Cost-effectiveness of atezolizumab (Tecentriq®) in combination with nab-paclitaxel for the treatment of adult patients with 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

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of atezolizumab (Tecentriq®). Following assessment of the Applicant's submission, the NCPE recommends that atezolizumab (Tecentriq®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Roche Products (Ireland) Ltd.) economic dossier on the cost effectiveness of atezolizumab (Tecentriq®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **September 2020**

Summary

In December 2019, Roche Products (Ireland) Ltd. submitted a dossier examining the clinical effectiveness, safety and economic evidence for atezolizumab in combination with nab-paclitaxel 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. Reimbursement is being sought under the Oncology Drugs Management Scheme. Atezolizumab is a checkpoint inhibitor which binds to PD-L1, preventing inhibition of the immune response in certain tumour cells. Atezolizumab is administered via intravenous infusion at a dose of 840 mg on days 1 and 15 of every 28-day cycle; nab-paclitaxel is administered at a dose of 100 mg/m^2 on days 1, 8 and 15 of every 28-day cycle. Treatment continues until disease progression or unmanageable toxicity.

TNBC is an aggressive type of breast cancer, which is often diagnosed at a more advanced stage than other forms of the disease and is associated with a poorer prognosis. There are no targeted drug therapies available for TNBC. Currently, metastatic TNBC is treated with systemic chemotherapy, with patients typically receiving multiple lines of therapy. In Ireland, the two most commonly used first-line regimens include paclitaxel monotherapy and capecitabine monotherapy. Both of these drugs are considered as comparators in the cost-effectiveness analysis.

1. Comparative effectiveness of atezolizumab

Direct comparative clinical evidence for atezolizumab in combination with nab-paclitaxel in patients with metastatic TNBC who have not received prior chemotherapy for metastatic disease is available from the IMpassion130 trial. This is a phase III, double-blinded, placebo-controlled trial which randomised participants on a 1:1 basis to receive either atezolizumab in combination with nab-paclitaxel or placebo in combination with nab-paclitaxel. The co-primary efficacy endpoints were investigator-assessed progression-free survival (PFS) and overall survival (OS). Secondary efficacy endpoints included investigator-assessed objective response rate (ORR), investigator-assessed duration of response (DOR) and time to deterioration (TTD) in health-related quality of life (HRQoL). The trial recruited an 'all-comer' population which included participants who had tumours that were either PD-L1 positive or

PD-L1 negative. As the licensed indication relates only to patients whose tumours are PD-L1 positive, only the efficacy results for the PD-L1 positive sub-population were considered.

A total of 369 participants that had tumours which were PD-L1 positive were recruited. Of these, 185 were randomised to atezolizumab in combination with nab-paclitaxel and 184 to placebo in combination with nab-paclitaxel. The mean (SD) age of the participants was 53.6 (12.5) years. At the time of the first data cut-off (final PFS analysis and first interim OS analysis), median PFS in the atezolizumab in combination with nab-paclitaxel group was 7.5 months versus 5.0 months in the placebo in combination with nab-paclitaxel group (hazard ratio [HR] 0.62; 95% CI: 0.49, 0.78; p<0.0001). Due to the nature of the statistical analysis plan, statistical significance of OS, DOR and TTD in HRQoL in the relevant PD-L1 positive population could not be formally tested, and therefore analysis of these endpoints should be regarded as providing supportive evidence of efficacy only. Median OS was 25.0 months in the atezolizumab in combination with nab-paclitaxel arm, compared to 15.5 months in the placebo in combination with arm (HR 0.62; 95% CI: 0.45, 0.86; not tested). At the second data cut-off (second interim OS analysis), the median OS in the atezolizumab in combination with group was 25.0 months versus 18.0 months in the placebo in combination with arm (HR 0.71; 95% CI 0.54, 0.93; not tested). Results for the secondary efficacy endpoints reported at the first data cut-off were as follows: 58.9% of patients in the atezolizumab in combination with nab-paclitaxel arm had an ORR versus 42.6% in the placebo in combination with nab-paclitaxel arm (difference 16.3%; 95% CI: 5.7%, 26.9%; p=0.0016); median DOR in those receiving atezolizumab and nab-paclitaxel was 8.5 months versus 5.5 months in those receiving placebo in combination with nab-paclitaxel (HR 0.60; 95% CI 0.43, 0.86; not tested); median TTD in HR-QoL was 8.2 months in those receiving atezolizumab in combination with nab-paclitaxel versus 6.4 months in those receiving placebo and nab-paclitaxel (HR 0.94; 95% CI 0.69, 1.28; not tested).

