Durvalumab with tremelimumab for treating untreated advanced or unresectable hepatocellular carcinoma

For screen - contains redacted CON information

Technology appraisal committee C [9 April 2025]

Chair: Prof Stephen O'Brien

External assessment group: Birmingham Centre for Evidence and Implementation Science (BCEIS)

Technical team: Chris Shah, Kirsty Pitt, Alexandra Sampson, Elizabeth Bell

Company: AstraZeneca

Durvalumab (Imfinzi, AstraZeneca UK) with tremelimumab (IMJUDO, AstraZeneca UK)

Marketing authorisation	• Durvalumab in combination with tremelimumab (STRIDE) is indicated for the first line treatment of adults with advanced or unresectable HCC • Received marketing authorisation from MHRA in June 2023
Mechanism of action	• Durvalumab is a humanised IgG monoclonal antibody that inhibits the PD-L1 checkpoint protein. PD-L1 blocks T-cell function and is upregulated in HCC. Through binding to PD-L1, durvalumab allows the cytotoxic T-cell response against PD-L1-expressing tumour cells. • Tremelimumab is a selective, fully human IgG2 antibody that enhances T-cell activation increasing T-cell diversity and activity • In combination with tremelimumab, durvalumab has an improved anti-tumour response

Cost 1st month = £28,652*

Ongoing monthly cost = £8,042 per month*

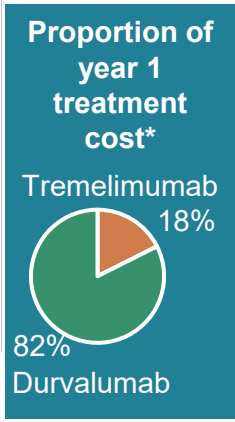
Total year 1 cost = £117,114*

Weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52	Ongoing
Durvalumab (1,500mg IV infusion)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Tremelimumab (300mg IV infusion)	✓														

*Based on list prices. A patient access scheme is in place for durvalumab.
Durvalumab: £592.00 per 2.4 ml vial (120 mg) or £2,466.00 per 10 ml vial (500 mg)
Tremelimumab: £20,610.00 per 15 ml vial (300mg)

✓ = treatment administered to patient

Median time on treatment = [redacted] months [redacted]Ŧ



NICE

Ŧ Data from HIMALAYA trial

Abbreviations: HCC, hepatocellular carcinoma; IgG, Immunoglobulin G; IV, intravenous PD-L1, programmed death-ligand 1

ACM 1 recap

NICE National Institute for Health and Care Excellence

Recap from ACM 1

Preliminary decision

- Durvalumab plus tremelimumab should not be used for untreated advanced or unresectable hepatocellular carcinoma (HCC) in adults.

Link to background on HCC .

Link to background on clinical perspective .

Abbreviations: HCC, hepatocellular carcinoma

Committee's conclusions at ACM 1 [1]

DG section	Committee's conclusion
3.2 Current treatment	Atezolizumab plus bevacizumab is most used treatment in this population. Lenvatinib and sorafenib used by a minority where atezolizumab plus bevacizumab is not suitable.
3.3 Unmet need	STRIDE particularly useful option where atezolizumab plus bevacizumab is unsuitable.
3.5 Clinical effectiveness	Potential bias from open-label nature of HIMALAYA, but STRIDE is an effective treatment.
3.6 Network meta-analysis	• Company NMA results similar to the EAG-preferred NMA results, except PFS hazard ratio for atezolizumab plus bevacizumab compared with sorafenib. • BICR PFS preferred as outcome measure over INV PFS. • EAG NMA (Vogel et al.) preferred vs. company NMA. But NMA is key area of uncertainty.
3.7 Modelling approaches for OS and PFS	• Limitations to company and EAG modelling of OS and PFS. • Not satisfied with clinical plausibility of crossing OS curves for STRIDE and atez+bev. • Requested updated OS modelling with equal hazard rate functions from point where atez+bev and STRIDE curves cross. • Generalised gamma preferred over 1-knot hazard curve for modelling OS with sorafenib.

