atezolizumab 1,200mg concentrate for solution for infusion (Tecentriq®)

SMC No 1297/18

Roche Products Ltd

9 February 2018

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 NHS Scotland. The advice is summarised as follows:

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

atezolizumab (Tecentriq®) is not recommended for use within NHS Scotland.

Indication under review: As monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.

In a single arm, open-label, phase II study of patients with locally advanced or metastatic urothelial carcinoma who had received no previous treatment for metastatic disease and who were ineligible for cisplatin therapy, treatment with atezolizumab resulted in an objective response in 19% of patients.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.

Dosing Information

The recommended dose is atezolizumab 1,200mg by intravenous (IV) infusion every three weeks until loss of clinical benefit or unmanageable toxicity. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

The SPC gives recommendations for delaying or discontinuing treatment due to specific adverse events.

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer.[1]

Product availability date

September 2017

Atezolizumab meets SMC end of life and orphan equivalent criteria.

Atezolizumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 23 January 2017.

Summary of evidence on comparative efficacy

Urothelial cancers (also known as transitional cell carcinomas) account for approximately 90% of bladder cancers. Atezolizumab is a humanised monoclonal antibody that binds to programmed death ligand-1 (PD-L1) and provides a dual blockade of the PD-1 and B7.1 receptors. Disrupting the PD-L1/PD-1 and PD-L1/B7.1 pathways abrogates inhibition of antitumor T-cell activity.[1,2] Atezolizumab is licensed as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.[1] The submitting company has requested that SMC considers the use of atezolizumab in adult patients with locally advanced or metastatic urothelial cancer who are considered cisplatin ineligible (first-line).

Evidence of efficacy in cisplatin ineligible patients comes from cohort 1 of the IMvigor 210 study.[2,3] This was an open-label, single-arm, phase II study which assessed the efficacy and safety of atezolizumab in patients with locally advanced or metastatic urothelial cancer. There were two cohorts: (1) patients who had not received previous treatment in the metastatic setting and were considered ineligible for cisplatin treatment[3] and (2) patients whose disease had progressed after previous platinum-based chemotherapy (not relevant to current submission).[4] In cohort 1, patients were aged ≥18 years with histologically or cytologically documented, inoperable, locally advanced or metastatic urothelial cancer (renal pelvis, ureters, bladder or urethra) and had received no previous treatment for metastatic disease. They had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and Eastern Co-operative Oncology Group (ECOG) performance status of ≤2. Patients were eligible if they had received neo-adjuvant or adjuvant chemotherapy provided there had been >12

months between previous treatment and present recurrence. Patients were considered cisplatin ineligible by meeting at least one of the following criteria: glomerular filtration rate of >30mL/minute and <60mL/minute; hearing loss of 25 dB at two contiguous frequencies; peripheral neuropathy of ≥grade 2 or ECOG of 2. All study patients received open-label atezolizumab 1,200mg intravenously (IV) every three weeks, continued until there was unacceptable toxicity or radiographic progression, assessed by the investigator. During treatment, dose interruptions were allowed but dose reductions were not.

The primary outcome in cohort 1 was objective response rate (ORR: defined as confirmed complete or partial response) assessed by independent, central review according to RECIST version 1.1. The primary analysis was performed after a minimum of six months of follow-up and used a hierarchical fixed-sequence testing procedure to compare the independently assessed ORR in three pre-specified subgroups of patients treated with atezolizumab according to level of PD-L1 expression (PD-L1 on ≥5%, PD-L1 on ≥1% and all patients) with a historical control ORR of 10%.[2, 3]

