Durvalumab with tremelimumab for treating untreated advanced or unresectable hepatocellular carcinoma

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Technology appraisal committee C [14 January 2025]

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Durvalumab with tremelimumab for treating untreated advanced or unresectable hepatocellular carcinoma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on untreated advanced or unresectable hepatocellular carcinoma

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

Patient perspective from BLT, endorsed by patient expert

HCC has a poor prognosis and high unmet need due to limited treatment options

Living with HCC

- HCC is a debilitating condition with poor prognosis and distressing symptoms
- HCC severely impacts quality and length of life, as well as family life and finances
- People also experience stigma and isolation due to the image of liver cancer

Treating HCC

- Patient concerns include; being diagnosed too late for curative options, lack of treatment options and lack of local access to treatments
- Most people have underlying liver cirrhosis, which complicates management. For example, using certain painkillers may worsen their liver condition

Durvalumab with tremelimumab

- People are desperate for further treatment options and encouraged by STRIDE data
- STRIDE would be particularly valuable option where atezolizumab + bevacizumab is not suitable (for example due to risk of variceal bleeding).
- Extension to life, even if just a few months, is an important treatment benefit to people with HCC – gives more time to get affairs in order and see family

People with HCC are often many years younger than those with other cancers, and extra time is of particular importance to people who may have young families and working lives.

Buying extra time can positively impact the patients but can also have a huge positive impact on families and the wider community

Abbreviations: BLT, British Liver Trust; CC, hepatocellular carcinoma

Clinical perspective from BASL and clinical expert

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

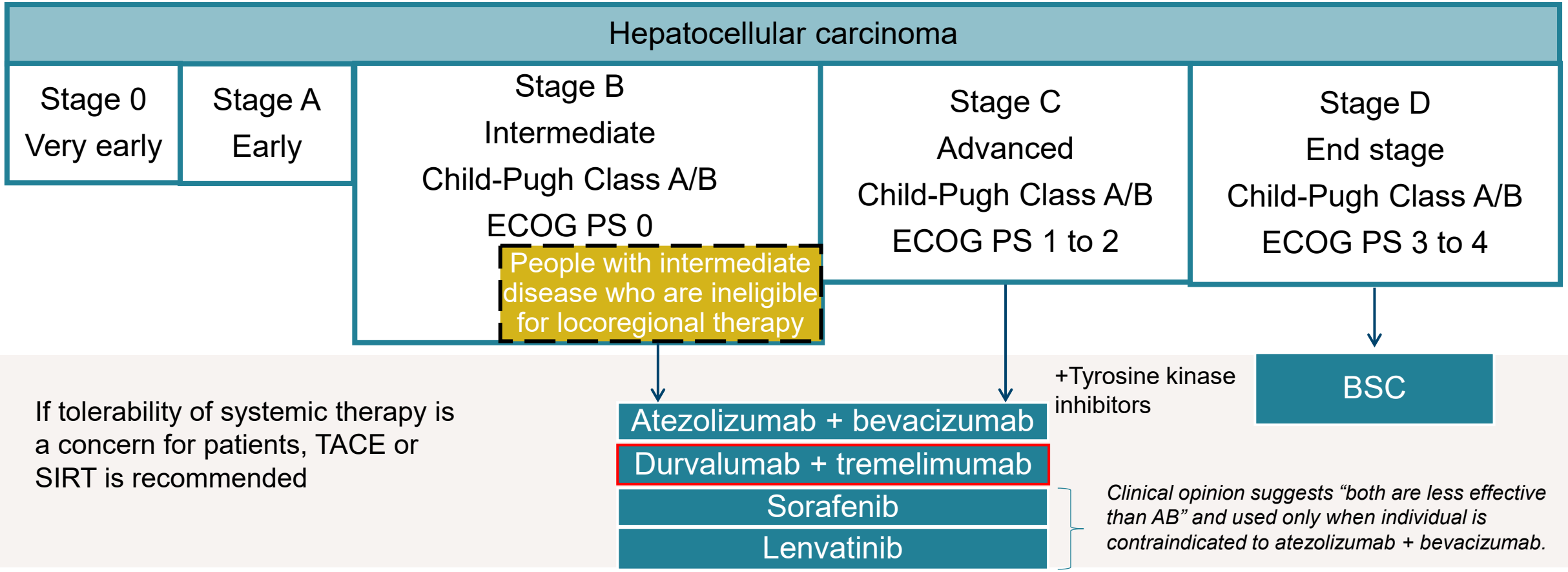
Durvalumab with tremelimumab

- 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

Treatment pathway

Company positioning STRIDE for 1L treatment of stage C and some stage B cases



Does the treatment pathway accurately represent standard care? Which comparators are most relevant?