Abbreviations: ACM, appraisal committee meeting; BICR, blinded independent central review; DG, draft guidance; EAG, external assessment group; HCC, hepatocellular carcinoma; INV, investigator-assessed; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Committee's conclusions at ACM 1 [2]

DG section	Committee's conclusion
3.8 Modelling time to treatment discontinuation	• Assuming equality between PFS and TTD for atez+bev would likely underestimate ICERs for STRIDE, but TTD data not available for atez+bev. • Consistent approach preferred, so PFS should be assumed equivalent to TTD for all treatments.
3.9 Retreatment with tremelimumab	• Requested cost-effectiveness results adjusted to include additional costs of retreatment with tremelimumab. • Retreatment with tremelimumab not in MA, but minority had retreatment in HIMALAYA.
3.11 Utility values	• Time-dependent utility values preferred to reflect declining utility as disease progresses.
3.12 Severity	• No modifier applies when STRIDE compared pairwise with atez+bev. • No conclusion reached on whether a severity modifier should be applied for comparisons between STRIDE and lenvatinib or sorafenib.
3.13 Acceptable ICER	• £30,000 per QALY gained

Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year TTD, time to treatment discontinuation

Consultation comments

NICE National Institute for Health and Care Excellence

British Liver Trust

Concerned about consequences of a negative recommendation, particularly for people with varices

Key themes: addressing unmet needs, freeing up patient time, and providing hope to patients

- STRIDE addresses unmet need for people with varices; doesn't carry same bleeding risk as other therapies.
- Provides access to immunotherapy for people who otherwise wouldn't be eligible due to co-morbidities.
- Liver disease and liver cancer disproportionally affect poorest in society. Also, HCC patients are often young and must balance hospital appointments with work and family life.
    - BLT said extra time is of particular importance. Since STRIDE does not require an endoscopy before treatment and requires less frequent infusions compared with atezolizumab plus bevacizumab, it may free up patient time and money for travel to appointments.
- Increasing the number of available treatment options can give patients hope and positively impact their QoL.
- HIMALAYA is the most mature survival data available in HCC.

Abbreviations: BLT, British Liver Trust; HCC, hepatocellular carcinoma; QoL, quality of life

Company response: Committee's preferred assumptions

DG section	Committee's preferred assumptions at ACM 1 (section 3.15)	Implemented in company base case?	For discussion?
3.6	Use hazard ratios from Vogel NMA	No – company base case retains company NMA	Yes
3.7	Use generalised gamma for sorafenib OS extrapolation	No – hazard 1-knot model retained in revised company base case	Yes
3.8	Assume TTD is equivalent to PFS for all treatments	No – alternative scenario provided	Yes
3.11	Use a time-dependent approach for utilities	Yes	No
3.10	Use a 40-year time horizon	Yes	No

Abbreviations: : ACM, appraisal committee meeting; DG, draft guidance; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Company response: Committee requests for additional analyses

DG section	Committee's requests for additional analyses (section 3.16)	Provided by company in response to DG?	For discussion?
3.7	Updated OS modelling that has equal hazard rate functions from the time point at which atezolizumab plus bevacizumab and STRIDE curves cross	Alternative analysis provided	Yes
3.9	Updated cost-effectiveness estimates that include the additional costs for retreatment of tremelimumab	Scenario provided	Yes

Abbreviations: DG, draft guidance; OS, overall survival

Key issues to discuss

Key issue	Issue	ICER impact
1	Appropriate comparator(s)	Large
2	Network meta-analysis	Large
3	Modelling approaches to OS	Large
4	Severity modifier	Small

Other issues with small ICER impact:

a) Modelling time to treatment discontinuation

b) Including additional costs of tremelimumab retreatment

Abbreviations: ICER, incremental cost - effectiveness ratio; OS, overall survival

Key issue 1: Appropriate comparator

Large ICER impact

Treatment pathway and company positioning STRIDE for 1L treatment of HCC

Hepatocellular carcinoma

Stage 0 Very early	Stage A Early	Stage B Intermediate Child-Pugh Class A/B ECOG PS 0	Stage C Advanced Child-Pugh Class A/B ECOG PS 1 to 2	Stage D End stage Child-Pugh Class A/B ECOG PS 3 to 4
		People with intermediate disease who are ineligible for locoregional therapy		BSC

	Market share 1L HCC treatment*
Atezolizumab + bevacizumab	69%
Durvalumab + tremelimumab	
Sorafenib	15%
Lenvatinib	16%

*Source: NHSE CDF lead

Clinical opinion suggests "both are less effective than atez+bev" and used only when atez+bev is contraindicated.

