Cost-effectiveness of atezolizumab (Tecentriq ®) in combination with bevacizumab for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy

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 ®) in combination with bevacizumab 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) Health Technology Assessment of atezolizumab ®. 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 **May 2023**

Summary

In July 2022, Roche Products (Ireland) Ltd submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of atezolizumab in combination with bevacizumab for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy. Reimbursement is sought under the Oncology Drugs Management System. Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7-1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. When used in combination with atezolizumab, bevacizumab can further enhance the effect of atezolizumab in killing tumour cells by inhibiting VEGF-related immunosuppression, promoting T cell infiltration in tumours and creating a favourable tumour microenvironment for T cell reactivation. The recommended dosage regimes for atezolizumab are 840 mg once every two weeks, or 1,200 mg once every three weeks, or 1,680 mg once every four weeks administered via intravenous (IV) infusion. Treatment with atezolizumab in combination with bevacizumab should be continued until loss of clinical benefit or unmanageable toxicity. The Applicant's submission investigated atezolizumab 1,200mg in combination with bevacizumab (15mg/kg of body weight), administered by IV infusion every three weeks. The current standard of care for the treatment of this patient population in Ireland is sorafenib or lenvatinib.

1. Comparative effectiveness of atezolizumab in combination with bevacizumab

The efficacy and safety of atezolizumab in combination with bevacizumab was assessed in the IMbrave 150 trial. This is an international, randomised, open-label, phase III study in adult patients (n=501) with untreated locally advanced or metastatic and/or unresectable HCC. Patients had not received prior systemic therapy, had measurable disease, had an ECOG PS of 0 or 1, and a Child-Pugh liver function class A. Patients were randomised in a 2:1 ratio to receive open-label treatment with atezolizumab in combination with bevacizumab, 1200mg administered once every three weeks, or sorafenib (400mg orally twice daily). Treatment was continued in both arms until unacceptable toxicity or loss of clinical benefit. Patients could continue treatment beyond disease progression, as defined by RECIST 1.1, if

there was evidence of clinical benefit as determined by the clinical investigator. Patients who transiently or permanently discontinued either atezolizumab or bevacizumab due to adverse events (AEs) were permitted to receive single-agent therapy until loss of clinical benefit.

The co-primary endpoints of the IMbrave 150 study were overall survival (OS) and Independent Review Facility (IRF) assessed progression free survival (PFS) (IRF-PFS) according to RECIST v1.1. Key secondary endpoints included IRF assessed objective response rate (IRF-ORR) according to RECIST v1.1 and according to HCC mRECIST criteria. At the pre-specified primary analysis of IRF-PFS and interim analysis of OS in the ITT population (median follow-up: 8.6 months, data-cut off: August 2019), atezolizumab in combination with bevacizumab was associated with longer OS and PFS. At the interim analysis of OS, median OS was not reached (NR) in the atezolizumab in combination with bevacizumab arm versus 13.2 months (95% CI 10.4 to NR) for sorafenib. The 6 and 12-month OS event free rates were 84.8% and 67.2% in the atezolizumab in combination with bevacizumab arm and 72.3% and 54.6% in the sorafenib arm. Treatment with atezolizumab in combination with bevacizumab reduced the risk of death, HR: 0.58 (95% CI 0.42 to 0.79, p= 0.0006). Median IRF-PFS was 6.8 months (95% CI 5.8 to 8.3) in the atezolizumab in combination with bevacizumab versus 4.3 months (95% CI 4.0 to 5.6) in the sorafenib arm. The 6-month PFS event free rates were 54.5% and 37.2% in the respective arms. Treatment with atezolizumab in combination with bevacizumab reduced the risk of progression or death, HR: 0.59 (95% CI 0.47 to 0.76, p= 0.0001). IRF-ORR was improved with atezolizumab in combination with bevacizumab, ORR rates were 27.3% versus 11.9% in the respective arms (difference: 15.4% (95% CI 7.9 to 22.8 p <0.0001)). Both IRF-PFS results and IRF-ORR results were consistent across RECIST v1.1 and HCC mRECIST v1.1.