Abbreviations: AB, atezolizumab + bevacizumab; BSC, Best supportive care; ECOG, Eastern Cooperative Oncology Group; PS, Performance status; SIRT, Selective Internal Radiation Therapy; TACE, Transarterial chemoembolization

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

Marketing authorisation	• Durvalumab in combination with tremelimumab 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
Durvalumab (1,500mg IV infusion)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓ → Ongoing
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

Ŧ Data from HIMALAYA trial

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

Key issues

Issue	Resolved?	ICER impact
1. Appropriate comparator(s)	No – for discussion	Large*
2. Network meta-analysis • Methods and approach • Modelling OS and PFS	No – for discussion	Large
3. Generalisability of the HIMALAYA trial	No – for discussion	Unknown
4. Company assumed that TTD for atezolizumab + bevacizumab is equivalent to PFS	No – for discussion	Medium
5. Severity modifier weight	No – for discussion	Medium
6. Company's use of treatment-related utilities	No – for discussion	Small

*Choice of comparator(s) impacts use of incremental vs. pairwise analysis and how severity modifier is implemented

Abbreviations: OS, overall survival ; PFS, progression free survival ; TTD, Time to treatment discontinuation

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Clinical trial results – HIMALAYA trial

Clinical trial design and outcomes

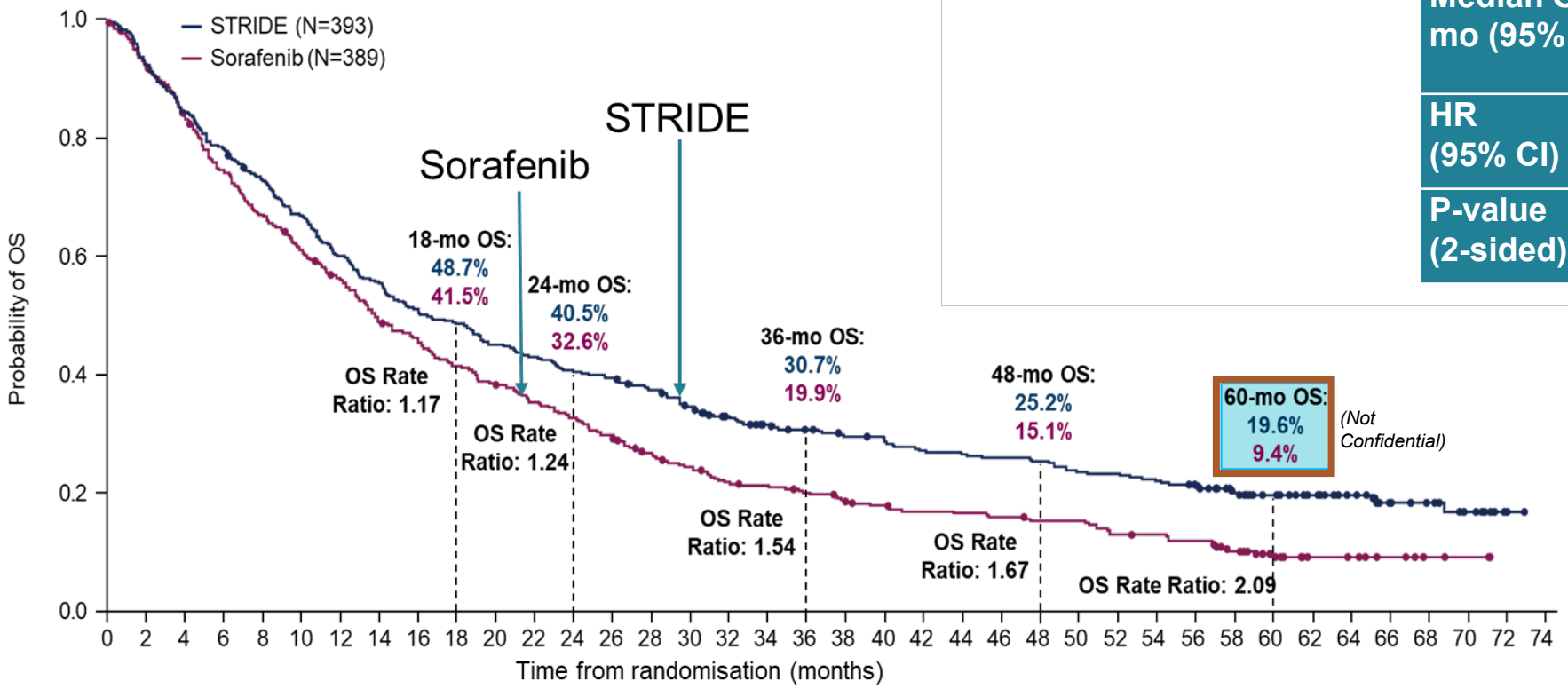
	HIMALAYA (NCT03298451)
Design	Randomised, multicentre, open-label, Phase III study
Population	• Adults with advanced or unresectable HCC (BCLC stage B or C) • Ineligible for locoregional therapy • No prior systemic therapy
Intervention	STRIDE (single dose of tremelimumab, 300 mg + durvalumab,1,500 mg Q4W)
Comparator	• Sorafenib • Durvalumab monotherapy • Tremelimumab [75 mg] Q4W x4 + durvalumab [1,500 mg] Q4W
Outcomes	• Primary endpoint: OS (and at 18, 24 and 36 months) • Secondary endpoints: PFS, TTP, ORR, DCR, DoR, and time to deterioration • Exploratory end point: EQ-5D-5L

