lack of randomisation according to PD-L1 status introduced uncertainty in the interpretation of the results and a larger risk for non-comparable patient populations between treatment groups.[2, 3]

The EMA noted that benefits of avelumab in patients with a PD-L1 negative status is less pronounced and that in these patients there was a modest PFS improvement with avelumab but no signs of a detrimental effect on overall survival. In patients with unknown PD-L1 status, the efficacy data were difficult to interpret due to very small subgroup size (n=72), and the EMA noted that no evident detrimental effect on PFS or overall survival was detected. Overall, the EMA concluded that no subgroup based on PD-L1 status displayed a detrimental effect on overall survival that would motivate an exclusion from the indication.[2]

Fewer patients in the avelumab group received a subsequent anti-cancer drug therapy compared with the control group (42% versus 62%). Specifically, only 6.3% received a PD-1 or PD-L1 inhibitor in the avelumab group versus 44% in the control group. The open-label design may also have led to earlier initiation of subsequent therapy in the control group.

In addition, all study patients had an ECOG PS ≤1 (four patients had an ECOG PS of 2 or 3), which limits generalisability to patients with poorer performance status.

Of note, in JAVELIN Bladder 100, the avelumab dose was based on bodyweight (at 10mg/kg once every 2 weeks); however, a flat dose (of 800mg every 2 weeks) was approved by the EMA as the benefit-risk balance was considered to be unchanged with the flat dose based on pharmacokinetic exposure comparisons.[2]

Although BSC is the most relevant comparator in the maintenance setting, clinical experts consulted by SMC generally considered that the introduction of avelumab as monotherapy would most likely displace the use of pembrolizumab in second-line. There is currently no information available on the effects of using a different immunotherapy in second line after progression on first line maintenance with avelumab.

Clinical experts consulted by SMC considered that avelumab is a therapeutic advancement offering improved overall survival and that its place in therapy was in-line with the licensed indication. They considered that the introduction of avelumab may impact on the service due to the infusion appointments every two weeks, however this would concern only a small number of patients.

## Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of avelumab, as an orphan equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Locally advanced unresectable or metastatic urothelial carcinoma is an aggressive malignancy with a very poor prognosis and a high burden of symptoms. Patients have significant local and systemic symptoms, including considerable pain and discomfort, which are challenging to treat and adversely affect quality of life of both patients and their carers and families.
- There is a high unmet need in this patient group. There is currently no treatment available, apart from best supportive care, in maintenance after first line chemotherapy (before disease progression).
- Avelumab, as maintenance treatment after chemotherapy, could increase overall survival without negatively affecting patients' quality of life. It offers patients and their carers and families hope and may help them to have quality time and function for longer. It may also help address the negative psychological effect of stopping treatment after chemotherapy and having to wait for disease progression to get an immunotherapy.
- Avelumab appears to be well tolerated and clinicians are well versed in managing its side effects.

**Additional Patient and Carer Involvement**

We received patient group submissions from Action Bladder Cancer UK and Fight Bladder Cancer, which are both registered charities. Action Bladder Cancer UK has received 29% pharmaceutical company funding in the past two years, including from the submitting company. Fight Bladder Cancer has received 39% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

## Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing avelumab monotherapy with BSC for the maintenance treatment of adult patients with locally advanced or metastatic urothelial cancer who are progression-free following platinum-based chemotherapy. The analysis adopted a time horizon of 25 years.

The economic analysis incorporated a partitioned survival model with three health states: progression-free, progressed and dead, and weekly cycles.

In the analysis, patients received avelumab at the recommended dose of 800mg every second week. This is inconsistent with the main clinical study where the dose of avelumab was weight-based, but as noted above, reflects the licensed dose. An estimated ratio of the mean number of infusions per treatment cycle was included to account for missed or delayed doses as observed in JAVELIN Bladder 100. Time to discontinuation was as observed in the main clinical study in the first 2 years with only 5% assumed to continue treatment until year 5, after which point all treatment would cease.

The main source for comparative efficacy data in the economic model was JAVELIN Bladder 100. Data on overall survival, investigator-assessed PFS and time to treatment discontinuation (TTD) (for avelumab only) were modelled beyond the median trial follow-up period. In both arms, the generalized gamma was selected for the extrapolation of overall survival based on statistical and visual fit but primarily on clinical expert opinion. For the extrapolation of PFS, the 3-knot-hazard model in the avelumab arm and the 3-knot odds model in the BSC arm were used based on best statistical fit. The log-normal distribution was used for the extrapolation of TTD up to 2 years, followed by an adjustment to reflect expected clinical practice in Scotland.