Results of a post-hoc, descriptive efficacy analysis (median follow-up: 15.6 months, data cut off: August 2020) were also submitted by the Applicant. Median OS was 19.2 months (95% CI 17.0 to 23.7) with atezolizumab in combination with bevacizumab arm versus 13.4 months (95% CI 11.4 to 16.9) with sorafenib arm; HR: 0.66 (95% CI 0.52 to 0.85, p=0.009). Median IRF-PFS, per RECIST v1.1, was 6.9 months (95% CI 5.7 to 8.6) versus 4.3 months (95% CI 4.0 to 5.6) in the respective arms; HR: 0.65 (95% CI 0.53 to 0.81, p=0.0001). The IRF-ORR

rate was 29.8% in the atezolizumab in combination with bevacizumab arm versus 11.9% in the sorafenib arm. Results for IRF-OS, IRF-PFS and IRF-ORR were consistent with the primary efficacy analysis. Health-related quality of life (HRQoL), was assessed using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) tool and the EQ-5D-5L tool, both of which were exploratory outcomes. Treatment with atezolizumab in combination with bevacizumab delayed deterioration of quality of life, physical functioning, and role functioning compared with sorafenib. However, no formal comparisons between arms were pre-planned therefore the Review Group highlight that all results are uncertain.

The IMbrave 150 was an open-label trial and, as such, there is potential for bias in outcomes, particularly patient-reported outcomes e.g. HRQoL and AEs. Although PFS was measured by a blinded IRF, discontinuation of treatment was on the basis of investigator assessment of clinical benefit. Thus, a risk of bias was introduced. In total, 21% of patients treated with atezolizumab in combination with bevacizumab and 12% of patients treated with sorafenib continued treatment beyond radiographic progression. It is unclear the magnitude, if any, this had on the efficacy outcomes. The Review Group also had concerns regarding the generalisability of the evidence. The IMbrave 150 study population was predominantly Asian (56%), and hepatitis B virus (48%) was the predominant underlying aetiology of disease. The study population may not be generalisable to the population of Ireland.

The Applicant included a network-meta analyses (NMA) to compare atezolizumab in combination with bevacizumab with lenvatinib in adult patients with advanced or unresectable HCC who have received no prior systemic therapies. Outcomes were reported for PFS and OS only. Hazard ratios for OS (HR: 0.72, 95% [Credible Interval] CrI 0.38 to 1.36) numerically favoured atezolizumab in combination with bevacizumab but did not for PFS (HR: 1.00, 95% CrI 0.24 to 3.87). We note that both credible intervals are wide and cross one.

2. Safety of atezolizumab in combination with bevacizumab

The safety of atezolizumab in combination with bevacizumab, for this submission, is informed by the IMbrave 150 trial. The median duration of treatment was 7.4 months with