Results of the primary and key secondary outcomes are presented in table 1 at the primary analysis (cut-off date 14 September 2015), after a median follow-up of 8.5 months and at the updated (cut-off date 4 July 2016), after a median follow-up of 17.2 months. Since there was no statistically significant difference between the first pre-specified subgroup (PD-L1 on ≥5%) and the historical control, further formal statistical testing was stopped. ORR was similar when independently assessed (table 1) and when assessed by the investigator. Progression-free survival (PFS: defined as the time from the first dose to disease progression or death) was assessed independently. An event occurred in 62% (20/32) of patients with PD-L1 on ≥5%, 69% (55/80) of patients with PD-L1 on ≥1%and in 68% (81/119) of all patients at the time of the primary analysis and in 75% (24/32), 74% (59/80) and 74% (88/119) of patients respectively at the time of the updated analysis. At the time of the primary analysis, 44% (14/32) of patients with PD-L1 on ≥5%, 40% (32/80) of patients with PD-L1 on ≥1%and in 39% (46/119) of all patients had died. At the time of the updated analysis, 56% (18/32), 53% (42/80) and 50% (59/119) of patients respectively had died. The 12-month survival rate was estimated as 57%.[1-3]

Table 1: Primary and key secondary outcomes in cohort 1 of the IMvigor 210 study[1-3]

	Primary analysis (cut-off date 14 September 2015)			Updated analysis (cut-off date 4 July 2016)		
	PD-L1 ≥5% (n=32)	PD-L1 ≥1% (n=80)	All patients (n=119)	PD-L1 ≥5% (n=32)	PD-L1 ≥1% (n=80)	All patients (n=119)
Primary outcome						
ORR (95% CI)	22% (9.3% to 40%)*	19% (11% to 29%)	19% (13% to 28%)	28% (14% to 47%)	24% (15% to 35%)	23% (16% to 31%)
Secondary outcomes						
Median PFS (months)	2.9	2.3	2.4	4.1	2.9	2.7
Median overall survival (months)	10.6	10.6	10.6	12.3	14.1	15.9

*Since the ORR in the PD-L1 ≥5% subgroup was not significantly different from the 10% ORR in historical controls (p=0.07), further formal statistical testing was stopped. In the updated analysis, the lower bound of the 95% CI excludes the 10% historical control rate in each cohort.
PD-L1: programmed death ligand-1; ORR: objective response rate; CI: confidence interval; PFS: progression-free survival.

The secondary outcome of duration of response had not been reached in any group at the primary or updated analysis.[2, 3]

Results of an ongoing, randomised, phase III study (IMvigor 130) in patients with previously untreated locally advanced or metastatic urothelial cancer are expected in 2020. This study is comparing atezolizumab monotherapy or in combination with platinum-based chemotherapy (gemcitabine plus carboplatin or cisplatin) versus platinum-based chemotherapy alone.[2]

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review of atezolizumab concluded that the adverse events reported for patients being treated with atezolizumab appear to be mostly of low grade and manageable, and the overall safety profile of atezolizumab is similar to that of other immune checkpoint inhibitors targeting the PD-1/PD-L1 signalling pathway.[2]

Since the study was single-arm, there are no comparative safety data. At the time of the updated analysis (cut-off date 4 July 2016), 96% (114/119) of patients had reported an adverse event and these were considered treatment-related in 66% (79/119) of patients and serious in 38% (45/119) of patients. Adverse events led to study drug modification or interruption in 34% (41/119) of patients and to study drug withdrawal in 7.6% (9/119).[2, 3]

The most commonly reported adverse events irrespective of relation to study drug were fatigue (45%), decrease appetite (24%), diarrhoea (22%), nausea (22%), anaemia (19%), pruritus (18%), increased blood creatinine (17%), arthralgia (16%), peripheral oedema (16%), urinary tract infection (16%), vomiting (16%), constipation (15%), back pain (14%), pyrexia (14%), cough (13%) and rash (10%). The most commonly reported treatment-related events were fatigue (30%), diarrhoea (12%), pruritus (11%), decrease appetite (9.2%) and hypothyroidism (6.7%).[3]

A number of immune-related adverse events were reported. Those reported in more than one patient were rash (3.4%), increased alanine aminotransferase (1.7%), increased bilirubin (1.7%) and rhabdomyolysis (1.7%).[3]

One patient experienced an adverse event (sepsis) resulting in death which was considered by the investigator to be possibly related to study treatment.[3]

Immune-related adverse events are considered the key risk with the class of immune checkpoint inhibitors that target the PD-1/PD-L1 or cytotoxic T-lymphocyte antigen signalling pathway and include hepatitis, pneumonitis, colitis, pancreatitis, endocrinopathies, neuropathies, and meningoencephalitis.[2]