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; DCR, Disease control rate; DoR, Duration of response; HCC, Hepatocellular carcinoma; ORR, objective response rate; OS, overall survival ; PFS, progression free survival ; TTP, Time to progression; Q4W, Every four weeks

Key clinical trial results – OS

STRIDE improves overall survival compared to Sorafenib

STRIDE vs Sorafenib – OS; DCO: 1st March 2024



	STRIDE	Sorafenib
Median OS, mo (95% CI)	16.43 (14.16 to 19.58)	13.77 (12.25 to 16.13)
HR (95% CI)	0.76 (0.65 to 0.89)	
P-value (2-sided)	0.0008	

- STRIDE demonstrated a statistically significant improvement in OS vs. sorafenib (16.43 vs. 13.77 months)
- At 5 years, survival probability was 19.6% for STRIDE vs. 9.4% for sorafenib

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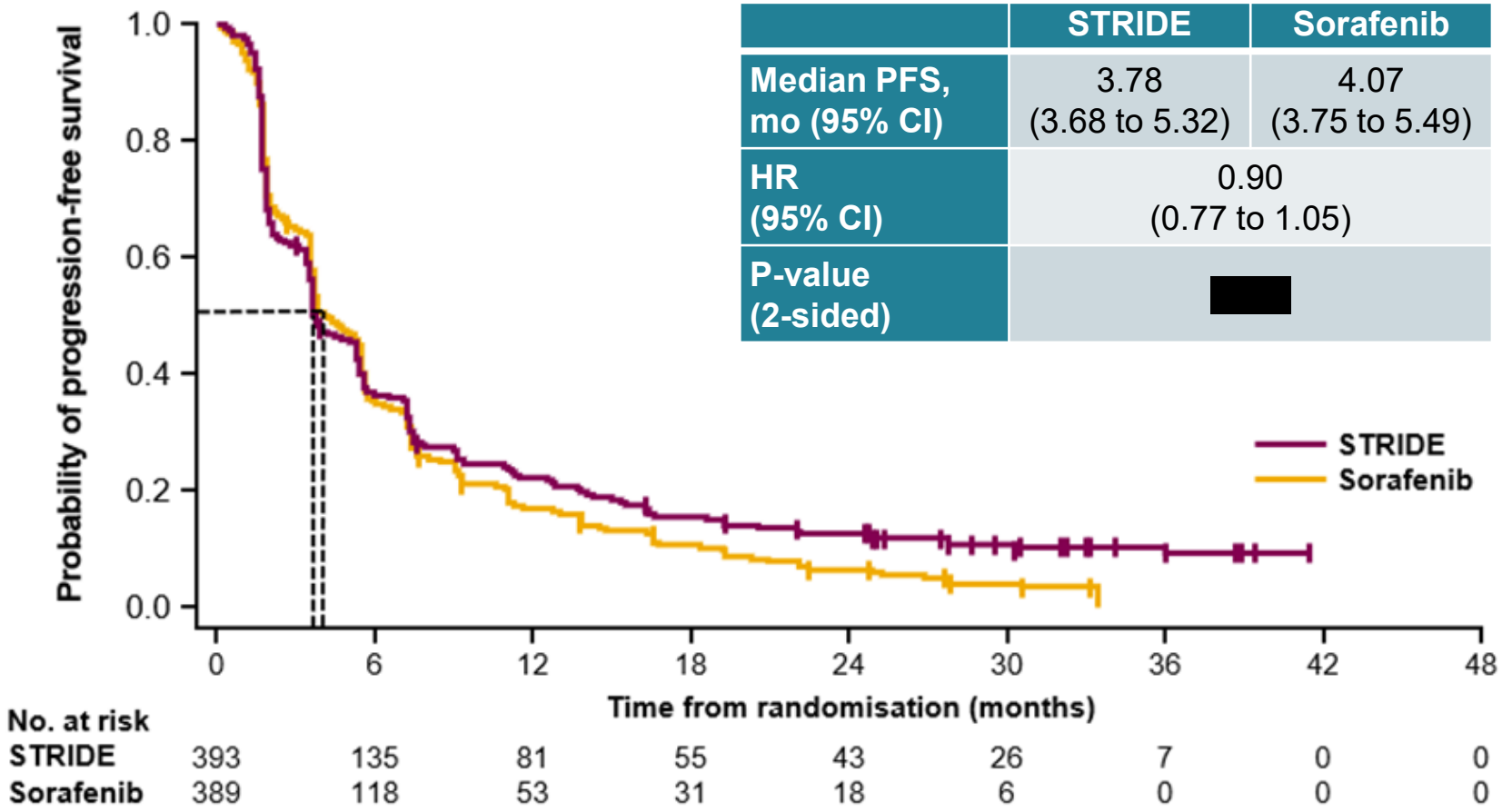
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; PFS, progression free survival

