NCPE Assessment

Technical Summary

Tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®)

23073

11 July 2025

Applicant: AstraZeneca

Tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®) for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®).

Following assessment of the Applicant's submission, the NCPE recommends that tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®) not be considered for reimbursement*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca) Health Technology Assessment of tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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 July 2024, AstraZeneca submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®) for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). AstraZeneca is seeking reimbursement of tremelimumab in combination with durvalumab on the Oncology Drug Management System. Tremelimumab, a CTLA-4 inhibitor and durvalumab, a PD-L1 inhibitor, target T-cells to produce an antitumour immune response. The dual immunotherapy regimen of tremelimumab in combination with durvalumab is known as STRIDE (single tremelimumab regular interval durvalumab). Both tremelimumab and durvalumab are administered as intravenous (IV) infusions. Tremelimumab is administered as a single dose of 300mg in combination with durvalumab at a dose of 1,500mg on Day 1 of Cycle 1, followed by durvalumab monotherapy at a dose of 1,500mg every four weeks thereafter. Although durvalumab is licensed until disease progression or unacceptable toxicity, some participants in the pivotal trial continued durvalumab beyond disease progression.

HCC is the most common type of primary liver cancer with the majority of patients diagnosed with advanced disease. STRIDE is positioned as a first-line treatment option for advanced or unresectable HCC. The current standard of care in this indication is atezolizumab in combination with bevacizumab. Currently in Irish clinical practice, patients with a contraindication to atezolizumab in combination with bevacizumab, for example due to bleeding risk or autoimmune disease, receive first-line treatment with either lenvatinib or sorafenib, although sorafenib use is limited.

1. Comparative effectiveness of tremelimumab in combination with durvalumab

The efficacy and safety data for STRIDE are from the ongoing randomised, open-label, phase three, HIMALAYA trial which provided direct comparative evidence for STRIDE versus sorafenib. Participants with unresectable HCC who were ineligible for locoregional therapy and had not received prior systemic therapy for HCC were enrolled. The primary endpoint was overall survival (OS). Progression free survival (PFS) by investigator was one of the key secondary endpoints. At the primary analysis (data cut-off date 27 August 2021), STRIDE

showed a statistically significant and clinically relevant improvement in OS of 2.66 months compared with sorafenib; Hazard Ratio (HR) of 0.78 (95% Confidence Interval (CI); 0.66 to 0.92). The OS benefit of STRIDE versus sorafenib was maintained across a number of subgroup analyses. No clinically or statistically significant improvement in PFS by investigator was demonstrated. At both the January 2023 data-cut off (DCO) and the March 2024 DCO, the OS benefit was consistent with the primary analysis; HR 0.78 (95% CI: 0.67 to 0.92) at the January 2023 data-cut and HR 0.76 (95% CI: 0.65 to 0.89) at the March 2024 data-cut. The Review Group noted a number of limitations of the clinical trial evidence including the open-label nature of the trial, which may bias investigator-assessed outcomes and uncertainty regarding the optimal treatment duration of treatment with durvalumab.

Due to the lack of direct comparative evidence for STRIDE versus the other comparators of interest, indirect treatment comparisons (ITCs) using matched adjusted indirect comparisons (MAICs) were conducted by the Applicant. The MAIC of STRIDE versus atezolizumab in combination with bevacizumab was performed using data from IMbrave 150; the MAIC of STRIDE versus lenvatinib was performed using data from REFLECT. Both MAICs utilised data from the primary analysis of HIMALAYA (DCO: 27 August 2021). The OS MAIC (STRIDE versus atezolizumab in combination with bevacizumab) indicated a point estimate in favour of atezolizumab in combination with bevacizumab (HR 1.09, 95% CI 0.80 to 1.48). The PFS MAIC (STRIDE versus atezolizumab in combination with bevacizumab) indicated a PFS benefit for atezolizumab in combination with bevacizumab (HR 1.73, 95% CI 1.30 to 2.32). The OS MAIC (STRIDE versus lenvatinib) indicated an OS benefit for STRIDE (HR 0.79, 95% CI 0.66 to 0.96); the PFS MAIC indicated a PFS benefit for lenvatinib (HR 1.32, 95% CI 1.05 to 1.67). Results of sensitivity analyses, computed by the Review Group using standard Bucher comparisons were broadly aligned with those of the MAIC. The Applicant declined to update the MAICs for OS with the latest DCO (01 March 2024) which is considered a limitation of the MAIC.