Summary of clinical effectiveness issues

Current guidelines recommend that first-line treatment of advanced or metastatic urothelial cancer is cisplatin-based chemotherapy.[5, 6] However approximately half of patients are thought to not be fit enough to receive cisplatin, due to poor performance status, inadequate renal function and co-morbidities.[5] In these patients, carboplatin-based chemotherapy (particularly carboplatin plus gemcitabine) is the main alternative or single agent chemotherapy with taxanes or gemcitabine. There may be patients who are also not considered fit enough for chemotherapy and these patients would most likely be managed with best supportive care. Atezolizumab is licensed for patients with advanced urothelial cancer after prior platinum-containing chemotherapy or ineligible for cisplatin. The submitting company has requested that SMC considers the use of atezolizumab in adult patients with locally

advanced or metastatic urothelial cancer who are considered cisplatin ineligible (first-line). Atezolizumab is the third immunotherapy for the treatment of urothelial cancer. Pembrolizumab is also licensed for patients who are ineligible for cisplatin and for patients who have received previous platinum-treatment.[7] Nivolumab is only licensed for second-line use after failure of prior platinum-containing therapy.[8] Atezolizumab meets SMC end of life and orphan equivalent criteria for this indication and was available for second-line use prior to licensing through the Early Access to Medicines Scheme.

In IMvigor 210, the proportion of patients with an ORR was 22% in the subgroup with PD-L1 ≥5% and the lower bound of the 95% CI was below 10%, the pre-specified threshold below which ORR was not considered an improvement over historical control ORR of 10% and so further statistical testing was stopped. The historical ORR of 10% was calculated as a weighted average in which 75% of patients received no treatment (expected ORR of 0%) and 25% of patients received carboplatin-based chemotherapy (expected ORR of 36%). This was not considered appropriate by the EMA (as the majority of patients were fit enough to receive carboplatin plus gemcitabine) and it was noted that a historical comparison with carboplatin plus gemcitabine may have been more relevant. The apparent benefits of atezolizumab over other interventions in terms of ORR may thus be over-estimated.

The study had a number of limitations including an absence of data versus relevant comparators (carboplatin-based chemotherapy or best supportive care). The primary outcome was ORR which although acceptable for a phase II study, is not sufficient to demonstrate clinical benefit. Duration of response, PFS and overall survival were secondary outcomes. Median duration of response had not been reached in any subgroups. In the updated analysis, the median overall survival was 15.9 months and the 12-month overall survival rate was 57%. Longer term survival data are awaited but may be confounded by subsequent treatments which at the time of the updated analysis had been received by 21% (25/119) of patients. There was no assessment of quality of life.

The EMA considered that the baseline and prognostic disease characteristics of patients in cohort 1 of IMvigor210 were generally comparable to patients who would be considered cisplatin ineligible in practice but would be eligible for a carboplatin-based combination chemotherapy. There is insufficient evidence (efficacy and safety) for the subgroup of patients that would be unfit for any chemotherapy. The EMA therefore suggests that atezolizumab should be used with caution in these patients, after careful consideration of the potential balance of risks and benefits on an individual basis.[2]

Pre-specified subgroup analyses found that 39% (13/33) of patients who had upper tract urothelial cancer (renal pelvis and ureters) achieved an ORR compared with 17% (14/85) of patients with primary tumours in the bladder or urethra. Patients with upper urothelial cancer have historically had poor outcomes.[3, 9] Subgroup analyses also found that the treatment effect was similar in subgroups with different levels of PD-L1 expression. However results of subgroup analyses should be interpreted with caution due to small numbers of patients.