atezolizumab, 6.9 months with bevacizumab, and 2.8 months with sorafenib. An AE due to any cause occurred in 98.2%, of the atezolizumab in combination with bevacizumab arm and 98.7% of the sorafenib arm. The most frequently occurring AEs in the atezolizumab in combination with bevacizumab arm were hypertension (29.8%), fatigue (20.4%) and proteinuria (20.1%). In the sorafenib arm, these were diarrhoea (49.4%) and palmar-plantar erythrodysaesthesia syndrome (48.1%). The incidence of Grade 3 to 5 AEs were similar; 56.5% versus 55.1% in the respective arms. A higher proportion of patients in the atezolizumab in combination with bevacizumab arm versus the sorafenib arm experienced a serious AE (38% versus 30.8%), however treatment related AEs were comparable across arms (17% versus 15.4%). Immune-mediated AEs of atezolizumab were comparable to the known safety profile of atezolizumab in combination with bevacizumab except for the following which occurred at a higher incidence than anticipated: immune-related hepatitis (43.2%), immune related hyperthyroidism (4.6%), and immune-mediated diabetes mellitus (2.4%). The discontinuation rate due to AEs were 15% and 10% in the atezolizumab in combination with bevacizumab and sorafenib arms. The most common reason for discontinuation in the atezolizumab in combination with bevacizumab arm was gastrointestinal (GI) disorders. Incidence rates of upper GI bleeds were 7% (atezolizumab in combination with bevacizumab) versus 4.5% (sorafenib). Higher incidences of bleeding, including fatal bleedings, infections, discontinuations and dose interruptions due to AEs were seen in the atezolizumab in combination with bevacizumab arm. There were more deaths in the sorafenib arm, both due to AEs and disease progression. In the sorafenib arm, nine (5.8%) patients died due to AEs compared to 15 (4.6%) patients in the atezolizumab in combination with bevacizumab arm. Six patients in the atezolizumab in combination with bevacizumab arm died due to fatal bleedings, of which, three were deemed to be related to bevacizumab. The European Public Assessment Report highlights that the use of bevacizumab in patients with HCC is challenging, because many of these patients have a higher risk of bleeding due to their underlying disease, however advise that sufficient warnings and precautions for use are highlighted in the SmPC.

3. Cost effectiveness of atezolizumab in combination with bevacizumab

Comparisons of atezolizumab in combination with bevacizumab to both lenvatinib and sorafenib are relevant as both are considered standard of care in Irish clinical practice.

Methods

A three health-state partitioned survival model was submitted by the Applicant. The treatment effects captured by the cost-effectiveness model (CEM) were the delay of disease progression and death. Key efficacy inputs were PFS and OS. The population were based on the IMbrave 150 trial. Treatment duration for atezolizumab in combination with bevacizumab and sorafenib was informed by time-to-treatment discontinuation data from the IMbrave 150 trial. PFS data from the REFLECT study (which compared sorafenib with lenvatinib in a population with advanced unresectable HCC) was used as a proxy for treatment discontinuation in the lenvatinib arm. Long term survival estimates were obtained from fitting parametric models to patient-level PFS and OS data collected in the ITT population of the IMbrave 150 trial. Lenvatinib estimates for PFS and OS came from HRs estimated from the NMA. Utility values were derived from EQ-5D-5L data collected in the IMbrave150 study which were mapped to EQ-5D-3L. The Applicant implemented proximity-to-death utilities which categorised patients into four groups depending on their proximity to death and whether they were on or off treatment. The Review Group identified a number of limitations in the Applicant's CEM, which were addressed through changes in the NCPE-adjusted base case. These changes included alternative parametric model selection for OS, an assumption of equivalent treatment effect implemented between lenvatinib and sorafenib for OS and PFS, and the removal of the Applicant's assumption of lifetime treatment effect associated with atezolizumab in combination with bevacizumab. Costs and outcomes were discounted at an annual rate of 4%. The analysis was conducted from the perspective of the HSE.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1 and 2. Results of the NCPE-adjusted base case are presented in Table 3 and 4. The probabilities of cost-effectiveness, for atezolizumab in combination with bevacizumab versus both sorafenib and lenvatinib, in the NCPE adjusted base case were all 0% at both thresholds of €20,000/QALY and €45,000/QALY. Deterministic sensitivity analysis indicated that the most influential parameters in the model related to the choice of parametric model for OS, costs associated with atezolizumab in combination with

bevacizumab and sorafenib, and the duration of treatment effect associated with atezolizumab in combination with bevacizumab on OS.