In the absence of direct comparative evidence against paclitaxel monotherapy and capecitabine monotherapy, a network meta-analysis (NMA) was performed. As the evidence networks constructed were not connected, unanchored matching-adjusted indirect comparisons (MAICs) were used. The NMA estimated that atezolizumab in combination with nab-paclitaxel would be associated with an increase in PFS compared with paclitaxel

(difference 4.08 months; 95% CrI: 1.02, 6.49) and with capecitabine (difference 5.15 months; 95% CrI: -2.65, 10.22). The analysis also estimated an increase in OS compared with paclitaxel (difference 8.62 months; 95% CrI: 1.95, 14.37) and with capecitabine (difference 12.33 months; 95% CrI: -1.91, 22.76) . The Review Group expressed significant concern regarding the validity of the results of the MAICs due to the failure to match on a number of important prognostic variables (including PD-L1 status). This resulted in a high risk of biased estimates of relative treatment efficacy, the likely direction and magnitude of which could not be determined. To reduce uncertainty, the Review Group recommended that the evidence network instead be connected through the assumption of clinical equivalence of nab-paclitaxel and paclitaxel (which was included as a scenario analysis in the submission). This assumption produced similar estimates to the MAIC-based network for PFS, and moderately reduced OS benefit for atezolizumab in combination with nab-paclitaxel nab-paclitaxel compared to paclitaxel (difference 6.09 months; 95% CrI: 0.83, 12.8) and capecitabine (difference 10.91 months; 95% CrI -6.01, 25.25). The Review Group considers this approach to be preferable, though acknowledges that considerable uncertainty remains.

2. Safety of atezolizumab

As there was no significant difference between the safety profile of atezolizumab for patients who are either PD-L1 positive or negative, safety data from the 'all-comer' population in the IMpassion130 trial was considered. At the time of the primary safety analysis, mean (SD) duration of therapy with atezolizumab was 31.6 (24.7) weeks. The only grade 3-4 adverse event (AE) which occurred more frequently in those who received atezolizumab was grade 3 peripheral neuropathy. The incidence of grade 5 (i.e. fatal) AEs was low in both arms (1.3% in the atezolizumab in combination with nab-paclitaxel arm vs. 0.7% in the placebo in combination with nab-paclitaxel arm), with one event in each arm considered to be related to the study drug. A total of 6.4% of participants discontinued atezolizumab in combination with nab-paclitaxel due to an AE. Immune-related AEs occurred at a higher frequency in the atezolizumab in combination with nab-paclitaxel nab-paclitaxel arm. However, the majority were grade 1-2. Results of an interim safety analysis were consistent with the primary safety analysis. The safety profile of atezolizumab in the IMpassion130 trial was in line with the established safety profile of atezolizumab.

3. Cost effectiveness of atezolizumab

Methods

The Applicant submitted a *de novo* cost-utility partitioned survival model consisting of three states: progression free, progressed disease (PD) and death. Cycle length was one week and a half-cycle correction was applied. A 35-year time horizon was used, with a starting age of 53.6 years.

Treatment effectiveness was modelled by estimating PFS and OS over time for each intervention. Survival curves were fit to the IMpassion130 trial data and extrapolated to a lifetime horizon, with the relative treatment effects derived from the NMA applied to these curves. The Review Group identified two significant sources of uncertainty in relation to the estimates of PFS and OS. First, the use of unanchored MAICs to inform the NMA. Second, the Weibull and Gompertz distributions (both plausible choices) resulted in materially different predictions for OS.