The EMA commented on a naïve historical comparison of atezolizumab from cohort 1 of IMvigor 210 (n=119) with carboplatin plus gemcitabine using results from a randomised phase II / III study of carboplatin plus gemcitabine (n=119) versus methotrexate plus carboplatin plus vinblastine (M-CAVI) in patients with advanced urothelial cancer, unfit for cisplatin-based chemotherapy (EORTC Study 30986). ORR was achieved by 23% of atezolizumab and 36% of carboplatin plus gemcitabine patients. The duration of response could not be estimated in atezolizumab patients (after a median follow-up of 17.2 months) and 5.3 months in carboplatin plus gemcitabine patients. Median PFS was 2.7 months and 5.8 months and median overall survival 15.9 months and 9.3 months respectively.[2, 10]

To support the economic case made to SMC, the submitting company presented an indirect comparison of atezolizumab and carboplatin plus gemcitabine when used as a first-line treatment for advanced urothelial carcinoma in patients considered ineligible for cisplatin-based regimens. In the absence of a common comparator, unanchored simulated treatment comparisons (STC) were used to predict overall

survival with atezolizumab, for patients enrolled in two carboplatin plus gemcitabine studies (including EORTC 30986).[10, 11] A STC of PFS was attempted for patients enrolled in one of the carboplatin plus gemcitabine studies but due to validity issues and poor model performance, this was not used in the economic analysis. Overall survival with atezolizumab was predicted from both carboplatin plus gemcitabine studies, and they were meta-analysed with a fixed-effects model. Hazard ratios were estimated to decrease over time with credible intervals excluding one from approximately three months onwards, suggesting the comparative efficacy of atezolizumab improved over time. The validity of the indirect comparisons rely on the strength of the prediction model that the company used. Four prognostic variables were included in the model (age, gender, performance status and presence of visceral disease). There are limited data for atezolizumab from the IMvigor 210 study to determine modifiers of its treatment effect which should have been included in the prediction model. Differences in the maturity of survival data and in the criteria for ineligibility for cisplatin were identified and were not accounted for in the indirect comparison. Statistical experts consulted by SMC advised that the model for overall survival could not be considered to have good predictive performance based on the concordance-index reported by the company. One of the carboplatin plus gemcitabine studies may not be representative of Scottish practice; sensitivity analysis was conducted in which this was excluded from the indirect comparison.

The open-label, phase III IMvigor 211 study compared atezolizumab with investigator's choice of chemotherapy (vinflunine, docetaxel, or paclitaxel) as a second-line treatment in 931 patients with locally advanced or metastatic urothelial cancer who had progressed during or following a platinum-containing regimen. There was no significant difference between treatment groups in the primary outcome of overall survival but atezolizumab appeared to be better tolerated than chemotherapy. Since this study assessed second-line atezolizumab treatment, it is not relevant to the submission but quality of life results were used in the economic analysis.[1, 2]

In patients who are ineligible for cisplatin-based chemotherapy, alternative treatment options are limited to carboplatin-based chemotherapy. Atezolizumab is administered every three weeks and would offer an advantage in administration over carboplatin plus gemcitabine which is administered in three-weekly cycles with dosing on days one and eight.

Summary of patient and clinician engagement

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

The key points expressed by the group were:
- Metastatic urothelial cancer is a devastating diagnosis for patients, family and carers. Normal life is suspended and the burden of disease and treatment is physically and emotionally demanding resulting in a negative impact on quality of life.
- There is an unmet need for effective and well tolerated treatment options for patients with metastatic urothelial cancer who are cisplatin ineligible. A proportion of patients may be suitable for carboplatin plus gemcitabine but this is associated with toxicity; other patients are managed by best supportive care.
- Atezolizumab appears to be well tolerated and offers the potential for a durable response allowing patients to make memories with family and friends. Even for patients in whom the duration of response is relatively short, this short period is spent in good quality of life.
- Hospital visits required for the administration of atezolizumab are shorter and less frequent than for chemotherapy which has a positive impact in allowing patients more quality time with family and friends.

- Atezolizumab appears to be better tolerated than chemotherapy and clinicians noted that they are becoming familiar with the management of the immune-related side effects of immunotherapy.
- The availability of a treatment option for patients who are ineligible for cisplatin is very important in providing hope to patients.