Key clinical trial results – PFS

No significant improvement in PFS for STRIDE

STRIDE vs Sorafenib – PFS. DCO: 27th August 2021 (primary analysis)



	STRIDE	Sorafenib
Median PFS, mo (95% CI)	3.78 (3.68 to 5.32)	4.07 (3.75 to 5.49)
HR (95% CI)	0.90 (0.77 to 1.05)	
P-value (2-sided)	[redacted]	

- No statistically significant difference in PFS between the two treatments
- 12.5% of participants were progression free in STRIDE arm vs. 4.9% for sorafenib
- Company says this aligns with the typical efficacy pattern of IO-IO therapies, where PFS benefits are minor, but OS improvement is significant

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Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; IO, Immuno-oncology; OS, overall survival; PFS, progression free survival;

Key issue 3: Generalisability of HIMALAYA to NHS

EAG has concerns about differences in baseline characteristics vs NHS population

Background

- HIMALAYA conducted in 181 sites globally but no UK sites
- Trial only included people with ECOG performance status 0 or 1
- EAG notes other differences between HIMALAYA population and NHS population

Company

- Both arms of HIMALAYA are representative of patients with advanced or unresectable HCC in the UK
- Audit of 361 people with advanced HCC in UK reported comparable baseline characteristics with HIMALAYA
- 7 clinical advisers (med oncs + hepatologist) confirmed HIMALAYA characteristics generalisable to NHS
- They noted differences in viral aetiology, but do not expect this to influence generalisability
- Mean age of IMBrave150 study (63.4) was seen as broadly generalisable to UK (TA666)

EAG comments

- EAG has concerns about generalisability of clinical effectiveness data to the NHS
- Key differences between UK audit and HIMALAYA include older age of diagnosis (median: 68 years vs 65 years), worse PS scores and higher incidence of non-viral HCC aetiology.
- Notes that lack of UK sites means that NHS likely has different ethnicity distribution to HIMALAYA population
- Gender balance and BMI also not generalisable (HIMALAYA less obese and more male than NHS HCC)
- EAG considers that additional evidence is required

Abbreviations: EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma, PS, performance status

Key issue 3: Generalisability of HIMALAYA to NHS

Parameter	HIMALAYA trial		UK audit n=361(%)
	STRIDE (n=393)	Sorafenib (n=389)	
Median age (range), yrs	65.0 (22 to 86)	64.0 (18 to 88)	68.0 (21 to 87)
ECOG performance status score, n (%)			
0	244 (62.1)	241 (62.0)	77 (21)
1	148 (37.7)	147 (37.8)	225 (62)
2	Not included	Not included	60 (17)
BCLC stage, n (%)			
B	77 (19.6)	66 (17.0)	Not reported
C	316 (80.4)	323 (83.0)	Not reported
Aetiology, n (%)			
HBV	122 (31.0)	119 (30.6)	33 (9)
HCV	110 (28.0)	104 (26.7)	71 (20)
Nonviral	161 (41.0)	166 (42.7)	196 (54)
Unknown	NR	NR	18 (5)

Professional organisation (BASL): *'Trial population characteristics and stage at treatment is consistent with treated systemic therapy in the UK'*

Red boxes indicate characteristics discussed on previous slide.

Is the HIMALYAYA population generalisable to the NHS population?

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Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma

