NCPE Assessment

Technical Summary

Durvalumab (Imfinzi®)

HTA ID:23009

December 2024

Applicant: AstraZeneca

Durvalumab in combination with gemcitabine and cisplatin for the first-line treatment of adults with unresectable or metastatic biliary tract cancer.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of durvalumab (Imfinzi®) in combination with gemcitabine and cisplatin for the first-line treatment of adults with unresectable or metastatic biliary tract cancer.

Following assessment of the Applicant's submission, the NCPE recommends that durvalumab (Imfinzi®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca) Health Technology Assessment of durvalumab (Imfinzi®). 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.

Summary

In September 2023, the Applicant (AstraZeneca) submitted a dossier investigating the clinical effectiveness, cost-effectiveness, and budget impact of durvalumab (Imfinzi®) in combination with GemCis (gemcitabine and cisplatin) for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). The Applicant is seeking reimbursement for durvalumab, for this indication, under the Oncology Drug Management Scheme.

Durvalumab is a humanised monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) with programmed cell death protein 1 (PD1) and CD80 on the surface of tumour cells. This blockade enhances anti-tumour responses and increases T-cell activation. The recommended dose of durvalumab is 1,500mg, administered via intravenous infusion, in combination with GemCis on the first day of a three-week cycle for up to eight treatment cycles; followed by 1,500mg durvalumab monotherapy once every four weeks. It is recommended that patients receive durvalumab monotherapy until disease progression or unacceptable toxicity occurs.

The Applicant anticipates that durvalumab plus GemCis will be used according to its licensed indication (as stated above). In line with current standard of care in Ireland, the comparator is GemCis.

1. Comparative effectiveness of durvalumab

The clinical evidence supporting the regulatory approval of durvalumab plus GemCis comes from the TOPAZ-1 trial. TOPAZ-1 is a phase III, double blind, placebo-controlled trial designed to evaluate the safety and efficacy of durvalumab plus GemCis (N=341) versus placebo plus GemCis (N=344). Eligible patients were adults with unresectable advanced or metastatic BTC. The primary endpoint was overall survival (OS), with progression-free survival (PFS) measured as a key secondary endpoint.

Three data cuts were planned: a first interim analysis (IA-1), a second interim analysis (IA-2) and a final analysis. Statistical significance for the primary endpoint of OS was reached at the IA-2 analysis, providing the final, formal statistical analysis for both OS and PFS. Median follow-up at IA2 was 16.8 months for durvalumab plus GemCis and 15.9 months for placebo

plus GemCis. Two further exploratory OS analyses have been conducted, providing approximately 6.5 months and 26.9 months of additional follow-up since IA-2. The TOPAZ-1 trial is ongoing, allowing for further exploratory follow-up analyses of OS. PFS was not assessed again after IA-2.

At IA2, median OS was 12.8 months with durvalumab plus GemCis and 11.5 months with placebo plus GemCis; hazard ratio (HR) of 0.80 (95% confidence interval (CI) 0.64 to 0.99). Median PFS was 7.2 months with durvalumab plus GemCis and 5.7 months with placebo plus GemCis; HR of 0.75 (95% CI 0.63 to 0.89). At the 26.9- month update, the median OS was 12.9 months with durvalumab plus GemCis compared to 11.3 months with placebo plus GemCis; HR of 0.74 (95% CI 0.63 to 0.87).

Limitations of the evidence from the TOPAZ-1 trial include the over-representation of Asian patients in the trial population, and the modest treatment effects observed with durvalumab plus GemCis. An imbalance in the proportion of patients receiving subsequent immunotherapy treatment may also confound assessment of OS.

2. Safety of durvalumab

Overall, the safety data from the TOPAZ-1 trial were consistent with the known safety profiles of durvalumab, gemcitabine, and cisplatin. Any grade adverse events (AEs) were reported in 99.4% of patients receiving durvalumab plus GemCis and 98% of those receiving placebo plus GemCis. Generally, AEs were reported at a similar frequency between treatment arms.

The most common grade 3+ AEs with durvalumab plus GemCis were anaemia, decreased neutrophil count, neutropenia, decreased platelet count, and cholangitis. Only cholangitis was observed in a significantly higher proportion of patients receiving durvalumab plus GemCis (6.5%) compared to those receiving placebo plus GemCis (3.2%). The durvalumab SmPC includes disease-specific precautions for BTC, including cholangitis and biliary tract infections.

