Cost effectiveness of durvalumab (Imfinzi®) as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer in adults whose tumours express PD-L1 on ≥1% tumour cells and whose disease has not progressed following platinum-based chemo-radiation therapy

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of durvalumab (Imfinzi®). Following assessment of the Applicant's submission, the NCPE recommends that durvalumab be considered for reimbursement if 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 (Astra Zeneca) dossier on the cost effectiveness of durvalumab. 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 2020**

Summary

In September 2019, Astra Zeneca submitted a dossier of clinical, safety and economic evidence for durvalumab for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥1% tumour cells and whose disease has not progressed following platinum-based chemo-radiation therapy. Durvalumab is a humanised monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 on the surface of tumour cells. Blockade enhances anti-tumour responses and increases T-cell activation. The recommended dose is 10mg/kg patient body weight (intravenous infusion over 60 minutes) every two weeks. It is for use in the hospital setting.

The existing standard of care in this setting is "watch and wait" (best supportive care). For this submission, best supportive care was informed by the placebo arm of the PACIFIC trial; this is appropriate.

1. **Comparative effectiveness of durvalumab**

Efficacy data for durvalumab versus placebo is derived from the on-going (recruitment complete) phase III randomised controlled trial, PACIFIC. Eligible patients were randomised (2:1) to durvalumab 10mg/kg via intravenous infusion every two weeks for up to 12 months (or a maximum of 26 doses) or placebo via intravenous every two weeks for up to 12 months. The intention-to-treat (ITT) population included patients regardless of PD-L1 expression status. The EMA licence is based on results in the PD-L1 ≥ 1% subgroup (post hoc analysis, not powered to detect significance). Primary endpoints were progression free survival (assessed by blinded independent central review according to RECIST criteria v1.1) and overall survival.

Results from the ITT population, at about 30 months post randomisation, demonstrated an improvement in progression free survival with durvalumab (median = 16.8 months, 95% CI 13.0 to 18.1) versus placebo (median = 5.6 months, 95% CI 4.6 to 7.8), HR 0.52, 95% CI 0.42 to 0.65. Results at about 36 months demonstrated an improvement in overall survival with durvalumab (median = not reached, 95% CI 34.7 months to 'not reached') versus placebo (median = 28.7 months, 95% CI 22.9 to 'not reached'), HR=0.68, 95% CI 0.53 to 0.87. In the post hoc analysis of the PD-L1 ≥ 1% subgroup, durvalumab was associated with

improvements in both progression free survival and overall survival. Uncertainty in the long-term benefits remain. The population in the trial (mean age of 63.1 years) is younger than the expected population in Ireland. Also, in the trial, subsequent treatment with immunotherapy had been received by only 22.4% of patients in the placebo-arm at the time of overall survival analysis. Currently, in Irish clinical practice, most patients with metastatic NSCLC will receive immunotherapy. Thus the treatment effect of placebo is likely underestimated in the trial.

2. Safety of durvalumab

Safety data is derived from the safety population of PACIFIC. Over 90% of patients in either arm experienced any adverse event. Treatment related adverse events were reported in 67.8% and 53.4% of patients treated with durvalumab and placebo respectively. Grade 3 to 4 adverse events were experienced in 32% and 27.8% of patients in the respective arms. Adverse events led to treatment discontinuation in 15.4% and 9.8% of patients in the respective arms. The safety profile of durvalumab is considered to be in line with that of other PD-L1 inhibitors.

3. Cost effectiveness of durvalumab

Methods

Cost effectiveness of durvalumab, versus best supportive care, was evaluated in a semi-Markov model with three states (progression-free, progressed disease, and death). Direct evidence was derived from PACIFIC. Of concern, the model did not accommodate a distinction between advanced metastatic disease progression and local recurrence. Post-progression survival estimates were based on pooling of data across trial arms. This introduces uncertainty regarding the impact of subsequent immunotherapy treatment. Efficacy was modelled using progression-free survival, time-to-progression and post-progression survival data; overall survival data was not used. This is a limitation. The Review Group considered that the log-normal distribution led to more reasonable estimates of longer term progression-free survival than the Applicant's choice of generalised gamma. The model assumed an enduring benefit for durvalumab for up to 10 years; efficacy was assumed to be equivalent to best supportive care thereafter. The Review Group considered

a 5-year cut-off point to be most appropriate (in line with the available data and previous cost-effectiveness evaluations of other immunotherapies).