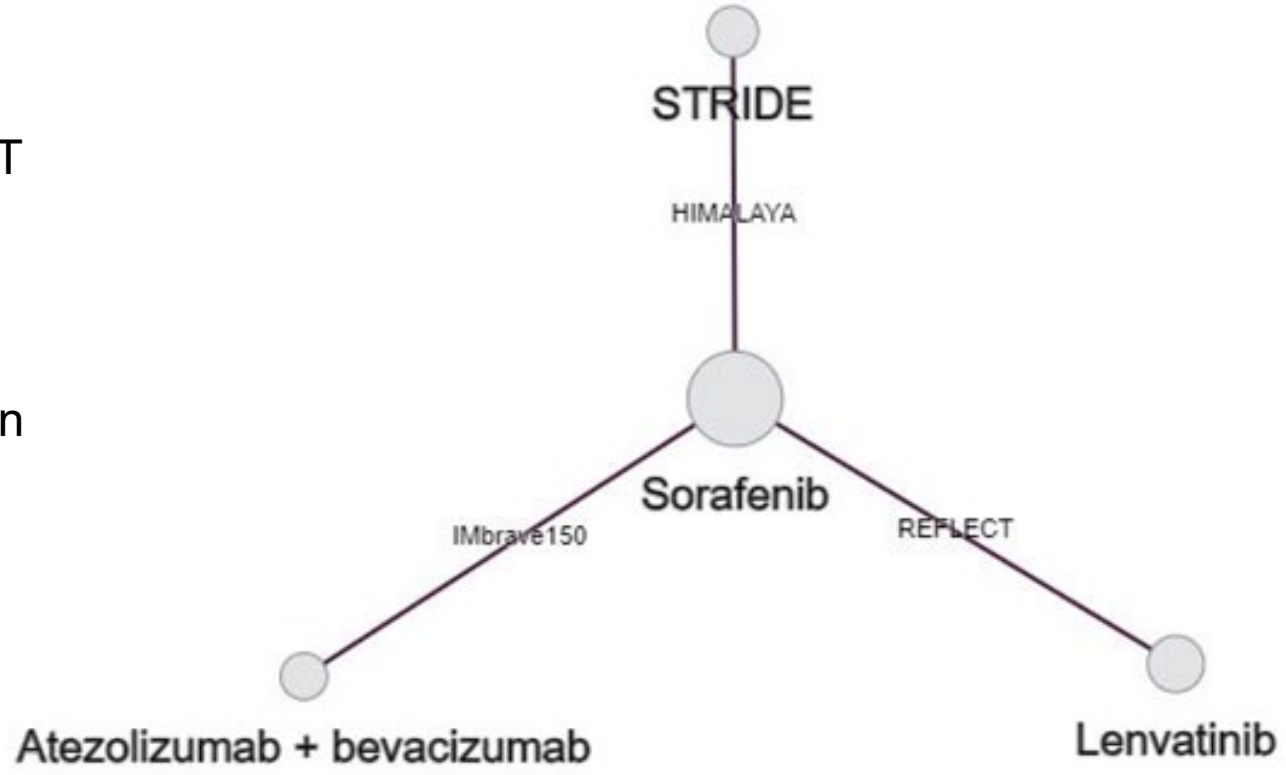
Network meta-analysis

NMA conducted to assess effectiveness of STRIDE vs comparators

- SLR identified 17 studies which were assessed for inclusion in the NMA
- After applying eligibility criteria, 3 studies were selected; HIMALAYA, IMbrave150 and REFLECT
- Trials were comparable in study design and baseline characteristics, but significant disparity in length of follow-up
- Evidence of proportional hazard (PH) assumption violation for HIMALAYA and REFLECT for OS and PFS
- Outcomes were:
  - OS
  - PFS INV

Network diagram NMA

Node size indicates the no. patients receiving each intervention



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Abbreviations: INV, investigator assessed; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; SLR, systematic literature review

NMA Results – OS/PFS

No significant difference seen between sorafenib and comparators

- All results are presented as HRs in comparison with Sorafenib

OS Results

- Atezolizumab + bevacizumab, lenvatinib and STRIDE showed numerical but non-significant improvement of OS vs. sorafenib

PFS Results

- Atezolizumab + bevacizumab, lenvatinib and STRIDE showed numerical but non-significant improvement of PFS vs. sorafenib

[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; OS, overall survival; PFS, progression free survival

Key issue 2: NMA: Methods for conducting NMA

HR derived from NMA used to model OS and PFS; key driver of model

Background:

- Company conducted an NMA and uses these results in its model
- EAG prefers to use results from existing published NMA (Vogel 2023), due to concerns about company NMA

EAG:

- Unclear inclusion/exclusion criteria, no specific search for previous NMAs, study heterogeneity, didn't include all data from included studies, too few studies to adjust for potential treatment effect modifiers (HBV aetiology)
- Wide CrIs highlight the considerable imprecision associated with NMA results; introduces uncertainty to model
- Results of EAG NMA (Vogel) and company NMA mostly very similar, but large difference in PFS for atezolizumab + bevacizumab vs sorafenib, and results aren't aligned with Imbrave150 results or other NMAs

Company:

- Company NMA includes same studies as EAG's preferred NMA, with more mature HIMALAYA data
- New NMA also ensures appropriate endpoints for modelling were included (PFS per INV not per BICR)
- Expanding the network to include the studies in Vogel 2023 would not change the point estimates as none of the additional evidence in the Vogel NMA informs the primary comparisons of interest for the decision problem
- None of the published NMAs contained any additional data for the treatments relevant to the decision problem
- Not appropriate to compare the results of Company NMA to other NMAs which use different trial data cuts, study populations and endpoints, and conclude that discrepancies are due to lack of data in NMA

Which NMA does committee prefer? Is either NMA appropriate for decision making?

Abbreviations: BICR, Blinded independent central review; CrI, credible interval; INV, investigator assessed, NMA, network meta-analysis; OS, overall survival; PFS, progression free survival

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Long-term modelling of efficacy inputs

Company and EAG have different approaches for modelling OS, PFS and TTD

- Company uses partitioned survival model, which EAG agrees is appropriate.

