Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2267

atezolizumab 840mg concentrate for solution for infusion (Tecentriq®)

Roche Products Ltd

9 October 2020

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 medicine process

atezolizumab (Tecentriq®) is accepted for use within NHSScotland.

Indication under review: Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have programmed death-ligand 1 [PD-L1] expression ≥1% and who have not received prior chemotherapy for metastatic disease.

In a randomised, double-blind, phase III study, the addition of atezolizumab to nab-paclitaxel significantly improved progression-free survival and numerically improved overall survival in patients with locally advanced or metastatic triple-negative breast cancer with PD-L1 expression ≥1% who had not received prior chemotherapy for metastatic disease.

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

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

Vice Chairman
Scottish Medicines Consortium

Indication

Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.[1]

Dosing Information

The recommended dose of atezolizumab is 840mg administered by intravenous infusion, followed by 100mg/m^2 nab-paclitaxel. For each 28-day cycle, atezolizumab is administered on days 1 and 15, and nab-paclitaxel is administered on days 1, 8 and 15. For TNBC, it is recommended that patients are treated with atezolizumab until disease progression or unmanageable toxicity.

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer. Patients with previously untreated TNBC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test.

Refer to the Summary of Product Characteristics (SPC) for further details on dose modifications, delays and discontinuation.[1]

Product availability date

26 August 2019

Atezolizumab received a positive scientific opinion under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency on 13 March 2019. The indication was in combination with nab-paclitaxel, as first-line treatment of adults with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥1%. EAMS status was withdrawn on 26 August 2019 when a licence from the European Medicines Agency (EMA) was granted. The EAMS closed for enrolment on 27th September 2019.

Atezolizumab meets SMC end of life and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

In triple-negative breast cancer, tumour cells test negative for oestrogen and progesterone receptors and do not overexpress human epidermal growth factor receptor 2 (HER2). These account for 12 to 20% of all breast cancers and are associated with more aggressive disease and poorer outcomes. Atezolizumab is a humanised monoclonal antibody that binds to programmed death–ligand 1 (PD-L1) and blocks its interactions with the programmed death-1 (PD-1) and B7.1 receptors on tumour cells and/or tumour-infiltrating immune cells. This prevents PD-L1/PD-1 mediated inhibition of the immune response , including reactivating the anti-tumour immune response without inducing antibody-dependent cellular cytotoxicity PD-L1 inhibitors.[1, 2]

The evidence for this indication comes from IMpassion130, an ongoing international, multicentre, randomised, double-blind, parallel group, phase III study, which is evaluating the efficacy and safety of atezolizumab plus nab-paclitaxel compared with placebo plus nab-paclitaxel in 902 patients with advanced triple-negative breast cancer, previously untreated for metastatic disease. Study patients were aged ≥18 years with metastatic or unresectable locally advanced, histologically documented triple-negative breast cancer who had received no previous chemotherapy or targeted therapy for metastatic disease and were eligible for taxane monotherapy. They had tissue evaluable for tumour PD-L1 expression, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Co-operative Oncology Group (ECOG) performance status score of 0 or 1 and adequate haematological and organ function. Eligible patients were randomised equally to receive atezolizumab (840mg by intravenous infusion) or placebo on days 1 and 15 of each 28-day cycle. Patients in both treatment groups also received nab-paclitaxel (100mg/m^2 intravenously on days 1, 8 and 15 of each 28-day cycle). Study treatment was continued until disease progression or unacceptable toxicity. Nab-paclitaxel was to be administered for ≥6 cycles (no maximum). Dose reductions of atezolizumab were not permitted but the nab-paclitaxel dose could be reduced/interrupted for toxicity and atezolizumab could be continued after nab-paclitaxel was stopped. Randomisation was stratified according to presence of liver metastases (yes or no), use of (neo) adjuvant taxane treatment (yes or no), tumour PD-L1 expression (<1% or ≥1%).[2, 3]