A proportion of patients who progressed as observed in the main clinical study were assumed to receive second line treatment. Of those in the BSC arm, the majority were assumed to receive pembrolizumab and the rest received standard chemotherapies. In the avelumab arm all treated patients post progression received standard chemotherapies.

Health state-specific utility weights were derived using EQ-5D-5L data from the main clinical study, mapped to EQ-5D-3L using the van Hout[7] crosswalk. Data were analysed using a mixed-effect linear regression model with baseline EQ-5D score and progression as covariates. The estimated utility weight in the progression-free state was 0.772 and 0.698 in the progressed state. A treatment-specific one-off utility decrement associated with Grade ≥3 adverse events was also included.

Aside from medicine acquisition and administration costs, other costs included were those associated with treatment of Grade ≥3 adverse events, disease management in the progression-free state and the progressed health states such as visits to oncologist, clinical nurse specialist, dietician, GP, urologist and district nurse. Additionally, the analysis included subsequent treatments (as discussed above) and end of life care costs.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price for avelumab. A PAS is also in place for pembrolizumab in NHSScotland.

The results presented do not take account of the PAS for avelumab or pembrolizumab in second line but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company, which used an estimate of the PAS price for avelumab and pembrolizumab due to commercial confidentiality and competition law issues. As such, results are presented below using list prices for all medicines.

In the base case analysis, the company estimated an incremental cost-effectiveness ratio (ICER) of £74,383 per quality-adjusted life-year (QALY) using list prices for all medicines.

The most substantial ICER increases from the presented scenarios in Table 2 below were associated with assumptions around treatment duration and associated treatment effect, long-term progression-free and overall survival benefit for avelumab and subsequent treatments.

**Table 2: Selected scenario analyses (list price for all medicines)**

| | **Base case** | **Scenario** | **ICER (£/QALY)** |
|---|---|---|---|
| 0 | Base case | - | £74,383 |
| 1 | Using log-normal for TTD for avelumab and assuming 95% discontinue by 2 years and 100% by 5 years. | Using the generalized gamma for TTD (best statistical and visual fit to the KM data) with no adjustment at 2 years but 100% discontinue by 5 years. | £105,423 |
| 2 | Using log-normal for TTD for avelumab and assuming 95% discontinue by 2 years and 100% by 5 years. | Using the generalized gamma for TTD (best statistical and visual fit to the KM data) with no adjustment at 2 or 5 years. | £149,583 |
| 3 | Treatment effect for avelumab: No adjustment to OS and PFS | Assuming patients discontinuing treatment at 2 years have treatment effect removed at 4 years (2-years post discontinuation) | £77,844 |
| 4 | OS: generalized gamma in both arms | OS: log-normal for avelumab (best statistical and visual fit) and generalized gamma for BSC; curves merge after year 8-9. | £135,349 |
| 5 | Investigator-assessed PFS: 3-knot hazard applied to avelumab and 3-knot-odds applied to BSC (best statistical fits and alignment with clinical expectation ) | Investigator-assessed PFS: 2-knot hazard applied to avelumab and 1-knot-hazard applied to BSC (best visual fits and alignment with clinical expectation ) | £82,117 |
| 6 | Investigator-assessed PFS: 3-knot hazard applied to avelumab and 3-knot-odds applied to BSC (best statistical fits) | BICR-assessed PFS: 3-knot normal applied to avelumab PFS and 3-knot odds applied to BSC (best statistical fits) | £83,039 |
| 7 | Second-line treatment in the avelumab arm: no pembrolizumab | Second-line treatment in the avelumab arm: a small proportion receive pembrolizumab (JAVELIN Bladder 100) | £78,509 |
| 8 | Proportion of progressed patients treated in second line as observed in JAVELIN Bladder 100 | 30% reduction in proportion of progressed patients treated in second line in both arms | £87,070 |
| 9 | Flat dose of 800mg as per licensed indication | Weight-based dose for avelumab as observed in JAVELIN Bladder 100 | £67,823 |

| | | | |
|---|---|---|---|
| 10 | Health-state specific utilities from in JAVELIN Bladder 100 | Treatment-specific and health state-specific utilities from JAVELIN Bladder 100 | £79,878 |
| Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; TTD, time to treatment discontinuation; K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; BSC, best supportive care; | | | |

Key limitations with the analysis were:

