Cost-effectiveness of atezolizumab (Tecentriq®) in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

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 in combination with carboplatin and etoposide not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

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.

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

National Centre for Pharmacoeconomics **September 2020**

Summary

In April 2020, Roche Products (Ireland) Ltd submitted a dossier examining the cost-effectiveness of atezolizumab in combination with carboplatin and etoposide (ATEZO + CE) for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). ATEZO + CE was granted marketing authorisation by the European Commission for this indication in September 2019. This is a licence extension. Atezolizumab is a PD-L1 inhibitor immunotherapy.

During the induction phase, the recommended dose of atezolizumab is 1,200mg followed by carboplatin (AUC 5mg/ml/min), and then etoposide (100mg/m^2) administered by intravenous (IV) infusion on day one. Etoposide is also administered by IV infusion on days two and three. This regimen is administered every three weeks for four cycles. The induction phase is followed by a maintenance phase in which 1,200mg atezolizumab is administered by IV infusion every three weeks. It is recommended that patients are treated with atezolizumab until disease progression or unmanageable toxicity. The Applicant is seeking reimbursement for this hospital only drug under the Oncology Drugs Management System.

The current standard of care for first-line ES-SCLC in Ireland is platinum-based chemotherapy plus etoposide. Carboplatin plus etoposide (CE) is the standard of care in Ireland. Cisplatin plus etopside (CiE), whilst not routinely used, was also identified as a possible treatment option for certain first-line ES-SCLC patients. Therefore, CE and CiE are considered the main comparators.

1. **Comparative effectiveness of atezolizumab (Tecentriq®)**

Direct comparative evidence for the effectiveness of ATEZO + CE versus placebo + CE, in patients with ES-SCLC, is available from the IMpower133 double-blind, randomised, controlled trial.

Patients were randomised in a 1:1 ratio to receive, in the induction phase, either ATEZO + CE (n=201) or placebo + CE (n=202); both regimens were given every three weeks for four

cycles. The induction phase was followed by a maintenance phase during which patients received either atezolizumab or placebo until unacceptable toxicity or disease progression. The co-primary endpoints were progression-free survival (PFS) (as assessed by the Investigator) and overall survival (OS). Secondary endpoints included objective response rate (ORR), duration of response (DOR), OS and PFS rate at predefined time points and adverse events (AEs). Health-related quality of life (HRQoL) measures were also collected using the EORTC QLQ-C30 and the supplemental lung cancer module (QLQ-LC13) questionnaires plus the EQ-5D-5L questionnaire. Results were reported from the primary PFS and interim OS analysis (clinical cut-off date (CCOD): 24 April 2018) and final OS analysis (CCOD: 24 January 2019). The median duration of follow-up was 13.9 months for the primary analysis and 22.9 months for the final OS analysis (ATEZO + CE: 23.1 months; placebo + CE: 22.6 months). The primary efficacy analyses were based on the intention-to-treat population.

Median PFS was 5.2 months (95% CI 4.4 to 5.6) in patients receiving ATEZO + CE and 4.3 months (95% CI 4.2 to 4.5) in patients receiving placebo + CE; hazard ratio (HR) = 0.77 (95% CI 0.62 to 0.96). Median OS was 12.3 months (95% CI 10.8 to 15.8) and 10.3 months (95% CI 9.3 to 11.3) in the respective arms; HR = 0.76 (95% CI 0.60 to 0.95) for the final OS analysis. Descriptive results only were reported for HRQoL measures. These did not indicate a clinically meaningful difference between treatments.

In the absence of direct head-to-head evidence for the comparison with CiE, a network meta-analysis (NMA) was performed using data from IMpower133 and two randomised-controlled trials of CiE and CE. The Review Group had concerns that the high level of heterogeneity between the three trial populations and the differences in treatment dose and frequency in the common comparator (CE) arm mean that the results of the NMA need to be treated with caution. The uncertainty in the HRs from the NMA will translate into uncertainties in the cost-effectiveness model.

2. Safety of atezolizumab (Tecentriq®)

In the IMpower133 trial, the safety population was defined as patients who received a dose of any treatment and was grouped according to treatment received, this included 198

patients who received at least one dose of ATEZO + CE and 196 who received at least one dose of placebo + CE. Safety results are reported for the CCOD of 24 April 2018. Results from the later CCOD were consistent with the primary analysis. The median duration of treatment was 4.7 months for ATEZO + CE and 4.1 months for placebo +CE. The median number of doses was seven for atezolizumab and six for placebo. The median number of doses of CE (equivalent to four treatment cycles) was the same in both patient groups.