IMpassion130 has two co-primary outcomes: progression-free survival (PFS), determined by the investigator and defined as the time from randomisation to the date of first progression, using RECIST v1.1, or death due to any cause; and, overall survival, defined as the time from randomisation to death due to any cause. A hierarchical statistical testing strategy was used to control for type I error for the co-primary outcomes and the secondary outcome (objective response rate [ORR]) in the intention-to-treat (ITT) population and the PD-L1 positive subgroup with no formal testing of outcomes after the first non-significant outcome in the hierarchy.[2, 3]

The addition of atezolizumab to nab-paclitaxel significantly improved investigator-assessed PFS in both the ITT population and the PD-L1 positive subgroup of IMpassion130. At the time of the first and second interim analyses of overall survival, the difference between groups did not reach statistical significance in the ITT population and in-line with the statistical testing strategy, no formal testing of overall survival in the PD-L1 positive subgroup was performed. Therefore the results reported for these outcomes are descriptive only and non-inferential (no p-values reported). Details of results are presented in Table 1 below.

Table 1: Results for the co-primary outcomes of the IMpassion 130 study[2-4]

	ITT population		PD-L1 positive subgroup	
	Atezolizumab plus nab-paclitaxel (n=451)	**Placebo plus nab-paclitaxel (n=451)**	**Atezolizumab plus nab-paclitaxel (n=185)**	**Placebo plus nab-paclitaxel (n=184)**
Progression-free survival (cut-off date April 2018)				
Median follow-up (months)	13.0	12.5		
Number of PFS events	358	378	138	157
Median PFS (months)	7.2	5.5	7.5	5.0
HR (95% CI)	0.80 (0.69 to 0.92), p=0.0025		0.62 (0.49 to 0.78), p<0.001	
Estimated 1-year PFS	24%	18%	29%	16%
Overall survival (first interim analysis; cut-off date April 2018)				
Median follow-up (months)	13.0	12.5		
Number of deaths	181	208	64	88
Median overall survival (months)	21.3	17.6	25.0	15.5
HR (95% CI)	0.84 (0.69 to 1.02), p=0.08		0.62 (0.45 to 0.86)[A]	
Estimated 2-year survival	42%	40%	54%	37%
Overall survival (second interim analysis; cut-off date January 2019)				
Median follow-up (months)	18.5	17.5		
Number of deaths	255	279	94	110
Median overall survival (months)	21.0	18.7	25.0	18.0
HR (95% CI)	0.86 (0.72 to 1.02), p=0.078		0.71 (0.54 to 0.93) [A]	
Estimated 2-year survival	42%	39%	51%	37%

[A] p-value not formally tested

ITT = intention to treat, PD-L1 = programmed death–ligand 1, PFS = progression-free survival, HR = hazard ration, CI = confidence interval.

Key secondary outcomes of IMpassion130 included objective response rate (defined as the proportion of patients with a partial or complete response assessed by the investigator using RECIST v1.1) and duration of response (defined as the time from documented objective tumour response to the time of radiographic progression, assessed by the investigator using RECIST v1.1 or death). At the time of the primary PFS analysis (cut-off date April 2018), an objective response was achieved by 56% (252/450) of atezolizumab plus nab-paclitaxel patients and 46% (206/449) of placebo plus nab-paclitaxel patients in the ITT population (difference 10% [95% CI: 3.4 to 17]) and by 59% (109/185) and 43% (78/183) respectively in the PD-L1 positive subgroup (difference 16% [95% CI: 5.7 to 27]). However, these results did not reach the pre-specified threshold for statistical significance of $p<0.001$. In the ITT population, the median duration of response was 7.4 months in the atezolizumab plus nab-paclitaxel patients (n=252) and 5.6 months in the placebo plus nab-paclitaxel patients (n=206); hazard ratio 0.78 (95% CI: 0.63 to 0.98). In the PD-L1 positive subgroup, this was 8.5 months (n=109) and 5.5 months (n=78); hazard ratio 0.60 (95% CI: 0.43 to 0.86). There was no formal statistical testing in either population.[2, 3]

The time to deterioration (defined as a sustained ≥10-point decline from baseline) of health-related quality of life measured by items 29 and 30 of the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) was also assessed as a secondary outcome. At the August 2018 data cut-off, this was similar in the two treatment groups in both the ITT population (hazard ratio 0.97) and PD-L1 positive subgroup (hazard ratio 0.94).[1, 2]