Utility values were derived from PACIFIC (EQ-5D-5L data mapped to EQ-5D-3L). The calculation of health-state utility values did not account for the allocated treatment. Adverse-event disutilities were calculated from values in the literature. The approaches taken in the calculation of health-state utility and disutility values were considered to produce values biased in favour of durvalumab. Instead, the Review Group calculated health-state utilities by including a treatment-specific effect; disutility values were not directly applied. An age-related decrement was not applied in the Applicant's base case; the Review Group implemented this. Costs comprised drug acquisition, administration, subsequent treatments, PD-L1 testing, treatment of adverse events, disease management and end-of-life care costs. Irish cost data were used. Within the model, outputs of age and time difference calculations were rounded down to the nearest integer. This would result in an underestimation of the age-related utility decrement and the effect of discounting. The Review Group removed this rounding down.

The Review Group made a number of adjustments to the Applicant's submitted cost-effectiveness model however sources of uncertainty remain in the model. The generalisability of PACIFIC data and the model to the Irish treatment setting remains uncertain. An annual discount rate of 4% is applied to costs and outcomes.

Results

The NCPE adjusted base case analysis resulted in a probabilistic incremental cost effectiveness ratio (ICER) (durvalumab vs. best supportive care) of €62,377/QALY (incremental cost = €73,360: incremental QALY = 1.18). Probabilities of cost-effectiveness are 0.1% and 9.8% at the €20,000/QALY and €45,000/QALY thresholds respectively. The deterministic ICER was comparable (€61,076/QALY).

The Applicant's submitted base case analysis resulted in a probabilistic ICER of €29,136/QALY (incremental cost = €73,917; incremental QALY = 2.54). Probabilities of cost-effectiveness are

6.2% and 92.6% at the €20,000/QALY and €45,000/QALY thresholds respectively. The deterministic ICER was €26,797/QALY.

Cost-effectiveness outputs were most sensitive to the proportions of patients receiving subsequent immunotherapies, the duration of treatment with subsequent immunotherapies, and the time to discontinuation of durvalumab. Two scenarios incorporate only some of the NCPE's adjustments to the Applicant's base case:

- Scenario 1: Inclusion of treatment-specific effect and age-related decrement in calculation of health-state utilities, integers not rounded down. ICER = €29,562/QALY (incremental cost = €72,187, incremental QALY = 2.44).
- Scenario 2: Inclusion of treatment-specific effect and age-related decrement in calculation of health-state utilities, integers not rounded down, 5-year treatment benefit for durvalumab. ICER = €36,363/QALY (incremental cost = €72,915, incremental QALY = 2.01).

4. Budget impact of durvalumab

The price, to wholesaler, of durvalumab, is €660 per 120mg vial (€776 including VAT/rebates) and €2,750 per 500mg vial (€3,231 including VAT/rebates). Assuming a mean duration of treatment of 7.79 months (from PACIFIC), the per-patient cost to the HSE is about €86,683 (incorporating administration costs and assuming no vial sharing).

The Applicant estimated that 72 patients would be eligible for treatment in year one, rising to 116 by year five. On applying market-share estimates, the Applicant estimates a gross budget impact of €5.29 million in year one, increasing annually to €7.32 million in year five; five-year impact of about €34.63 million. No net budget offsets in terms of best supportive care are assumed; cost-offsets in subsequent treatments may occur. A net budget impact (drug acquisition) of €5.29 million in year one, decreasing to €3.93 million in year five is estimated; five-year cumulative impact of about €21.57 million. Vial sharing is assumed.

The Review Group consider that the eligible patient numbers may be higher. In line with PACIFIC, the Applicant's estimate assumes that all eligible patients will have completed at least two cycles of platinum-based chemo-radiation therapy. Also that all patients would

commence cycle one of durvalumab within 42 days of completing chemo-radiation therapy. These are not requirements of the license; the Review Group removed these. The Review Group assume no vial sharing. A gross budget impact of €7.37 million in year one, increasing to €10.04 million in year five is estimated; 5-year impact of about €47.95 million. A net budget impact of €7.37 million in year one, decreasing to €5.55 million in year five is estimated; five-year cumulative impact of about €30.58 million.

The Applicant provided scenarios that assumed that some patients who relapse following best supportive care would be eligible for pembrolizumab (with chemotherapy). In line with current NCCP Regimens (which allow only one course of treatment with a PD-1 or PD-L1 targeted treatment) it was assumed that patients who relapse following durvalumab would not would be eligible for pembrolizumab (with chemotherapy). The Review Group consider these scenarios to be of limited value given that pembrolizumab (with chemotherapy) is not currently reimbursed in Ireland for this setting.

5. Patient submissions

No patient submissions were received during the course of this appraisal.

6. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that durvalumab (Imfinzi®) be considered for reimbursement if 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.