Additional Patient and Carer Involvement

We received a patient group submission from Fight Bladder Cancer, which is a registered charity. Fight Bladder Cancer has received 5.3% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Fight Bladder Cancer participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing atezolizumab to gemcitabine + carboplatin in adult patients with locally advanced or metastatic urothelial carcinoma who are considered cisplatin ineligible. The submitting company requested that SMC consider atezolizumab for use in adult patients with locally advanced or metastatic urothelial cancer who are considered cisplatin ineligible (first-line). Feedback from SMC clinical experts suggested the chosen comparator was broadly appropriate. Best supportive care, and weekly paclitaxel and carboplatin monotherapy were also mentioned by some of the SMC clinical experts as used in first line advanced urothelial carcinoma patients ineligible for cisplatin.

A three-state partitioned survival model was used, with health states consisting of PFS, post-progression, and death. The time horizon was 20 years, and a weekly cycle length was adopted. PFS and overall survival estimation for atezolizumab was based on extrapolation of the observed Cohort 1 data (i.e. patients who had not received previous treatment in the metastatic setting and were considered ineligible for cisplatin treatment) from the single arm IMVigor 210 study. Based on best statistical fit, in the base case the generalised gamma and log-normal functions were fitted to the data for extrapolation of atezolizumab PFS and overall survival respectively. Due to a lack of head- to- head evidence, STC (as described in the comparative effectiveness section of the DAD) was performed to assess the PFS and overall survival treatment effect of atezolizumab versus gemcitabine plus carboplatin. However, the STC resulted in implausible results for the PFS assessment due to a reliance for the comparator on a small, single arm study of gemcitabine plus carboplatin in untreated urothelial carcinoma patients in which PFS crossed overall survival so that PFS was estimated to exceed overall survival.[11] Therefore a hazard ratio of one was assumed, based on evidence of no statistically significant difference in PFS from clinical studies of atezolizumab or pembrolizumab versus chemotherapy in previously treated urothelial carcinoma patients.[2, 12]

For relative overall survival estimation the STC was based on two comparator studies in previously untreated urothelial carcinoma patients, with a fractional polynomial model (Gompertz) applied for extrapolation.[10, 11] The fractional polynomial approach does not rely on an assumption of proportional hazards, but its application led to a continually increasing overall survival treatment effect for atezolizumab over the comparator, which was considered by the company to be implausible. Hence, the treatment effect was capped at the overall survival hazard ratio of 0.54 estimated at 8 months follow-up in the model, with this time point chosen as it corresponded to the follow-up in the Bamias et al study for gemcitabine plus carboplatin.[11] After this time point proportional hazards was assumed (i.e. no further change in the HR assumed).

Due to the absence of health-related quality of life data in the IMvigor 210 study, utility estimates were

based on EQ-5D data sourced from IMVigor211 study comparing atezolizumab with chemotherapy in previously treated advanced urothelial carcinoma patients.[2] Utilities were estimated for time on and off treatment with atezolizumab or gemcitabine plus carboplatin (proxied by chemotherapy arm in IMvigor 211), with values of 0.684 and 0.660 for atezolizumab and gemcitabine plus carboplatin on-treatment respectively, the difference reflecting differences in clinical benefit and adverse events impact, and an estimated utility of 0.547 in the off-treatment state. For atezolizumab, time on treatment was estimated by extrapolating time to treatment discontinuation data from IMvigor 210 (a Weibull function was applied in the base case). Treatment with atezolizumab is until loss of clinical benefit, hence treatment duration and therefore application of the on-treatment utility could be shorter or exceed PFS. For gemcitabine plus carboplatin treatment is until disease progression, hence an assumption was made that treatment duration, and so on-treatment utility, equates to time in the PFS state for the comparator.

Costs included in the economic analysis were medicine acquisition and administration costs, supportive care costs in PFS and progressive disease states, and adverse event management costs.

The base case result for atezolizumab was an incremental cost-effectiveness ratio (ICER) of £65,159 per quality adjusted life year (QALY) vs. gemcitabine plus carboplatin, based on an incremental cost of £54,373, incremental life years gained of 1.58 and incremental QALYs of 0.83. A key driver of the incremental cost of atezolizumab is the additional medicine acquisition costs, with additional supportive care costs in progressive disease also incurred. All the QALY gain for atezolizumab is associated with incremental QALYs obtained in the progressive disease state, with a QALY loss associated with the PFS state (see table 2 below).