Table 1: Applicant base case incremental cost-effectiveness results for the comparison atezolizumab in combination with bevacizumab with sorafenib

Treatments	Total costs (€)*	Total QALYs*	Incremental costs (€)	Incremental QALYs	ICER [a] (€/QALY)
Sorafenib	61,617	1.27	-	-	-
Atezolizumab in combination with bevacizumab	153,107	1.86	91,490	0.59	154,721

Abbreviations: **ICER:** incremental cost effectiveness ratio, **QALY:** quality adjusted life years. Figures in the table are rounded, and so calculations may not be directly replicable.
[a] Corresponding probabilistic ICER using 2,000 iterations =€158,952/QALY.
*Total costs and QALYs presented are discounted (4%).

Table 2: Applicant base case incremental cost-effectiveness results for the comparison of atezolizumab in combination with bevacizumab with lenvatinib

Treatments	Total costs (€)*	Total QALYs*	Incremental costs (€)	Incremental QALYs	ICER [a] (€/QALY)
Lenvatinib	100,029	1.32	-	-	-
Atezolizumab in combination with bevacizumab	153,107	1.86	53,078	0.54	97,506

Abbreviations: **ICER:** incremental cost effectiveness ratio, **QALY:** quality adjusted life years. Figures in the table are rounded, and so calculations may not be directly replicable.
[a] Corresponding probabilistic ICER using 2,000 iterations =€115,368/QALY
*Total costs and QALYs presented are discounted (4%).

Table 3: NCPE adjusted base case incremental cost-effectiveness results atezolizumab in combination with bevacizumab versus sorafenib

Treatments	Total costs (€)*	Total QALYs*	Incremental costs (€)	Incremental QALYs	ICER [a] (€/QALY)
Sorafenib	59,652	1.21	-	-	-
Atezolizumab in combination with bevacizumab	151,890	1.60	92,238	0.39	237,984

Abbreviations: PtW: *price to wholesaler* ***QALY****: quality adjusted life years.* Figures in the table are rounded, and so calculations may not be directly replicable.
[a] Corresponding probabilistic ICER using 2,000 iterations =€246,215/QALY
*Total costs and QALYs presented are discounted (4%).

Table 4: NCPE adjusted base case incremental cost-effectiveness results atezolizumab in combination with bevacizumab versus lenvatinib

Treatments	Total costs (€)*	Total QALYs*	Incremental costs (€)	Incremental QALYs	ICER [a] (€/QALY)
Lenvatinib	71,465	1.22	-	-	-
Atezolizumab in combination with bevacizumab	151,890	1.60	80,424	0.37	215,813

Abbreviations: PtW: *price to wholesaler* ***QALY****: quality adjusted life years*
[a] Corresponding probabilistic ICER using 2,000 iterations =€225,975/QALY. Figures in the table are rounded, and so calculations may not be directly replicable
*Total costs and QALYs presented are discounted (4%).

4. Budget impact of atezolizumab in combination with bevacizumab

The price to wholesaler for one 1,200mg vial of atezolizumab is €4,342.87. The total cost of atezolizumab in combination with bevacizumab, per patient, per treatment course is €133,682 (comprising €90,440 and €43,243 for atezolizumab and bevacizumab respectively). This is based on the assumption that patients receive 18.1 three- week-cycles of atezolizumab and 17.1 three- week-cycles of bevacizumab.

The Applicant predicted that 38 patients will be treated with atezolizumab in combination with bevacizumab in Year 1 rising to 58 patients in Year 5; total of 249 patients over five years. The 5-year cumulative gross drug budget impact was an estimated €33.10 million (€26.59 million excluding VAT). The 5-year cumulative net drug budget impact (assuming displacement of sorafenib and lenvatinib) was an estimated €23.01 million (€16.50 million excluding VAT). Clinical opinion, obtained by the Review Group, anticipates higher levels of displacement of lenvatinib over sorafenib. Using this clinical opinion, the Review Group estimate a 5-year cumulative net drug budget impact of €19.88 million (€13.37 excluding VAT).

5. Patient submission

No Patient Organisation Submissions were received during the course of this assessment**.**

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that atezolizumab (Tecentriq ®) in combination with bevacizumab 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.