	PFS base case		OS base case		TTD base case	
	Company	EAG	Company	EAG	Company	EAG
STRIDE	HIMALAYA IPD + Hazard - 3 knots	NMA§ HR vs sorafenib	HIMALAYA IPD + Normal - 1 knot	NMA§ HR vs sorafenib	HIMALAYA TTD IPD + Weibull	Equal to EAG STRIDE PFS
Atez + Bev	NMA† HRs vs sorafenib	NMA§ HR vs sorafenib	NMA† HRs vs sorafenib	NMA§ HR vs sorafenib	Equal to atez + bev company PFS	Equal to EAG atez + bev PFS
Lenvatinib	NMA† HRs vs sorafenib	NMA§ HR vs sorafenib	NMA† HRs vs sorafenib (HR = 1)	NMA§ HR vs sorafenib	Equal to lenvatinib company PFS	Equal to EAG lenvatinib PFS
Sorafenib	HIMALAYA IPD + Hazard - 2 knots	Same as company	HIMALAYA IPD + Hazard - 1 knot	HIMALAYA IPD + Generalized Gamma	HIMALAYA TTD IPD + Lognormal	Equal to EAG sorafenib PFS

† = Company NMA § = EAG NMA (Vogel)

Abbreviations: HR, hazard ratio; IPD, Individual patient data; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TTD, time-to-discontinuation

= Evidence of PH violation vs sorafenib

Efficacy input values and survival curves in appendix

Base case OS parametric survival extrapolations

Parametric survival extrapolation informed by the HRs in previous slide

Company base case

EAG base case

[redacted]

Abbreviations: HR, hazard ratio; OS, overall survival

Key issue 2: Consistency of modelling approaches for OS/PFS

EAG concerned about inequity of modelling approach across treatments

EAG comments

- OS and PFS, different methods used for STRIDE and sorafenib vs. atezolizumab + bevacizumab and lenvatinib; may lead to inconsistency
- STRIDE and sorafenib; use HIMALAYA IPD
- atezolizumab + bevacizumab and lenvatinib; use NMA HR output applied to the spline model for sorafenib
- HIMALAYA has a much longer follow-up time than IMbrave150 and REFLECT; complicates comparisons

Company

- Evidence of PH violation for STRIDE vs. sorafenib (PFS and OS) so fitting independent models to the data was the best approach and follows NICE DSU guidelines. Inappropriate to apply a constant HR
- Company also found the PH violation for lenvatinib vs sorafenib, but application of a constant HR for lenvatinib yields conservative cost-effectiveness estimates when compared with STRIDE

Is it appropriate to use a constant HR for STRIDE OS & PFS given PH violation?
Does committee prefer Hazard - 1 knot or Generalized Gamma for sorafenib OS?

Abbreviations: EAG, external assessment group; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PH, proportional hazards

PFS survival curves in **appendix**

Key issue 4 : Company assumes TTD equivalent to PFS for atezolizumab + bevacizumab and lenvatinib

EAG concerned about inequity of modelling approach across treatments

Background

- In the absence of TTD information for atezolizumab + bevacizumab and for lenvatinib, TTD was assumed to be equivalent to the modelled PFS

Company

- TA666 used observed TTD data for atezolizumab plus bevacizumab and sorafenib but used PFS as a proxy for lenvatinib TTD, as TTD data was not available
- Subsequent treatments are initiated only in the progressed disease state, so it's an appropriate proxy

EAG comments

- Equating TTD with PFS is hard to justify, may inaccurately reflect treatment duration, impact cost and introduce bias in cost-effectiveness estimates, especially when TTD data is used for STRIDE and sorafenib
- For most of the observed period, STRIDE PFS and TTD do not align
- However, this method may be necessary due to lack of evidence, TTD data exists but is unavailable to EAG
- Using PFS as proxy for TTD across all treatments may still be more appropriate approach for consistency

Is assuming equivalence between PFS and TTD appropriate? Should this be applied for all treatments?

Company TTD for STRIDE and atez + bev in Appendix

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

Key Issue 5: QALY weightings for severity

Background

- Company applies different severity weight for each comparator. EAG applies same weight to all comparisons (=1), based on best available current treatment

Company

- Severity modifier of 1.2 applied for STRIDE vs lenvatinib and STRIDE vs sorafenib
- Severity modifier of 1 applied for STRIDE vs atezolizumab + bevacizumab
- For fully inc. analysis, relevant weighting used for each comparison once dominated comparators excluded
- Lenvatinib and sorafenib are used when other treatments are contraindicated, or oral therapy is preferred

Company base case	QALYs without condition	QALYs on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Weight used in company model
Atez +Bev	[redacted]	2.42	[redacted]	[redacted]	1
Sorafenib		1.48	[redacted]	[redacted]	1.2
Lenvatinib		1.48	[redacted]	[redacted]	1.2