- What are the appropriate comparator(s) for STRIDE?
  - Impacts decision making for severity and pairwise vs incremental

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Abbreviations: 1L; first-line; atez+bev, atezolizumab plus bevacizumab; BSC, Best supportive care; CDF, Cancer Drugs Fund; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; NHSE, NHS England; PS, Performance status

Key issue 2: Methods for conducting NMA

Large ICER impact

	Committee preference at ACM1	Company base case at ACM2	EAG base case at ACM2
Base case	Vogel et al NMA	Company NMA	Vogel et al NMA

Rationale	• Vogel et al NMA used BICR PFS which is preferred by committee as an outcome measure to INV PFS.	• Company NMA used most recent 5-year follow-up data for OS from HIMALAYA.
		• Company NMA used INV PFS as it was consistently collected across studies:
		• Not clear if Vogel used INV or BICR PFS
		• Committee and authors of Vogel et al did not identify or comment on the limitations of differences in BICR PFS
			• Retain previous response
			  • Concerns about methodology of Company NMA due to 'outlier' PFS hazard ratio for atez+bev.
			  • This could be because the company NMA used INV PFS rather than BICR PFS.

	HIMALAYA	REFLECT
INV PFS	Secondary endpoint	Secondary endpoint
BICR PFS	Exploratory endpoint at interim analysis (32wk f/u)	Post-hoc analysis

Does the committee still prefer the NMA previously published by Vogel et al to the company NMA?

Abbreviations: BICR, blinded independent central review; EAG, external assessment group; F/U, follow-up; HR, hazard ratio; ITC, indirect treatment comparison; INV, investigator assessed; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Company and Vogel et al NMA results

- No statistically significant differences observed between treatments in both NMAs

	Company NMA HR vs Sorafenib*	Vogel et al NMA HR vs Sorafenib*
Overall survival		
STRIDE	[redacted]	0.78
Atez+bev	[redacted]	0.68
Lenvatinib	[redacted]	0.92
Progression-free survival		
STRIDE	[redacted]	0.90
Atez+bev	[redacted]	0.66
Lenvatinib	[redacted]	0.65

Considered an outlier by EAG

Abbreviations: Atez+bev, atezolizumab plus bevacizumab; EAG, external assessment group; HR, hazard ratio; NMA, network meta-analysis

Key issue 3: Modelling approaches to OS (1/2)

Large ICER impact

Recap from ACM 1 (see DG section 3.7)

	Company*	EAG*
Sorafenib	OS using HIMALAYA IPD (Hazard 1 knot curve)	Curve fitted to HIMALAYA IPD for sorafenib (gen. gamma)
STRIDE	OS using HIMALAYA IPD (Normal 1 knot curve)	Vogel NMA HRs
Atez+bev	NMA HRs applied to spline model for sorafenib	Vogel NMA HRs
Lenvatinib	NMA HRs applied to spline model for sorafenib	Vogel NMA HRs

Committee conclusion

- Limitations to company and EAG approaches
- Not satisfied with crossing of STRIDE and atez+bev OS curves (see extrapolations).
- Requested further analysis using equal hazard rate functions from point where curves cross

Company maintained approach in ACM 2 base case, justifying:

- PH assumption considered to hold for atez+bev vs sorafenib.
- Clinical experts in ACM 1 considered durable treatment effect for STRIDE plausible given MoA of tremelimumab. Same conclusion was drawn about IMBrave150 OS data in TA666 (atez+bev in HCC).
- Scenario analysis requested by committee is highly conservative and inflates long-term benefit of atez+bev; not supported by data or clinical opinion.
- Did provide analysis that implements equal hazard functions for OS from start of model, since STRIDE and atez+bev OS initially cross at week 3. Incremental QALYs in this scenario are zero.