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a discount is offered on the price of the medicine.

SMC is unable to present the with-PAS cost-effectiveness estimates that informed the SMC decision due to commercial in confidence issues. As such, only the without-PAS figures can be presented.

Table 2: Base case results

Atezolizumab vs gemcitabine plus carboplatin	Incremental cost	Incremental QALY in PFS state	Incremental QALY in Progressive disease state	Total QALY gain	ICER
List price	£54,373	-0.27	1.10	0.83	£65,159

Scenario analysis indicated that the results were sensitive to the choice of function for extrapolating atezolizumab time to treatment discontinuation, but there was also some sensitivity to the source of health state utilities, time horizon and discount rate (see the table 3 below).

Table 3: Key scenario Analysis results

Scenario analysis	ICER at list price
Use of BNF rather than eMIT for comparator medicine acquisition costs	£60,499
Time to treatment discontinuation with log-logistic function	£97,938
Time to treatment discontinuation with Generalised Gamma function	£67,287
Overall survival with log logistic function	£65,586
Overall survival with generalised Gamma function	£52,660
Diminishing atezolizumab treatment effect (HR) after 8 months	£68,675
Utilities of 0.731 for PFS and 0.641 for progressed disease from a NICE submission for 2nd line pembrolizumab in advanced UC	£55,644
Off- treatment utility of 0.5	£73,503
Time horizon of 15 years	£70,601
Time horizon of 10 years	£82,524
Discount rate of 1.5% for costs	£68,424
Discount rate of 1.5% for QALYs	£56,764

There are several weaknesses with the economic analysis:

- Only single arm clinical study evidence was available for atezolizumab in previously untreated patients, with relatively small patient numbers. The lack of comparative evidence versus gemcitabine plus carboplatin for the patient population of interest meant a range of assumptions and indirect treatment comparison methods had to be used. Several assumptions had to be made regarding treatment effect due to limitations in the clinical data used for PFS and overall survival estimation e.g. PFS hazard ratio of one assumed, and capping of survival benefit due to implausible OS extrapolation.

- There were weaknesses in the STC and fractional polynomial model used for the estimation of the overall survival hazard ratios, and the proportional hazards assumption used for long term treatment effect (i.e. application of a hazard ratio of 0.54 beyond 8 months) is uncertain and may lead to over-optimistic post-progression and overall survival estimates. The company was requested to provide a scenario analysis in which the treatment effect was assumed to decline over time (hazard ratio diminishing linearly to 1 over the time horizon), which resulted in an ICER of £68,675 QALY without PAS (Table 3).

- There is uncertainty regarding the plausibility of the extrapolated overall survival estimates for atezolizumab. The company provided estimates of the 5 year survival rates predicted by the model which was estimated at 21.6%, which seems over-optimistic given the IMVigor trial estimates of an ORR of 23% from the 17.2 month updated analysis follow-up (see Table 1). Hence, there is uncertainty over the survival estimates with atezolizumab and a concern associated with limited clinical data follow-up that these may be over-estimated in the model.

- The time horizon of 20 years in the base case is long given the observed median overall survival of just 15.9 months in the most recent data analysis. Long-term survival benefit (e.g. beyond 10 years) is highly uncertain – that it has been (to some extent) accepted in the economic assessment of other immune-oncology medicines does not serve to reduce the uncertainty. Reducing the time horizon increases the ICER (table 3).

- Utilities are defined by time on/off treatment for each treatment arm with higher on-treatment utilities estimated. A significant proportion of patients appear to discontinue treatment before progression, resulting in a QALY loss in the PFS state compared to the comparator. As all the QALY gain for atezolizumab is derived post- progression, there is high sensitivity to the off-treatment utility; a requested scenario analysis reducing this from the base case 0.547 to 0.5 increases the ICER to £73,503 without PAS.
- There is uncertainty in the relative treatment duration and cost. Different methods have been used for estimating treatment duration, atezolizumab duration based on extrapolated time to treatment discontinuation (TTD) data, whilst gemcitabine plus carboplatin is based on an assumption that duration is the same as PFS. Scenario analysis indicated sensitivity of the ICER to the choice of function for the extrapolation of TTD data (£67k to £98k/QALY without PAS – see table 3).
- No account has been taken of subsequent therapy cost, even though 24% of atezolizumab patients received subsequent therapies, and it is not known what proportion of gemcitabine plus carboplatin patients are assumed to have received subsequent therapies and what this would be. Due to the longer post progression survival estimated for atezolizumab it is possible that additional subsequent therapy costs could be incurred, which could impact on the ICER (dependent also on the impact on survival).