2. Safety of tremelimumab in combination with durvalumab

The proportion of participants who experienced at least one adverse event (AE) and the proportion of participants who experienced grade three or four AEs were similar between the STRIDE and the sorafenib treatment arms in the HIMALAYA trial. Based on the updated

analysis (DCO: 23 January 2023), serious treatment-related AEs occurred in 17.5% of participants treated with STRIDE. The most common grade three or four treatment-related AEs in the STRIDE arm were lipase increase (4.4%), diarrhoea (3.4%), amylase increased (2.6%) and aspartate aminotransferase increased (2.3%). Immune-mediated AEs occurred more frequently in the STRIDE arm compared to the sorafenib arm (10.3% vs 1.1%) and included pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and rash. However, immune-mediated AEs are considered manageable. The toxicity profile of STRIDE is not considered worse than that of sorafenib

3. Cost effectiveness of tremelimumab in combination with durvalumab

Methods

A partitioned survival model included three mutually-exclusive health states; progression-free, progressed disease and death. The treatment effects captured by the model were the delay of disease progression and death. OS and PFS for STRIDE and sorafenib are modelled using treatment group-specific parametric distributions fitted to time-to-event data from the HIMALAYA trial. To model OS and PFS for atezolizumab in combination with bevacizumab and for lenvatinib, HRs derived from the Applicant's MAIC were applied to the baseline hazard from the STRIDE arm. The Review Group agreed that the choice of a MAIC was appropriate for these comparators.

The Applicant chose the generalised gamma distribution to extrapolate OS and PFS data from the HIMALAYA trial. The Review Group broadly agreed with the selection of the generalised gamma for OS extrapolation. For the extrapolation for PFS, the Review Group considered the log-normal distribution for both arms to be a better choice, as PFS predictions using this distribution were in line with clinical opinion and more appropriate with regards the relative treatment benefit assumed over time.

EQ-5D-5L data, mapped to EQ-5D-3L utility index scores, collected in the HIMALAYA trial were used to inform health-state utility values in the cost-effectiveness analysis. The Review Group considered that there was insufficient evidence to justify the addition of treatment regimen as a covariate in the utility model. Health-state utility values based on progression status alone were used in the NCPE adjusted base case.

The Review Group noted a number of limitations to the Applicant's base case, which were addressed, via changes, to develop the NCPE-adjusted base case. These included updating the price-to-wholesaler of lenvatinib, using the log-normal distribution instead of generalised gamma to model PFS for the STRIDE and sorafenib arms, using progression status only to model health state utility values and changing the time-on-treatment assumptions for atezolizumab in combination with bevacizumab and lenvatinib, respectively.

Results

The results of the Applicant and NCPE-adjusted base case incremental cost-effectiveness analysis are presented in Tables 1 and 2, respectively.

Table 1: Applicant base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Pairwise comparison of STRIDE[d] versus atezolizumab[d] in combination with bevacizumab [a]					
Atezolizumab + bevacizumab	382,774	2.63	-	-	-
STRIDE	207,178	2.37	-175,597	-0.27	Less costly, less effective
Pairwise comparison of STRIDE[d] versus sorafenib[b]					
Sorafenib	91,086	1.46			
STRIDE	207,178	2.37	116,091	0.91	127,256
Pairwise comparison of STRIDE[d] versus lenvatinib[c,d]					
Lenvatinib	158,076	1.62			
STRIDE	207,178	2.37	49,102	0.75	65,658

ICER: incremental cost-effectiveness ratio; **QALY**: Quality-adjusted life year; **STRIDE**: Single tremelimumab regular interval durvalumab; **WTP**: willingness to pay

[a] Corresponding probabilistic ICER using 5,000 iterations =less costly, less effective (incremental costs: -€157,141.95; incremental QALYs -0.30). Figures in the table are rounded, and so calculations may not be directly replicable

[b] Corresponding probabilistic ICER using 5,000 iterations =€126,797/QALY. Figures in the table are rounded, and so calculations may not be directly replicable.

[c] Corresponding probabilistic ICER using 5,000 iterations =€70,463/QALY. Figures in the table are rounded, and so calculations may not be directly replicable.

[d] A commercial in confidence PAS is in place for atezolizumab and lenvatinib, not considered in this table. A commercial in confidence PAS is offered for durvalumab, not considered in this table.

[e] The Incremental Net Monetary Benefit is the value added by an intervention over a comparator, conditional on the willingness to pay threshold for an added QALY. A positive net monetary benefit indicates that value is added by the intervention at a specific threshold, however it should be noted that value can be added in spite of poorer health outcomes if costs are sufficiently reduced.

Table 2: NCPE adjusted base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Pairwise comparison of STRIDE[d] versus atezolizumab[d] in combination with bevacizumab [a]					
Atezolizumab + bevacizumab	209,682	2.61	-	-	-
STRIDE	209,422	2.34	-260	-0.26	Less costly, less effective
Pairwise comparison of STRIDE[d] versus sorafenib[b]					

Sorafenib	90,933	1.51	-	-	-
STRIDE	209,422	2.34	118,488	0.83	142,626
Pairwise comparison of STRIDE[d] versus lenvatinib[c,d]					
Lenvatinib	113,124	1.72	-	-	-
STRIDE	209,422	2.34	96,297	0.63	153,739

ICER: incremental cost-effectiveness ratio; **QALY**: Quality-adjusted life year; **STRIDE:** Single tremelimumab regular interval durvalumab; **WTP:** willingness to pay

[a] Corresponding probabilistic ICER using 5,000 iterations =less costly, less effective (incremental costs -€397, incremental QALYS -0.30). Figures in the table are rounded, and so calculations may not be directly replicable

[b] Corresponding probabilistic ICER using 5,000 iterations =€144,545/QALY. Figures in the table are rounded, and so calculations may not be directly replicable.