*Note: Company and EAG used same approach for PFS as OS

Abbreviations: ACM, appraisal committee meeting; Atez+bev, atezolizumab plus bevacizumab; DG, draft guidance; DSU, Decision Support Unit; EAG, external assessment group; HCC, hepatocellular carcinoma; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; MoA, mechanism of action; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; QALY, quality-adjusted life year; TA, technology appraisal

Base case OS parametric survival extrapolations

Company base case

EAG base case

NICE Technical Team

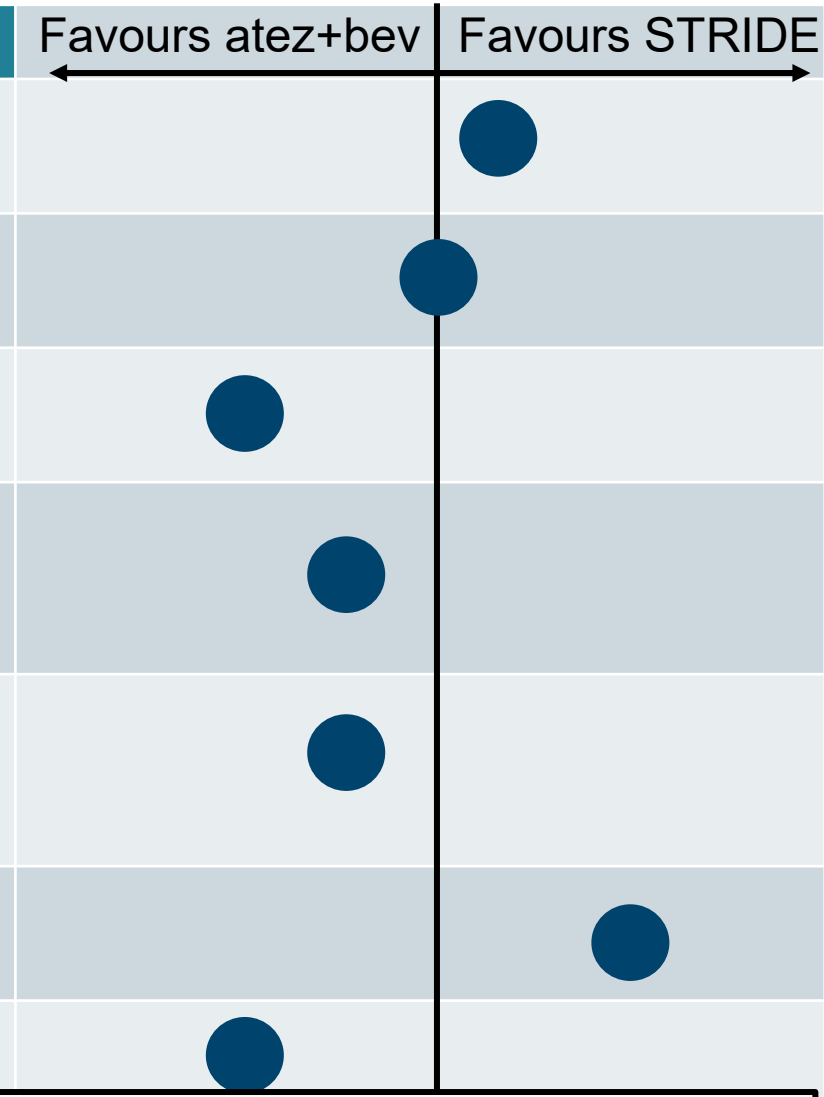
- Note that EAG durvalumab plus tremelimumab OS curve does not appear to fit KM curve well

Abbreviations: Atez+bev , atezolizumab plus bevacizumab; HR, hazard ratio; KM, Kaplan -Meier; OS, overall survival

Key issue 3: Modelling approaches to OS

Large ICER impact

	Modelling approach*		Direction of effect on inc. QALYs
	Atez + bev	**STRIDE**	Favours atez+bev / Favours STRIDE
Company base case	Company NMA HRs vs sorafenib	HIMALAYA	
Company scenario (equal OS)	OS equal to STRIDE OS from start of model	HIMALAYA	
EAG base case	EAG (Vogel) NMA HR vs sorafenib	EAG (Vogel) NMA HR vs sorafenib	
EAG scenario (equal OS from crossing of atez+bev and STRIDE curves)	OS curve equal to STRIDE OS curve from point of crossing	HIMALAYA	
EAG scenario (equal OS from crossing of atez+bev and STRIDE curves)	Vogel et al NMA HR vs sorafenib	OS curve equal to atez+bev OS curve from point of crossing	
EAG scenario (company approach but Vogel NMA)	Vogel et al NMA HR vs sorafenib	HIMALAYA	
EAG scenario (assume PH assumption holds)	Company NMA HR vs STRIDE	HIMALAYA	



What is committee's preferred approach to modelling OS?