Utilities were derived from EQ-5D data (EQ-5D-5L data mapped to EQ-5D-3L) collected during the IMpassion130 trial. Health-state specific values were generated, with separate values for each treatment arm in the progression-free health state. Utilities for both paclitaxel and capecitabine were assumed to equal the values predicted for placebo in combination with nab-paclitaxel . Costs applied included: drug costs, drug administration costs, cost associated with PD-L1 testing (included cost of negative tests), treatment monitoring costs, AE event costs (for all treatment-related AEs of grade 3 or more which occurred in ≥2% of patients) and health state costs (included health care utilisation costs, post-progression treatment costs and a once-off end of life cost).

Results

The results of the Applicant's base case analysis (with coding errors corrected) are presented in Table 1. The Review Group identified a number of limitations to the Applicant's base case which were addressed in the NCPE adjusted base case (results in Table 2). Key changes included: assuming clinical equivalence of nab-paclitaxel and paclitaxel and an

increase the number of post-progression treatment cycles from three to six 28-day cycles. The probabilistic sensitivity analyses results for both the Applicant's and NCPE adjusted base cases were consistent with the deterministic analyses. The probability of cost-effectiveness of atezolizumab in combination with nab-paclitaxel versus each of paclitaxel monotherapy and capecitabine monotherapy is 0% at the thresholds of €20,000 per QALY and €45,000 per QALY under both the Applicant's and the NCPE's adjusted assumptions.

Table 1 Results of deterministic incremental cost-effectiveness analysis - NCPE adjusted base case

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)*
Atezolizumab and nab-paclitaxel	147,402	1.58			
Paclitaxel	50,468	1.22	96,934	0.362	267,419
Capecitabine	31,736	1.05	115,665	0.532	217,581

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2 Results of deterministic incremental cost-effectiveness analysis - Applicant's corrected base case

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)*
Atezolizumab and nab-paclitaxel	145,232	1.58			
Paclitaxel	45,789	1.08	99,443	0.50	199,637
Capecitabine	29,368	0.94	115,865	0.64	180,659

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

The Review Group was concerned that there was a high degree of uncertainty associated with the comparisons. Using the NCPE adjusted base case, changing the parametric distribution for OS from Weibull to Gompertz increases the ICER to €313,412 per QALY versus paclitaxel and €243,096 per QALY versus capectiabine.

4. Budget impact of atezolizumab

The price to wholesaler of atezolizumab is €3,153.14 per pack (pack size one 840 mg vial). Assuming that the number of cycles received was the same as the median duration of therapy (DoT) in the IMpassion130 trial, the Applicant proposed a cost per treatment course for atezolizumab in combination with nab-paclitaxel of €65,762, including 23% VAT. Using

the mean DoT from the IMpassion130 trial resulted in a cost per treatment course of €89,632, including VAT.

The Applicant proposed that the number of patients treated will increase from 41 in year 1, to 68 in year 5. The Review Group noted that the numbers who receive treatment will depend on access to PD-L1 testing. Using the Applicant's proposed eligible population and the mean DoT, the NCPE adjusted 5-year cumulative gross drug budget impact is €25.6 million, including VAT. The Applicant presented the results of two separate net drug budget impact estimates: one assumed that 100% of patients treated with atezolizumab in combination with nab-paclitaxel would otherwise be treated with paclitaxel; the other assumed that 100% would be treated with capecitabine. The NCPE adjusted 5-year cumulative net drug budget impact is €25.4 million versus paclitaxel, and €25.2 million versus capecitabine (both including VAT). When the costs of PD-L1 testing and drug administration costs are included, the NCPE adjusted 5-year cumulative net health budget impact is €25.9 million versus paclitaxel, and €29.6 million versus capecitabine (both including VAT). A confidential patient access scheme is currently in place for nab-paclitaxel. Therefore, the actual net drug budget impact to the HSE would be lower than the estimates presented here. Also noted is the potential for a generic for nab-paclitaxel to enter the market in the near future. This will further decrease the budget impact of atezolizumab in combination with nab-paclitaxel nab-paclitaxel.

5. Patient Submission

No patient submissions were received for this assessment.

6. Conclusion

The NCPE recommends that atezolizumab in combination with nab-paclitaxel not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.