The EORTC QLQ-C30 and its breast cancer module (QLQ-BR23) and the EuroQoL 5-Dimension (EQ-5D-5L) were assessed as exploratory outcomes and there were similar changes from baseline in both treatment groups.[2]

The company presented results of an unanchored, population-adjusted indirect comparison (PAIC) of atezolizumab plus nab-paclitaxel with weekly standard paclitaxel. This matched a number of prognostic factors and effect modifiers associated with triple-negative breast cancer from individual patient level data (IPD) from the PD-L1 positive subgroup of IMpassion130 for atezolizumab plus nab-paclitaxel with IPD from the triple-negative breast cancer subgroups of the MERIDIAN and E2100 studies (which compared weekly standard paclitaxel with weekly standard paclitaxel plus bevacizumab).[3-6] Propensity scores for each patient randomised to atezolizumab plus nab-paclitaxel were transformed into odds ratios, which were subsequently used to re-estimate hazard ratios for atezolizumab plus nab-paclitaxel versus the weekly standard paclitaxel for PFS and overall survival. The PAIC results suggested that atezolizumab plus nab-paclitaxel was superior to weekly standard paclitaxel for PFS and for overall survival.

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

Summary of evidence on comparative safety

The safety profile of atezolizumab when used in combination with nab-paclitaxel for the treatment of triple-negative breast cancer was as expected, consisting of a combination of chemotherapy and immune-related adverse events. No new safety signals were identified and the reported toxicities were generally manageable.[2]

In the ITT population of IMpassion130, at data cut-off April 2018, the median duration of treatment in the atezolizumab plus nab-paclitaxel group was 24.1 weeks (atezolizumab) and 22.1 weeks (nab-paclitaxel) and in the placebo plus nab-paclitaxel group was 21.8 weeks (nab-paclitaxel). Any treatment-emergent adverse event was reported by 99% (449/452) of patients in the atezolizumab plus nab-paclitaxel group and 98% (429/438) in the placebo plus nab-paclitaxel group and these were considered treatment-related in 96% and 94% respectively. In the atezolizumab plus nab-paclitaxel and placebo plus nab-paclitaxel groups respectively, 50% versus 43% of patients reported a grade 3 or higher adverse event; 23% versus 18% reported a serious adverse event; 47% versus 40% required a dose reduction or interruptions and 16% versus 8.2% discontinued therapy due to an adverse event.[2, 3]

The most frequently reported treatment-emergent adverse events of any grade were similar in the atezolizumab plus nab-paclitaxel group versus placebo plus nab-paclitaxel group including: alopecia (56% versus 58%), fatigue (47% versus 45%), nausea (46% versus 38%), diarrhoea (32% versus 34%), anaemia (28% versus 26%), constipation (25% versus 25%), cough (25% versus 19%), headache (23% versus 22%), neuropathy peripheral (22% versus 22%), neutropenia (21% versus 15%), decreased appetite (20% versus 18%),vomiting (19% versus 17%), pyrexia (19% versus 11%) and hypothyroidism (14% versus 3.4%).[3]

Adverse events of special interest, suggestive of a potential immune-related cause, were reported in 57% of atezolizumab plus nab-paclitaxel patients and 42% of placebo plus nab-paclitaxel patients and included: rash (34% versus 26%), hypothyroidism (17% versus 4.3%), any hepatitis (15% versus 14%), hyperthyroidism (4.4% versus 1.4%) and pneumonitis (3.1% versus 0.2%).[3]

Summary of clinical effectiveness issues

Current guidelines recommend conventional chemotherapy for the first-line treatment of triple-negative breast cancer, generally as monotherapy with anthracyclines or taxanes, depending on previous therapy and time since this finished. There are currently no data to suggest that one medicine is better than another, treatment choice includes the following potential comparators: docetaxel/paclitaxel, capecitabine and carboplatin +/- gemcitabine. PD-L1 expression has been reported to range from 40 to 65% of tested breast cancer cases and offers the potential of a targeted treatment option.[7] Atezolizumab, for use in combination with nab-paclitaxel, is the first

immunotherapy to be licensed for patients with triple-negative breast cancer and is specifically for use in those with PD-L1 expression ≥1%.[1, 2] Clinical experts consulted by SMC considered that there is an unmet need for more effective treatment for triple-negative breast cancer which has a poor prognosis.