*Note: Focus on comparison with atez+bev because of ICER impact

Abbreviations: Atez+bev, atezolizumab plus bevacizumab; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; QALY, quality-adjusted life year

Small ICER impact

Issue 3a: Approach to parametric extrapolation for sorafenib

	Company	EAG
Recap (see DG section 3.7)	Applied 1-knot hazard curve to sorafenib OS curve	Preferred generalised gamma
	→ Committee preferred EAG approach	
Rationale and DG response	• Followed DSU guidance and sought external clinical expert validation. • 1:1 interviews with 7 UK clinical experts: advised that most clinically plausible scenario predicted lowest survival expectations (hazard 1-knot), noting that all extrapolations may overestimate survival for sorafenib. • EAG rationale for preferring generalised gamma is unclear, so company retained hazard 1-knot model in revised base case.	• Reconstructed OS KM data from Rimassa et al and fitted several parametric models. • Selected generalised gamma as most appropriate model following DSU guidance. • Generalised gamma model produced similar results to the company's hazard 1-knot model.
	→ Both models provide very similar extrapolations	

Abbreviations: DG, draft guidance; DSU, Decision Support Unit; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; KM, Kaplan-Meier; UK, United Kingdom

Does committee still prefer EAG approach to parametric extrapolation for sorafenib?

Key issue 4: Severity modifier

Small ICER impact

Recap (see DG section 3.12)

Scenario	Company	EAG	Committee
Pairwise: atez+bev	No modifier	No modifier	No conclusion
Pairwise: sorafenib or lenvatinib	x1.2	No modifier (because of availability of atez+bev)	
Fully incremental	x1.2 for sorafenib and lenvatinib		

Company

- Different treatments can have different QALY weights, and sorafenib and lenvatinib are standard of care for a substantial proportion of patients

EAG

- Applying a weighted market share approach for the full population using market share assumptions confirmed by NHS England Cancer Drugs Fund lead, EAG estimated proportional shortfall to be [redacted]
- Since the estimated proportional shortfall is [redacted], no modifier should apply to any comparisons

*Using company's inputs for age and sex distribution and total QALYs for comparator, and assuming 69% of people with HCC receive atez+bev first-line treatment, 16% receive lenvatinib and 15% receive sorafenib.

Should a severity modifier of 1.2 apply for comparisons with sorafenib and lenvatinib?

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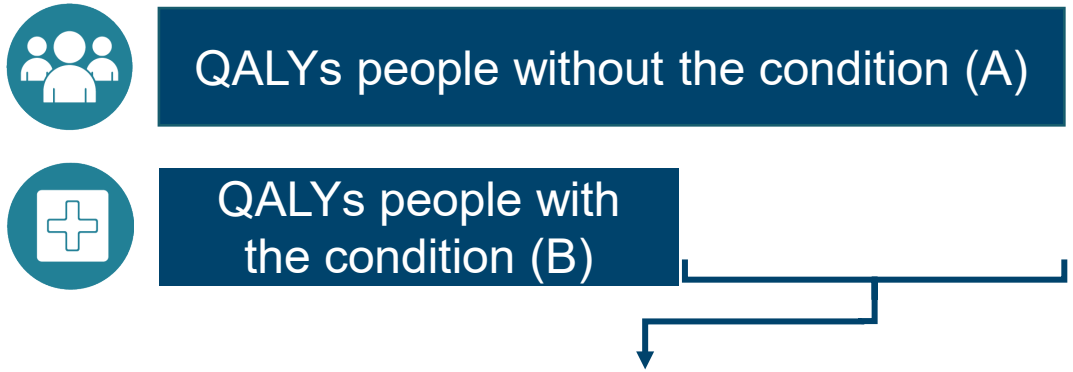
Abbreviations: Atez+bev; atezolizumab plus bevacizumab; DG, draft guidance; EAG, external assessment group; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

Issue a: Modelling time to treatment discontinuation

Small ICER impact

Link to TTD/PFS ratios

Recap (see DG section 3.8)

	STRIDE	Sorafenib	Atez+bev	Lenvatinib
TTD from HIMALAYA	Yes	Yes	No	No
Company	Trial TTD	Trial TTD	PFS=TTD	PFS=TTD
EAG	PFS=TTD	PFS=TTD	PFS=TTD	PFS=TTD

- Company approach may underestimate costs for atez+bev and lenvatinib because people would have treatment after progression (clinical experts).
- Committee concluded consistent approach preferred (EAG base case).
- But this approach risks underestimating ICERS for STRIDE.