EAG comments

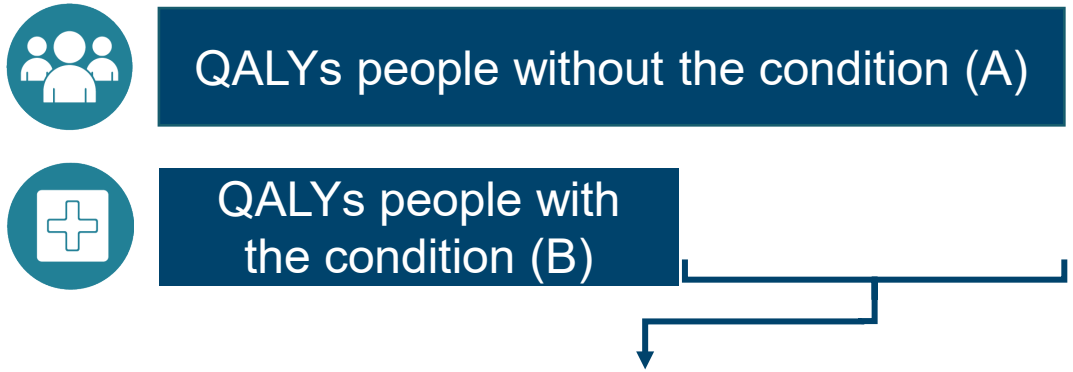
- The company's use of a QALY weight of 1.2, based on sorafenib, is inappropriate; the QALY weight should reflect established standard of care in the NHS, which is atezolizumab + bevacizumab

Does the committee prefer EAG or company approach for applying severity modifier?
How should this apply in fully incremental analysis?

Abbreviations; EAG, external assessment group; QALY, quality-adjusted life years

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

Key issue 6: Company's use of treatment-related utilities

Background

- Utility values based on EQ-5D-5L data collected in HIMALAYA
- Company assumes atezolizumab + bevacizumab has same utility value as STRIDE, and lenvatinib has same utility value as sorafenib (to capture impact of AEs from TKIs)
- Same utility values were used for progression free and progressed disease
- Company and EAG use different data sources for age-adjustment coefficients

EAG comments

- Prefer time-to-death utility values to reflect declining utility as disease progresses; consistent with TA666
- Prefer to use same utility value across different treatments
- Company approach does not differentiate utility values for subsequent treatments - same utility values for patients receiving first-line treatments (e.g. STRIDE) as for those subsequent treatments (e.g, sorafenib)
- Given that the company assigns a lower utility value for sorafenib, and that sorafenib is a common subsequent treatment, it is more reasonable to assume that the utility for patients on subsequent treatments would be at most equal to that of sorafenib – [rather than that of STRIDE]
- For age-adjustment, Ara & Brazier (2010) provide a smoother trend in age-adjustment vs Hernandez Alava

Company

- The utility values were derived across the trial time horizon (on and off treatment) and so capture the utility off-treatment and when patients receive subsequent treatment, e.g., sorafenib, too

Abbreviations: AE, adverse event; EAG, external assessment group; EQ-5D, EuroQol-5 Dimensions; TKIs, Tyrosine kinase inhibitor

Utility values used in the model

Treatment	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib	Source	Age adjustment	Utility perspective
Company values	[redacted]	[redacted]	[redacted]	[redacted]	HIMALAYA	HSE 2014 (Hernandez Alava 2022)	Treatment-dependent
EAG values	<= 5 weeks from death = [redacted] 5 to 15 weeks from death = [redacted] 15 to 30 weeks from death = [redacted] >30 weeks from death = [redacted]				HIMALAYA	Ara & Brazier (2010). Used in TA666.	Time-dependent

Does committee prefer time-dependent or treatment-dependent approach for utility values?
Which source is preferred for age-adjustment coefficients?

Other issues and corrections:

Time horizon

- Company uses 40-year time horizon (as 4% remain alive at 20 years). The EAG believes a 20-year time horizon is sufficient to capture differences in costs and benefits and is consistent with previous STAs (EAG projects 1% alive at 20 years).

Long-term adverse effects

- EAG have concerns regarding potential long-term immune-related adverse effects and immunogenicity from STRIDE. Company says HIMALAYA provides robust evidence base on safety and effectiveness.

Half-cycle correction

- Company half-cycle correction method for tremelimumab costs overestimated total expenses by misallocating costs, and inflating figures beyond the actual drug cost. EAG corrected this in their model; company accepted the correction and updated its base case.

Abbreviations: EAG, external assessment group; HCC, hepatocellular carcinoma; STA, single technology appraisal

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case	ICER impact of EAG assumption
Time horizon	40 years	20 years	Small ↑
Source of NMA data	Company NMA results	Vogel et al NMA	Large ↑
OS/PFS modelling approaches	STRIDE: HIMALAYA+ splines and knots parametric curves Sorafenib: HIMALAYA+ splines and knots parametric curves	STRIDE: NMA HRs Sorafenib: HIMALAYA+ generalised gamma (for OS)	
TTD	For atezolizumab + bevacizumab and lenvatinib TTD is assumed equal to PFS	TTD curve is equal to the PFS curve for all comparators	Medium ↑
Utilities	Utilities are treatment-dependent, same for each disease state	Progression dependent (time from death), same for all treatments	Small ↑
Severity modifier	x1.2 and x1 depending on comparator	x1 all comparators	Medium ↑