The Committee considered the benefits of atezolizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as atezolizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifier, the Committee was unable to accept atezolizumab for use in NHS Scotland.

Other data were also assessed but remain commercially confidential.*

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published national guideline 2; Bladder cancer: diagnosis and management, in February 2015. In patients with locally advanced or metastatic muscle-invasive bladder cancer, first-line chemotherapy is cisplatin-based. For patients with locally advanced or metastatic urothelial bladder cancer and an ECOG performance status of 0 to 2 who are unsuitable for cisplatin-based chemotherapy due to poor performance status, inadequate renal function or co-morbidities, carboplatin plus gemcitabine is recommended.[6]

The European Society for Medical Oncology (ESMO) published Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up, in 2014. This recommends cisplatin-based chemotherapy as standard first-line treatment for patients with advanced surgically unresectable and metastatic patients who are fit enough to tolerate cisplatin. The guideline suggests that approximately half of patients are unfit for cisplatin-based chemotherapy due to poor performance status, impaired renal function or co-morbidities. It is recommended that these patients may be palliated with carboplatin-based chemotherapy (carboplatin plus gemcitabine or methotrexate plus carboplatin plus vinblastine [M-CAVI]). These regimens are active for patients unfit for cisplatin but do not offer a statistically significant advantage in PFS or overall survival. Since toxicity is slightly higher with M-CAVI, carboplatin plus gemcitabine is the preferred treatment for unfit patients.[5]

The European Association of Urology (EAU) updated their guideline on Muscle-invasive and metastatic bladder cancer, in 2017. Cisplatin-based chemotherapy is recommended as standard of care for fit patients with metastatic bladder cancer. However more than half of patients are unfit for cisplatin. Carboplatin-based chemotherapy (carboplatin plus gemcitabine or M-CAVI) was inferior to cisplatin-based regimens but provided limited benefit in patients with performance status of 2 and impaired renal function who were unfit for cisplatin.[13]

The EAU also updated their guideline on upper urinary tract urothelial cancer in 2017. This states that there are currently insufficient data on which to base recommendations but notes that platinum-based combination chemotherapy is expected to be efficacious based on extrapolation from literature on bladder cancer and small, single-centre studies in upper urinary urothelial cancer.[14]

Additional information: comparators

Carboplatin-based chemotherapy (e.g. carboplatin plus gemcitabine) or best supportive care.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Atezolizumab	**1,200mg IV every three weeks**	**3,808**
Carboplatin plus gemcitabine	carboplatin AUC 4.5* IV on day 1 gemcitabine 1,000mg/m^2 IV on days 1 and 8	192

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMIMS and dm&d on 6 November 2017. Costs calculated using 1.8m^2 body surface area and using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. *assumes creatinine clearance 60mL/min resulting in dose of 400mg. IV=intravenous; AUC=area under curve.*

Additional information: budget impact

The submitting company estimated there would be 57 patients eligible for treatment with atezolizumab in all years to which confidential estimates of treatment uptake were applied.

Without PAS
The gross impact on the medicines budget was estimated to be £467k in all years. As other drugs are expected to be displaced the net medicines budget impact is expected to be £397k in all years.

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

References

1. Roche Products Ltd. Tecentriq 1200mg concentrate for solution for infusion, summary of product characteristics. Last updated 27 September 2017.

2. European Medicines Agency. Assessment Report for atezolizumab (Tecentriq), EMA/505694/2017, 20 July 2017.

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This assessment is based on data submitted by the applicant company up to and including 13 December 2017.

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_statements/Policy_Statements

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 drug 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 NHS Scotland 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 NHS Scotland 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.