Company

- Maintained original approach in revised base case.
- Assuming PFS=TTD does not reflect observed data from HIMALAYA and is inconsistent with previous TAs (e.g. TA666 atez+bev in HCC).
- Provided alternative scenario:
  - Calculated ratio between TTD and PFS curves for STRIDE and sorafenib and applied to PFS for atez+bev and lenvatinib respectively.
  - Ratios are captured at annual timepoints (evidence of non-proportionality).

EAG

- Maintained PFS=TTD for all treatments in base case.
- If using ratio approach, EAG prefers:
  - Estimate TTD/PFS ratios using KM data not parametric modelled data.
  - Continuous representation of TTD/PFS ratios not tabulated annualised values.

What is committee's preferred approach to modelling TTD?

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Abbreviations: Atez+bev , atezolizumab plus bevacizumab; EAG, external assessment group; ICER, incremental cost effectiveness ratio; PFS, progression-free survival; TTD, time to treatment discontinuation

Small ICER impact

Issue b: Additional costs of tremelimumab retreatment

Recap (**see DG section 3.9**)

- 8% of people in STRIDE arm of HIMALAYA had 1 additional dose of tremelimumab.
- Committee requested cost-effectiveness results adjusted to include costs of tremelimumab retreatment.

Company

- Retreatment is not permitted under MHRA licence.
- Provided scenario: including additional cost of tremelimumab retreatment has minimal impact on ICER.
- Small proportion of patients had retreatment in HIMALAYA so unlikely to be meaningful bias in survival extrapolations.
- Not included in updated base case.

EAG

- Satisfied that scenario shows small ICER impact.
- Not included in EAG base case as inconsistent with MA and UK clinical practice.

Should additional costs of tremelimumab retreatment be included?

Abbreviations: DG, draft guidance; EAG, external assessment group; ICER, incremental cost effectiveness ratio; MHRA, Medicines and Healthcare products Regulatory Agency

Summary of base case assumptions at ACM 2

Assumption	Committee preference at ACM1	Company base case at ACM2	EAG base case at ACM2
Time horizon	40 years	40 years	40 years
Source of NMA data	Vogel et al NMA	Company NMA	Vogel et al NMA
OS/PFS modelling approaches	• Sorafenib: HIMALAYA+ generalised gamma parametric curve • Not satisfied with modelling of OS; requested further analysis	• STRIDE and sorafenib: HIMALAYA+ independently fit spline and knot parametric curves • Atez+bev and lenvatinib: Company NMA HRs	• Sorafenib: HIMALAYA+ generalised gamma parametric curve • STRIDE, atez+bev, lenvatinib: Vogel et al NMA HRs
Modelling TTD	• TTD equivalent to PFS for all treatments	• STRIDE and sorafenib: TTD data from HIMALAYA • Atez+bev and lenvatinib: TTD equivalent to PFS	• TTD equivalent to PFS for all treatments
Utilities	Time-dependent utilities	Time-dependent utilities	Time-dependent utilities
Severity modifier	Undecided	• Vs atez+bev: no modifier • Vs sorafenib and lenvatinib: 1.2x modifier	No modifier for any comparisons

Abbreviations: Atez+bev , atezolizumab plus bevacizumab; ACM, appraisal committee meeting; EAG, external assessment group; HR, hazard ratio NMA, network meta -analysis; OS, overall survival; PFS, progression -free survival; PH, proportional hazards; TTD, time to treatme nt discontinuation

Summary of issues

Issue	Questions for committee
Appropriate comparator(s)	• What are the appropriate comparator(s) for STRIDE? • Impacts decision making for severity and pairwise vs incremental
NMA	• Does committee still prefer the NMA previously published by Vogel et al to the company NMA?
Modelling OS	• What is committee's preferred approach to modelling OS? • Does committee still prefer EAG approach to parametric extrapolation for sorafenib?
Severity modifier	• Should a severity modifier of 1.2 apply for comparisons with sorafenib and lenvatinib?
Modelling TTD	• What is committee's preferred approach to modelling TTD?
Tremelimumab retreatment	• Should additional costs of tremelimumab retreatment be included?