[c] Corresponding probabilistic ICER using 5,000 iterations =€157,514/QALY. Figures in the table are rounded, and so calculations may not be directly replicable.

[d] A commercial in confidence PAS is in place for atezolizumab and lenvatinib, not considered in this table. A commercial in confidence PAS is offered for durvalumab, not considered in this table.

[e] The Incremental Net Monetary Benefit is the value added by an intervention over a comparator, conditional on the willingness to pay threshold for an added QALY. A negative net monetary benefit indicates that the intervention is not cost-effective at a specific threshold, however it should be noted that value can be added in spite of poorer health outcomes if costs are sufficiently reduced.

Sensitivity analysis

The probability of cost-effectiveness in the Applicant and NCPE-adjusted base cases for sorafenib and lenvatinib are shown in Table 3. The Review Group do not present the probability of cost effectiveness for STRIDE versus atezolizumab in combination with bevacizumab as most samples for this comparison indicate that STRIDE is less costly and less effective than atezolizumab in combination with bevacizumab.

Table 1: Probability of cost effectiveness

	STRIDE vs sorafenib		**STRIDE vs lenvatinib**	
Threshold (€/QALY)	Applicant base case (%)	NCPE adjusted based case (%)	Applicant base case (%)	NCPE adjusted base case (%)
20,000	0	0	2.18	0.08
45,000	0.36	0.14	10.94	0.38

STRIDE: Single tremelimumab regular interval durvalumab; **QALY**: Quality-adjusted life year; **vs**: versus

[a] Results based on probabilistic analysis using 5,000 iterations. Note only iterations with ICER between 0 and the threshold which also had positive incremental QALYs associated with them were considered cost effective.

Results of a price-ICER analysis, conducted using the NCPE-adjusted base case for sorafenib and lenvatinib are shown in Table 4. A Price-ICER analysis for the comparison of STRIDE with atezolizumab in combination with bevacizumab was not conducted as STRIDE was less effective when compared with atezolizumab in combination with bevacizumab.

Table 4: Results of Price-ICER analysis

	STRIDE vs sorafenib	**STRIDE vs lenvatinib**
Threshold (€/QALY)	Percent reduction [a] in durvalumab PtW (%)	Percent reduction [a] in durvalumab PtW (%)
20,000	N/A[b]	92.99

45,000	90.32	77.29

ICER: incremental cost-effectiveness ratio; **N/A:** not applicable; **PtW:** price to wholesaler; **STRIDE:** Single tremelimumab regular interval durvalumab; **QALY**: Quality-adjusted life year; **vs**: versus

[a] Expressed as a total rebate (inclusive of the Framework Agreement Rebate)

[b] Not possible to be reached due to the cost of tremelimumab

4. Budget impact of tremelimumab in combination with durvalumab

The price-to-wholesaler (PtW) of one 300mg vial of tremelimumab is €20,000, while the PtW of one 500mg vial of durvalumab is €2,465.08. Per-patient, treatment course costs for STRIDE are estimated to be €141,924 (including VAT) which is based on a mean treatment duration of durvalumab of 14.13 x four-week-cycles (56.52 weeks), estimated from the cost effectiveness model (CEM).

The estimated eligible patient population is uncertain. The Review Group were unable to validate a number of assumptions made by the Applicant in estimating the eligible population. The Applicant estimated that five patients will be treated with STRIDE in Year one, increasing to 23 patients in Year five. The Review Group considered the Applicant's anticipated market share for STRIDE to be underestimated based on clinical opinion to both the Review Group and the Applicant.

The Applicant's Budget Impact Model (BIM) considered atezolizumab in combination with bevacizumab as the only comparator and did not capture the potential impact of STRIDE displacing lenvatinib and sorafenib monotherapies (estimated as having a combined market share of approximately 20% currently). As a result, the Review Group considered that the cost of the comparator was likely overestimated and the resulting net drug-budget impact was likely underestimated in the Applicant's BIM.

The Review Group updated the mean treatment duration of STRIDE to align with assumptions in the CEM. The Review Group estimated that the five-year cumulative gross drug budget impact of STRIDE will be €11.04 million (including VAT). The cumulative five-year net drug budget impact of STRIDE was estimated to be €898,618 (including VAT). Budget impact estimates are highly uncertain and likely underestimated.

5. Patient Organisation Submission

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

6. Conclusion

The NCPE recommends that tremelimumab in combination with durvalumab (STRIDE) not be considered for reimbursement*.

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