Evidence to support the licensed indication for atezolizumab comes from subgroup analysis of IMpassion130, for which the study was powered. One of the primary outcomes, PFS, met statistical significance in both the ITT population and PD-L1 positive subgroup. The PFS benefit of 2.5 months in the relevant subgroup was considered clinically relevant by the EMA. The results for overall survival were not statistically significant in the ITT population and so could not be formally tested in the PD-L1 positive subgroup. However, at the latest available survival analysis in this subgroup, the survival benefit was 7 months with atezolizumab plus nab-paclitaxel compared with nab-paclitaxel alone (median 25.0 months versus 18.0 months). This was considered clinically relevant by the EMA and was greater than in the ITT population and in the PD-L1 negative subgroup, where there was no evidence of effect. Final overall survival results are awaited, although 59% of events had occurred at the time of latest analysis, representing 80% of the information fraction; thus, the results were fairly mature. The primary outcomes were supported by results of secondary outcomes. In the PD-L1 positive subgroup, the differences in objective response rate (16%) and duration of response with atezolizumab plus nab-paclitaxel versus nab-paclitaxel (median of approximately 3 months) were also considered to be clinically relevant, particularly since these patients have multiple metastatic sites, often including visceral metastases. Time to deterioration from baseline in health-related quality of life was similar in both treatment groups which suggested that the addition of atezolizumab to nab-paclitaxel did not adversely affect quality of life.[2-4]

In IMpassion130, atezolizumab plus nab-paclitaxel was compared with nab-paclitaxel alone. However, nanoparticles albumin bound (nab)-paclitaxel is not commonly used for breast cancer in clinical practice and this formulation was not considered a relevant comparator. It was selected for use in combination with atezolizumab to avoid the need for steroid premedication as there was concern that this could potentially inhibit the immunotherapy effect of atezolizumab.[2, 8]

There are a number of factors about the IMpassion130 study population that may affect the generalisability of the results to clinical practice. IMpassion130 excluded patients with CNS metastases, other than those with treated asymptomatic brain metastases, and in this small number of patients in the PD-L1 positive subgroup, there was no evidence of efficacy of atezolizumab plus nab-paclitaxel (n=15, median PFS of 2.2 months) compared with nab-paclitaxel (n=11, median PFS of 5.6 months); hazard ratio 1.40 (95% CI: 0.57 to 3.44). This may affect the generalisability of the study results to patients with CNS metastases in clinical practice, particularly since patients with triple-negative breast cancer have a higher risk of brain metastases compared to other breast cancer. The majority of study patients (900/902) had good performance status (ECOG ≤2) at baseline and it is unclear if the study results would be generalisable to those in clinical practice who are less fit.

Exploratory subgroup analysis in the PD-L1 positive subgroup has suggested that the treatment effect of atezolizumab plus nab-paclitaxel may be less in patients who have previously received (neo) adjuvant treatment. In those who had received a prior (neo) adjuvant treatment (n=242), the hazard ratios were 0.79 for PFS and 0.82 for overall survival compared with those who had not received a prior (neo) adjuvant treatment (n=127), the hazard ratios were 0.44 for PFS and 0.53 for overall survival. However further analysis, adjusted for strong prognostic factors, has confirmed a PFS benefit and lack of detrimental effect on survival and patients who have received previously (neo) adjuvant therapy have not been excluded from the marketing authorisation.