3. Cost effectiveness of durvalumab

Methods

The Applicant submitted a cost-utility analysis using a partitioned survival model developed

in Microsoft Excel®. The model included three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death. The model assumed a cycle length of one week and a lifetime horizon, with a half-cycle correction applied. Spline-based models were used to extrapolate PFS and OS data from the TOPAZ-1 trial, and treatment arms were extrapolated separately.

The short duration of follow-up relative to the model time horizon results in considerable uncertainty in the survival extrapolations derived from the TOPAZ-1 trial. The choice of survival distribution for OS is a major driver of cost-effectiveness. The Review Group considered that the Applicant's OS curve selection produced unrealistically high long-term survival predictions, and preferred the use of an alternative curve which provided an acceptable fit to both the observed data and external data, and was more clinically plausible. The Review Group also had concerns regarding the maintenance of treatment effect of durvalumab for the model time horizon. There is a very high level of maturity in the available outcome data from the TOPAZ trial, which does not indicate a waning of treatment effect. However, a significant proportion of surviving patients were still receiving treatment by the end of follow-up. The Review Group therefore conducted a scenario analysis assuming treatment effect waning.

Health-related quality of life utility estimates for the PF and PD health states were informed by TOPAZ-1. There is a degree of uncertainty in the PD utility estimate due to the low number of observations obtained from patients with progressed disease in TOPAZ-1. The cost-effectiveness model is sensitive to the utility used in the PD health state. Health state utility values were adjusted for age, and disutilities were included for AEs.

Direct medical costs were included for drug acquisition (including administration), disease management, subsequent treatments and AEs. A one-time end-of-life cost was applied. Irish costs were applied where available. The Review Group had concerns with the use of PFS data to estimate treatment duration for durvalumab in the model. The Review Group considered it more appropriate to use time to treatment discontinuation (TTD) data from TOPAZ-1 to estimate treatment duration, given that the clinical efficacy estimates were based on treatment duration from TOPAZ-1.

Results

Due to uncertainty in the assumptions used in the submitted cost-effectiveness model, the Review Group made several changes to the Applicant's base case, based on more plausible alternative assumptions in an NCPE-adjusted base case. These included selecting an alternative survival distribution for OS and using TTD from the TOPAZ-1 trial to estimate durvalumab treatment duration. The cost-effectiveness results arising from the Applicant's and the NCPE-adjusted base-case analyses are presented in Table 1.

Table 1: Incremental cost -effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analysis[b]					
Durvalumab + GemCis	134,925	1.34			
GemCis	48,235	0.89	86,690	0.45	191,957
NCPE-adjusted analysis[c]					
Durvalumab + GemCis	156,599	1.21			
GemCis	48,318	0.88	108,281	0.33	330,331

GemCis: gemcitabine + cisplatin; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality adjusted life year

[a] A commercial-in-confidence patient access scheme is in place for durvalumab, not included in this table

[b] Corresponding probabilistic ICER using 1,000 iterations = €202,274/QALY

[c] Corresponding probabilistic ICER using 1,000 iterations = €327,117/QALY

Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analysis

Sensitivity analyses indicated that the main drivers of cost-effectiveness related to the survival distribution for OS, the choice of PFS or TTD to estimate durvalumab treatment duration, the application of a treatment-effect waning, and the health-related quality of life utility in the PD health state. The application of a treatment waning effect increased the NCPE-adjusted base case ICER to €361,258 per QALY.

A price-ICER analysis, under the NCPE-adjusted base case assumptions, indicated that a reduction of approximately 92.9% in the price-to-wholesaler (PtW) of durvalumab would be required to meet the €45,000 per QALY threshold. Cost-effectiveness at the €20,000 per QALY threshold could not be achieved at any discount.

4. Budget impact of durvalumab

The PtW of durvalumab is €2,481.71 for a 500mg vial. The estimated total cost to the HSE per patient per treatment course for durvalumab plus GemCis is €140,324 (including VAT),

assuming a mean treatment duration for durvalumab, of 16.33 cycles, based on TTD derived from the cost-effectiveness model. The Applicant used several sources to inform the eligible patient estimates, including National Cancer Registry of Ireland (NCRI) data, the published literature, and clinical opinion. Many of the inputs are uncertain, leading to considerable uncertainty associated with budget impact estimates. The Applicant estimated that 458 patients will receive treatment over five years. The five-year cumulative net drug budget impact for durvalumab was estimated by the Applicant to be €37.9 million (including VAT). The NCPE estimated a five-year cumulative net drug budget impact, based on a more plausible treatment duration, of €47.7 million (including VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that durvalumab not be considered for reimbursement (for the indication under assessment) 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.