- There are uncertainties around the treatment duration with avelumab monotherapy in Scottish clinical practice. A large proportion of patients in the main study were treated after progression with a median number of infusions of 3. Additionally at 2 years, a minority of patients were still on treatment. The company's base case economic model assumed a sharp drop in the proportion of patients continuing treatment after 2 years with 100% discontinuing treatment by 5 years, using the log-normal distribution for the long term extrapolation of the TTD curve in the base case. When the generalized gamma was used, which had the best statistical and visual fit to the K-M data from the trial, but keeping the assumption of all patients discontinuing by 5 years, the ICER increases substantially (Scenario 1). Clinical experts consulted by SMC considered the assumption of 100% treatment discontinuation by 5 years as generally acceptable. However, one of the two clinicians who provided a response to this specific question suggested that the proportion on treatment at 2 years is more likely to reflect the observed in the main study. There is an even bigger increase in the ICER when both adjustments to the TTD curve are removed (Scenario 2).

- SMC considered the limitations of the various treatment duration scenarios provided by the company and concluded on balance that scenario 1 is most likely to reflect treatment duration in practice.

- There are uncertainties around the long-term duration of treatment effect for avelumab given the proposed shorter treatment duration in the economic model. Clinical experts consulted by SMC suggested that treatment effect of avelumab might continue after treatment discontinuation but there are no data to support this and maintained long-term treatment effect remains uncertain. The company provided a scenario analysis assuming treatment waning effect for avelumab at 5 years. However, given the assumptions made the impact on the ICER was minimal.

- There are uncertainties around the long-term survival benefit for avelumab. When the parametric model with best statistical and visual fit (log-normal) is used for the long-term extrapolation of OS in the avelumab arm, the ICER increases substantially (Scenario 4). It should be noted that the OS curves for the two comparators cross approximately at year 8 which suggests a loss of survival benefit for avelumab after that time point. Given that patients in the BSC arm are treated with more effective treatments in second line (pembrolizumab), a diminishing long-term survival benefit for avelumab can be expected.

- There is a slight uncertainty around the long-term extrapolation of progression-free survival data for both comparators. Although the company's base case uses the best statistical fit models (3-knot hazard in the avelumab arm and 3-knot odds in the BSC arm), a different pair of models seem to have a better visual fit and still be aligned with clinical expectation. The ICER increases when those models are used (Scenario 5). Additionally, the company used the investigator-assessed PFS in their economic model but clinical efficacy was based on the BICR definition of PFS as outlined in the clinical section above. When using the BICR PFS in the economic model, the ICER increases (Scenario 6).

- There are uncertainties around second-line therapies following avelumab. The company's base case assumed only treatment with standard chemotherapies, which is not aligned with the main clinical study. Two out of five SMC clinical experts suggested that avelumab might not completely displace pembrolizumab in second line. When a small proportion of patients were assumed to receive pembrolizumab in second line as observed in JAVELIN Bladder 100, the ICER increased (Scenario 7). Additionally, clinical experts suggested that the proportions of treated patients after progression observed in the main study and included in the model might be too high. An arbitrary 30% reduction in the proportion of treated patients in both arms leads to an increase in the ICER (Scenario 8).

- There is a small uncertainty associated with quality of life of progressed patients. EQ-5D data from JAVELIN Bladder 100 showed similar utility weight for progression-free patients, although slightly lower in the BSC arm. However, the data showed a bigger difference in utilities of progressed patients between the two arms. That could be explained by patients in the BSC arm being treated with therapies generally associated with better long-term outcomes than progressed patients after maintenance with avelumab. However, the company noted that due to the fact progression is delayed with avelumab, patients who had progressed at the time of the data cut are likely sicker patients as healthier patients would not have progressed yet and therefore may have lower quality of life than the full study population would have once progressed. When the treatment and health state-specific utility values are used, the ICER increases (Scenario 10).

The Committee also considered the benefits of avelumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, as avelumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted avelumab for use in NHSScotland.

## Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up in 2014.[8] The guidance was subsequently updated in 2019[9] and 2020.[10] It noted that platinum combination chemotherapy is the standard of care for advanced or metastatic urothelial cancer. Gemcitabine with cisplatin or gemcitabine with carboplatin are the most widely used regimens and six cycles of chemotherapy is considered standard therapy. The guidance makes the following relevant recommendations for treatment-naive advanced or metastatic urothelial carcinoma:

- Cisplatin eligible: cisplatin-based chemotherapy followed by maintenance avelumab for tumours which have not progressed on chemotherapy
- Cisplatin ineligible and PD-L1 unknown or negative: gemcitabine/carboplatin followed by maintenance avelumab for tumours which have not progressed on chemotherapy
- Cisplatin ineligible and PD-L1-positive: gemcitabine/carboplatin followed by maintenance avelumab for tumours which have not progressed on chemotherapy **or** atezolizumab or pembrolizumab.[8, 10]

In patients with platinum-refractory disease, immune checkpoint inhibitors are standard options and treatment should continue until progression. Treatment with chemotherapy is an alternative for patients in whom anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy is not possible. Erdafitinib is an option in platinum-refractory or platinum- and immune checkpoint inhibitors-refractory urothelial tumours with selected fibroblast growth factor receptor (FGFR) DNA alterations.