There is no direct comparative evidence with chemotherapy likely to be used in clinical practice and the company used the matched data from the indirect comparison in the economic case. The indirect comparison results suggested that atezolizumab plus nab-paclitaxel significantly improved PFS and overall survival compared with weekly standard paclitaxel. However a number of limitations affect the validity of these results including the unanchored nature of the comparison which makes it difficult to validate the matching process and the reduced effective sample size. Since PD-L1 status was unavailable at the time of the paclitaxel studies and was not known for patients treated with weekly paclitaxel, the populations could not be matched and the indirect comparison population was wider than the licensed indication. There was variation in the duration of follow-up and hence maturities of data for the studies. In addition, the E2100 study was started almost 20 years ago and the results may be less generalisable to current management. The indirect comparison was performed in a subgroup of each study and matching further reduced the effective sample size of atezolizumab plus nab-paclitaxel patients. Given the uncertainty in these results, comparison with weekly paclitaxel was also performed in the economic case based on the conservative assumption that nab-paclitaxel was similar to weekly paclitaxel and using the nab-paclitaxel results from IMpassion130 as a proxy for weekly paclitaxel. Results of a comparative study, meta-analysis and of a retrospective observational study were presented to support the assumption of similar efficacy of nab-paclitaxel and weekly paclitaxel.[8-10]

The introduction of atezolizumab plus nab-paclitaxel would offer patients with previously untreated metastatic triple-negative breast cancer an immunotherapy option which has been associated with improved PFS and overall survival. Clinical experts consulted by SMC considered that atezolizumab plus nab-paclitaxel was a therapeutic advancement offering improved PFS and overall survival and that its place in therapy was in-line with the licensed indication. Although PD-L1 expression is tested in other cancer, this would be a new service implication for patients with triple-negative breast cancer.

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 atezolizumab, as an end of life and orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- TNBC is a devastating condition that disproportionately affects younger, premenopausal woman and is associated with the highest risk of recurrence and death of all the subtypes of breast cancer. Symptoms of metastatic cancer severely impact on quality of life. As one of the most aggressive forms of breast cancer, TNBC also has a significant psychological toll for both patients and family members.

- There is a high unmet need in locally advanced or metastatic TNBC and new treatment options are desperately needed. There are no targeted therapies available in TNBC as there are in other breast cancer subtypes.
- A diagnosis of metastatic TNBC has a substantial negative emotional, physical and financial impact on family members. As younger woman are disproportionately affected by TNBC, there is a potential of patients having young children and caring responsibilities, which may have to be passed on to family members. These women may also still be in employment, with families being dependent on their income. Atezolizumab is expected to alleviate some of the burden placed on families.
- Atezolizumab in combination with nab-paclixtaxel offers hope to patients with TNBC. The PFS benefit observed in the study is important as it enables patients to spend quality time with their friends and families, as well as increasing the likelihood of people being able to continue with their daily activities, which can improve the emotional wellbeing of both patients and their families. Prolonging disease recurrence will also lengthen the time until patients have to receive further lines of chemotherapy.
- The toxicity profile of atezolizumab plus nab-paclitaxel can be considered both tolerable and manageable. Patients are willing to accept a moderate increase in risk of side effects in order to avoid rapid disease progression, which is associated with substantial morbidity and mortality. Oncology departments have experience of using atezolizumab from other settings and in this setting via the Early Access to Medicines Scheme.

Additional Patient and Carer Involvement

We received a patient group submission from Breast Cancer Now, which is a registered charity. Breast Cancer Now has received 5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Breast Cancer Now participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of atezolizumab in combination with nab-paclitaxel versus standard weekly paclitaxel, for the treatment of adult patients with metastatic or unresectable locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease. SMC clinical experts indicated that weekly paclitaxel is a relevant comparator.

The economic analysis used a partitioned survival model with three health states (pre-progression, post-progression and death). The model used a weekly cycle with half-cycle correction applied, and adopted a lifetime horizon of 15 years.

The clinical data for atezolizumab in combination with nab-paclitaxel was taken from a planned subgroup of patients (PD-L1 expression ≥1%) from the phase 3 study IMpassion130, as described above. IMpassion130 informed PFS, overall survival, treatment duration, utilities and adverse events in the economic model.

The company presented two base case analyses. One base case used the matched data from the indirect comparison, described in the efficacy and clinical effectiveness sections above, to enable a comparison with weekly paclitaxel, using the E2100 study for weekly paclitaxel in the base case and MERIDIAN study data in scenario analysis. An alternative base case presented assumed the nab-paclitaxel arm outcomes in the IMpassion130 study as a proxy for weekly paclitaxel outcomes.