AEs were more common in patients receiving ATEZO + CE (any 100%; grades 3-4 67.2%) compared to those receiving placebo + CE (any 96.4%; grades 3-4 63.8%). However, the incidence of grade 5 AEs was lower in the ATEZO + CE arm (2.0%) compared with the placebo + CE arm (5.6%). The most common grade 3 or 4 AEs related to the trial regimen were neutropenia (ATEZO + CE: 22.7%; placebo + CE: 24.5%), anaemia (ATEZO + CE: 14.1%; placebo + CE: 12.2%), neutrophil count decreased (ATEZO + CE: 14.1%; placebo + CE: 16.8%), and thrombocytopenia (ATEZO + CE: 10.1%; placebo + CE: 7.7%). Infusion related reaction was the only AE leading to any study treatment withdrawal that was reported with more than 2% difference in incidence between treatment arms (2.5% ATEZO + CE vs 0% placebo + CE). Overall, the safety profile of IMpower133 was consistent with the defined toxic effects of the individual agents.

3. Cost effectiveness of atezolizumab (Tecentriq®)

Methods

The cost-effectiveness of ATEZO + CE was assessed using a three-state partitioned survival cost-utility model with a cycle length of one week and a life-time horizon of 20-years. All patients begin in the PFS health state, where they remain until their disease either progresses (transition into the progressed disease (PD) health state) or they experience death. Following disease progression, patients remain in the PD health state until death, incurring the costs of follow-up treatment. Costs and utilities were allocated to each health state. The partitioned survival approach uses the “area under the curve” approach, where the number of patients in each health state at a given time is taken directly from survival curves fitted to clinical trial data.

Clinical data for ATEZO + CE and the comparison with CE in the model base case were obtained from the IMpower133 trial. The Review Group had concerns surrounding implausible ICERs for the comparison with CiE when using the HR from the NMA to inform this comparison. The HRs from the NMA indicated that CE and CiE have equal efficacy, therefore the Kaplan-Meier (KM) data from the CE arm was used directly. However, outputs from the NMA are uncertain. The key effectiveness inputs in the model were PFS, time to off treatment (TTOT) and OS from IMpower133.

The 'proximity to death' approach using HRQoL data derived directly from the IMpower133 trial was used to estimate utilities in the cost-effectiveness model. Four 'proximity to death' sub-states were used which were further stratified according to whether patients were on- or off-treatment. The same utilities were used regardless of treatment received. Disutilities were not included for AEs. The Review Group considers that relevant costs were included in the model. Costs were included for active treatment, routine care and monitoring, terminal care, treatment specific monitoring and AEs. Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group suggested changes to the Applicant base case based on plausible alternative assumptions. These included using the survival curve from the beginning of the model for OS and assuming treatment effect was capped at five years for both PFS and OS. The NCPE adjusted ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1: NCPE adjusted base case*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
ATEZO + CE versus CE	43,343	0.26	169,686
ATEZO + CE versus CiE	43,626	0.26	170,794

ATEZO: atezolizumab; **CE:** carboplatin + etoposide; **CiE:** cisplatin + etoposide; **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: Applicant base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
ATEZO + CE versus CE	43,061	0.30	145,429
ATEZO + CE versus CiE	43,343	0.30	146,384

ATEZO: atezolizumab; **CE:** carboplatin + etoposide; **CiE:** cisplatin + etoposide; **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 probabilistic sensitivity analysis using both base cases gave similar results to the deterministic models. The probability of ATEZO + CE being cost-effective was estimated at 1% at thresholds of €20,000 per QALY and €45,000 per QALY, for the comparisons with CE and CiE, using the NCPE adjusted base case. The probability was 0% at thresholds of €20,000 per QALY and €45,000 per QALY, for both comparisons using the Applicant base case.

Many scenario analyses were presented addressing structural uncertainty and model assumptions. The scenarios that had the largest effect on the results were the extrapolation curves used in TTOT and OS. ICERs ranged from €135,154 (KM with log-normal tail for OS) to €501,133 (log-normal for TTOT) per QALY for the NCPE adjusted comparison with CE. ICERs ranged from €136,042 (KM with log-normal tail for OS) to €502,204 (log-normal for TTOT) per QALY for the NCPE adjusted comparison with CiE.

4. Budget impact of atezolizumab (Tecentriq®)

The price to wholesaler of atezolizumab is €4,504.49 for a 1,200mg vial (excluding VAT). The total per-patient treatment drug acquisition cost of atezolizumab, including all relevant fees, mark-ups, rebates and VAT is €37,049.43. The total per-patient treatment drug acquisition cost of ATEZO + CE is €42,253.52. Total treatment costs assume 100% treatment dosing intensity, seven cycles of atezolizumab and four cycles of CE (as derived from IMpower133).

The Applicant estimated that 56 patients would be treated with ATEZO + CE in year one, rising to 102 in year five. The projected cumulative five-year gross drug budget impact of ATEZO + CE is €18.7 million. The projected cumulative five-year gross drug budget impact of atezolizumab alone is €16.4 million.

The Applicant also presented a net drug budget impact assuming ATEZO + CE will displace CE and CiE separately. For the CE comparison the incremental five-year cost is equivalent to the cost of atezolizumab alone i.e. €16.4 million. For the CiE comparison the projected cumulative five-year net drug budget impact is €16.9 million.

5. Patient submissions

No patient submissions were received in support of the application.

6. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that ATEZO + CE for the first-line treatment of adult patients with ES-SCLC is not 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.