Abbreviations: 1L, first-line; HCC, hepatocellular carcinoma; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Other considerations

Uncaptured benefits

Company has mentioned:

- Positive impact on caregivers and family members from alleviation of financial and psychological strain arising from informal care costs.
- Improved patient experience compared to atez+bev arising from less frequent trips to hospital, no need for endoscopy and reduced burden of extra monitoring.
- HIMALAYA 5-year follow-up data reinforces certainty around long-term survival and gives patients hope of living to access future novel therapies in development

Abbreviations: Atez+bev , atezolizumab plus bevacizumab; HCC, hepatocellular carcinoma

Cost-effectiveness results

- Cost-effectiveness results for the base case and scenario analyses are presented in Part 2 of the committee meeting because they include confidential information.
- Due to regional variation in the MPSC prices for atez+bev, the cost-effectiveness results for STRIDE are presented in comparison to the highest, lowest and midpoint MPSC prices for atez+bev.

Abbreviations: atez+bev ; atezolizumab plus bevacizumab; EAG, external assessment group; MPSC, Medicines Procurement and Supply Chain

Supplementary appendix

NICE National Institute for Health and Care Excellence

Background on untreated advanced or unresectable hepatocellular carcinoma

Link to ACM 1 recap.

Stage of diagnosis has a significant impact on survival

Causes

- HCC occurs predominantly in people with chronic liver disease and cirrhosis; typically associated with viral hepatitis, excessive alcohol consumption, non-alcoholic steatohepatitis and hemochromatosis

Epidemiology

- There were ~3,000 new diagnoses of HCC in England in 2021 (~79% male)

Diagnosis and classification

- HCC is typically categorised using the BCLC staging system, which considers size/number of tumours, overall health, and liver function (assessed using Child-Pugh score).

Symptoms and prognosis

- Prognosis for HCC depends on the severity of underlying liver dysfunction and the prognosis remains poor due to rapid disease progression
- People with advanced HCC have a poorer prognosis than people with early-stage HCC
- The 1-year survival rate is 38.1%, and at 5 years is 12.7% in UK

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma

Clinical perspective from BASL and clinical expert

Link to ACM 1 recap.

Contraindications indicate unmet need for another treatment

Current treatment options and unmet need

- Treatment aims to improve symptoms, delay progression and prolong life
- Advanced HCC is managed with systemic therapy; a combination of atezolizumab and bevacizumab, or where contraindicated, sorafenib or lenvatinib (considered less effective)
- Cirrhosis and cardiovascular comorbidities limit the utilisation of systemic therapy, multiple therapeutic options will increase the number of people that can benefit from anti-cancer immunotherapy

Durvalumab with tremelimumab

- Will be used in the same way as atezolizumab with bevacizumab but potentially will need less monitoring
- Will be useful in people who are not candidates for bevacizumab, as an alternative to sorafenib
- Health-related benefits include; delay in deterioration of quality of life, improved survival, non-overlapping toxicity compared to other treatments
- May be increased requirement for high dose steroids to manage autoimmune toxicity

Abbreviations: BASL, British Association for the Study of the Liver; HCC, hepatocellular carcinoma

TTD/PFS ratios applied in company scenario

Link to modelling TTD issue slide

Company calculated ratio between modelled TTD and PFS for STRIDE

Month	Modelled PFS	Modelled TTD	Absolute Difference	Ratio of hazards (TTD vs. PFS)	Applied to A+B PFS between months:
12	21%	****	****	****	0-<12
24	13%	****	****	****	>12-< 24
36	10%	****	****	****	>24-<36
48	8%	****	****	****	>36 - <48
60	6%	****	****	****	>48 - <60
72	6%	****	****	****	>60

Company calculated ratio between modelled TTD and PFS for sorafenib

Month	Modelled PFS	Modelled TTD	Absolute Difference	Ratio of hazards (TTD vs. PFS)	Applied to lenvatinib PFS between months:
12	18%	****	****	****	0-<12
24	6%	****	****	****	>12-< 24
36	3%	****	****	****	>24-<36
48	1%	****	****	****	>36 - <48
60	1%	****	****	****	>48 - <60
72	0%	****	****	****	>60

Abbreviations: PFS, progression -free survival; TTD, time to treatment discontinuation