The European Association of Urology (EAU) updated its guideline on "Muscle-invasive and metastatic bladder cancer" in 2020.[6] It recommends as first-line treatment:

- For platinum-fit patients: cisplatin-containing combination chemotherapy with gemcitabine or high-dose methotrexate, vinblastine, doxorubicin and cisplatin (HD-MVAC)
- In patients unfit for cisplatin but fit for carboplatin: combination of carboplatin and gemcitabine.
- In patients achieving stable disease, or better, after first-line platinum-based chemotherapy: maintenance treatment with avelumab.

As second-line treatment, the guideline recommends treatment with the checkpoint inhibitor pembrolizumab in patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease (or if not possible, another checkpoint inhibitor). After platinum- and immunotherapy, treatment within a clinical trial should be considered; or in case of patients with FGFR3 alterations, FGFR tyrosine kinase inhibitors.

The National Institute for Heath and Care Excellence (NICE) guideline Bladder cancer: diagnosis and management (NG2), which was published in 2015 and predates approvals of immune checkpoint inhibitors in urothelial carcinoma, recommends in patients with locally advanced or metastatic muscle invasive bladder cancer:[11]

- As first line chemotherapy:

- for patients who are otherwise physically fit (ECOG PS of 0 or 1) and have adequate renal function: a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or HD-MVAC in combination with granulocyte-colony stimulating factor [G-CSF])
- if a cisplatin-based chemotherapy regimen is unsuitable (for example, because of ECOG performance status, inadequate renal function or comorbidity): carboplatin in combination with gemcitabine.

- As second-line chemotherapy
  - for patients whose condition has progressed after first-line chemotherapy if their renal function is adequate and they are otherwise physically fit: gemcitabine in combination with cisplatin, or HD-MVAC in combination with G-CSF.
  - for patients for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it: carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel.

## Additional information: comparators

Best supportive care.

## Additional information: list price of medicine under review

| Medicine | Dose Regimen | Cost per year (£) |
|---|---|---|
| **Avelumab** | **800mg administered intravenously every 2 weeks** | **79,872** |

*Costs from BNF online on 02 April 2021. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.*

## Additional information: budget impact

The submitting company estimated there would be 56 patients eligible for treatment with avelumab in year 1 and in year 5. The estimated uptake rate was 45% in year 1 and 80% in year 5. This resulted in 25 patients estimated to receive treatment in year 1 rising to 45 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

**References**


1. Merck - Pfizer. Avelumab concentrate for solution for infusion (Bavencio®). Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated: 01.02.2021.
2. European Medicines Agency (EMA): European Public Assessment Report (EPAR). Avelumab (Bavencio®). EMEA/H/C/004338/II/0018. Available at: www.ema.europe.eu [Last updated 10 December 2020].
3. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H*, et al.* Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. New England Journal of Medicine. 2020;383(13):1218-30.
4. Powles TB, Kopyltsov E, Su PJ, Parnis FX, Park SH, Yamamoto Y*, et al.* Patient-reported outcomes (PROs) from JAVELIN Bladder 100: Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma (UC). Annals of Oncology. 2020;31 (Supplement 4):S578-S9.
5. European Society of Medical Oncology. eUpdate – Bladder Cancer Treatment Recommendations. 2020 [cited; Available from: https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer/eupdate-bladder-cancer-treatment-recommendations4.
6. European Association of Urology. EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). Available at: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/ Last updated March 2021.
7. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
8. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2014;25:iii40-iii8.
9. European Society for Medical Oncology (ESMO). eUpdate – Bladder cancer treatment recommendations 2019. Available at: https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer.
10. European Society for Medical Oncology (ESMO). eUpdate – Bladder cancer treatment recommendations 2020. Available at: https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer.
11. NICE. Bladder cancer: diagnosis and management. NICE guideline [NG2]. Available at: https://www.nice.org.uk/guidance/ng2/ Published date: 25 February 2015.


This assessment is based on data submitted by the applicant company up to and including 14 May 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*