The estimation of long-term PFS and overall survival in both treatment arms used the fitting of parametric curves to the population-adjusted Kaplan-Meier data from the IMpassion130 and to the E2100 study. For the alternative base case analysis parametric functions were fitted to both arms of the IMpassion130 study assuming that nab paclitaxel outcomes are representative of paclitaxel outcomes (equivalence analysis). For PFS, parametric functions were fitted to the Kaplan-Meier data where 15% of patients remained at risk, in both base case analyses.

Time on treatment (ToT) in the population-adjusted base case analysis estimated by applying hazard ratios observed between PFS and ToT in IMpassion130 to the population-adjusted data. For the equivalence analysis base case, ToT was estimated separately for atezolizumab, nab-paclitaxel as combination therapy, and nab-paclitaxel and monotherapy, based on IMpassion130. Parametric functions were selected based on statistical fit, visual inspection and clinical plausibility estimated by UK clinical experts.

Utility values were derived using EQ-5D-5L data collected in PD-L1 positive patients in the IMpassion130 study, mapped to the EQ-5D-3L using the Van Hout algorithm which was conducted using a mixed-model linear regression.[11] Disutilities associated with adverse events of grade 3 or above were assumed to be captured in the utility data from IMpassion130 so were not separately applied in the base case.

Costs included medicine acquisition, medicine administration, pre-treatment costs, health state management, subsequent therapies including administration, PD-L1 testing, treatment of adverse events, and terminal care.

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 NHS Scotland. Under the PAS, a discount was offered on the list price of atezolizumab.

The results presented do not take account of the PAS for nab-paclitaxel but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for nab-paclitaxel when used in combination with atezolizumab due to commercial confidentiality and competition law issues.

In the base case for atezolizumab in combination with nab-paclitaxel versus weekly paclitaxel, based on population-adjusted indirect comparison data the incremental cost-effectiveness ratio (ICER) is estimated at £28,187/QALY (at PAS price for atezolizumab, list price for nab-paclitaxel). The base case which assumes nab-paclitaxel in IMpassion130 as a proxy for comparator paclitaxel estimated an ICER of £34,132/QALY (at PAS price for atezolizumab, list price for nab-paclitaxel). These results were based on higher incremental life years and QALYs as well as higher incremental costs for the population adjusted indirect comparison base case compared to the equivalence analysis (Table 2). While it is acknowledged that the analysis using the equivalence assumption may be conservative, it was the preferred base case given the limitations of the indirect comparison.

Table 2: Base case results atezolizumab in combination with nab-paclitaxel versus weekly paclitaxel (PAS price for atezolizumab, list price for nab-paclitaxel)

Analysis	Incremental life years	ICER (cost/ QALY)*
Using population adjusted indirect comparison data	1.070	£28,187
Using nab paclitaxel data as a proxy for weekly paclitaxel	0.636	£34,132
ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year		

In one-way sensitivity analysis the ICER for atezolizumab in combination with nab-paclitaxel versus weekly paclitaxel was most sensitive to variation in discount rates for outcomes and costs, administration costs at first attendance, and utility values for progressive disease and progression-free survival. A range of scenario analyses were performed, with the potentially most plausible scenarios presented in Table 3 below. The scenario analyses which had the greatest upward impact on the ICER for atezolizumab in combination with nab-paclitaxel in both base case analyses were alternative overall survival extrapolation and a scenario which assumed no vial sharing.

Table 3: Scenario analysis results atezolizumab in combination with nab-paclitaxel versus weekly paclitaxel (PAS price for atezolizumab, list price for nab-paclitaxel)

	Scenario Analysis	ICER using population-adjusted data	ICER assuming equivalence
1	Overall survival atezolizumab + nab-paclitaxel – log-logistic	£18,591	£18,829
2	Overall survival atezolizumab + nab-paclitaxel – gompertz	£31,961	£42,617
3	Overall survival placebo + nab-paclitaxel – Weibull	£28,370	£37,449
4	Overall survival weekly paclitaxel – Generalised Gamma	£54,761	N/A
5	Overall survival weekly paclitaxel – Weibull	£28,148	N/A

6	Utility for progression free survival differs by treatment arm	£27,116	£32,082
7	Vial sharing is not permitted	£31,233	£38,436
8	Dose of weekly paclitaxel set to 90 mg/m^2	£27,035	£32,138
ICER, incremental cost-effectiveness ratio; mg/m2, milligram/square metre; N/A, not applicable; PAS, patient access scheme			

The economic analysis was associated with a number of weaknesses and uncertainties:

- There is a lack of head-to-head clinical evidence versus a relevant comparator (weekly paclitaxel) for Scottish clinical practice in the main clinical evidence study IMpassion130. Hence, assumptions of equivalence (between nab-paclitaxel and weekly paclitaxel) or population-adjusted indirect comparisons were required to estimate the relative effectiveness of atezolizumab + nab-paclitaxel versus weekly paclitaxel. There are limitations associated with the indirect comparison conducted, such as reduced patient numbers in the population-adjusted data and the generalisability of the data to a Scottish patients with metastatic or unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.
- As noted above, due to limitations with the indirect comparison, the base case assuming equivalence between nab-paclitaxel and weekly paclitaxel from IMpassion130 may be a more appropriate estimate of clinical and cost-effectiveness, with less uncertainty than the population-adjusted analysis. This base case does not assume any benefit of nab-paclitaxel over weekly paclitaxel so is more conservative than the population-adjusted indirect comparison analysis. Clinical data comparing paclitaxel to nab-paclitaxel showed no significant difference in efficacy (see clinical effectiveness section).
- There is uncertainty in the relative overall survival estimates and long-term extrapolation, despite overall survival being relatively mature. The company provided a range of scenario analyses to explore this uncertainty. Alternative parametric functions using the Gompertz for atezolizumab arm or Weibull for the comparator arm may be reasonable alternative estimates for OS and both had an upward impact on the ICER (Table 3).

The Committee also 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 the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied In addition, 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 modifiers, the Committee accepted atezolizumab for use in NHSScotland.

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

Additional information: guidelines and protocols

The National Comprehensive Cancer Network (NCCN) published Clinical practice guidelines in oncology (NCCN guidelines): Breast cancer (version 3) in 2019.[12] This guidance recommends platinum based chemotherapy as the best treatment for triple negative breast cancer. The guidance specifically recommends that the PD-L1 status of patients with triple negative breast cancer should be assessed so that patients likely to benefit from atezolizumab plus nab-paclitaxel can be identified.[12]

The European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO) published the 4th International consensus guidelines for advanced breast cancer (ABC 4) in 2018.[13] This guidance states that chemotherapy "remains the only available non-investigational systemic treatment option for non-BRCA-mutated advanced TNBC [triple negative breast cancer], with no specific recommendations regarding types of agents, with the possible exception of platinum compounds."[13] This guideline predates the availability of atezolizumab for breast cancer.

The National Institute for Health and Care Excellence (NICE) published clinical guideline 81 "Advanced breast cancer: diagnosis and treatment" initially in February 2009 and updated in August 2017.[14] For chemotherapy options on disease progression, the guidance recommends systemic sequential therapy with combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine:
- third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line)

Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. This guideline predates the availability of atezolizumab for breast cancer.

The Scottish Intercollegiate Guidelines Network (SIGN) published Treatment of primary breast cancer (SIGN 134) in September 2013.[15] The guideline recommends that efficacy of chemotherapy regimens for patients with triple negative breast cancer is an area where further research is required.[15] This guideline predates the availability of atezolizumab for breast cancer.

Additional information: comparators

Monotherapy with chemotherapy including taxanes, capecitabine, vinorelbine and carboplatin +/- gemcitabine.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle (£)
atezolizumab **plus** **nab-paclitaxel**	**840mg by intravenous infusion on days 1 and 15** **plus** **100mg/m^2 by intravenous infusion on days 1, 8 and 15 of each 28-day cycle**	**6,807**

Costs from BNF online on 9 March 2020. The cost for nab-paclitaxel is based on an adult with a body surface area of 1.8m^2. 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 31 patients treated with atezolizumab plus nab-paclitaxel in year 1 and 62 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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

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This assessment is based on data submitted by the applicant company up to and including 17 July 2020.

**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.