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TTD, time-to-discontinuation

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Other considerations

- **Equality**: British Association for the Study of the Liver noted that liver cancer disproportionally affects poorest in society. Many patients with HCC come from disadvantaged backgrounds and have complex lives. There are strong links with deprivation (including homelessness, heavy alcohol and drug use, obesity)
- **Managed access**: company has not submitted a managed access proposal
- **Uncaptured benefits:**
  - Clinical expert and company suggest reduced capacity burden for the NHS through reduced endoscopy, dosing admin and monitoring vs. atezolizumab and bevacizumab
  - Company also mentions:
    - Positive impact on carers from improved outcomes with STRIDE
    - Increased confidence given highly mature long-term survival data

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List of Key Questions:

Questions for committee discussion following key issues

Does the treatment pathway accurately represent standard care? Which comparators are most relevant?

Is the HIMALYAYA population generalisable to the NHS population?

Which NMA does committee prefer? Is either NMA appropriate for decision making?

Is it appropriate to use a constant HR for STRIDE OS & PFS given PH violation?
Does committee prefer Hazard - 1 knot or Generalized Gamma for sorafenib OS?

Is assuming equivalence between PFS and TTD appropriate? Should this be applied for all treatments?

Does the committee prefer EAG or company approach for applying severity modifier?
How should this apply in fully incremental analysis?

Does committee prefer time-dependent or treatment-dependent approach for utility values?
Which source is preferred for age-adjustment coefficients?

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PH, proportional hazards, TTD, time-to-discontinuation

– – – – – = company base case

Key decisions for committee

Questions for committee discussion following key issues

1. Comparator & approach ➡ **2. Severity modifier** ➡ **3. NMA approach** ➡ **4. Utilities** ➡ **5. TTD**

1. Comparator & approach	2. Severity modifier	3. NMA approach	4. Utilities	5. TTD
Pairwise vs specific comparator(s)	Variable severity modifier (1 or 1.2 depending on comparison)	Company approach: • Company NMA (newly conducted) • HIMALAYA IPD for STRIDE • 1 knot for sorafenib OS	• Treatment-dependent • Age adjustment: HSE 2014	PFS as a proxy of TTD for atezolizumab + bevacizumab & lenvatinib
Fully incremental	Severity modifier = 1 for all comparisons	EAG approach: • Vogel NMA • NMA HRs for STRIDE • Gen. gamma for sorafenib OS	• Time-dependent • Age adjustment: Ara & Brazier	PFS as proxy of TTD in all treatments

1a. Appropriate comparator
1b. Incremental or pairwise

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TTD time to treatment discontinuation

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem

Population, intervention, comparators and outcomes from the scope

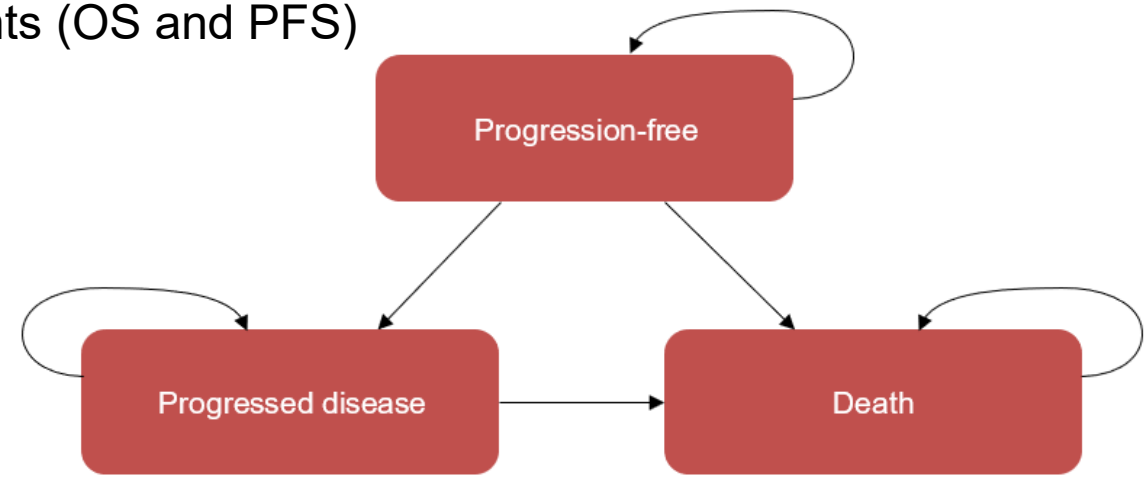
	Final scope	Company	EAG comments
Population	People with advanced or unresectable HCC	Individuals with advanced or unresectable HCC who are ineligible for locoregional therapy and have not undergone systemic therapy	The company's population is narrower than NICE's scope. The EAG's clinical advisor confirmed the company's justification. The EAG finds the company's justification acceptable.
Intervention	Durvalumab plus tremelimumab	STRIDE: durvalumab (1,500 mg Q4W) and a single dose of tremelimumab (300 mg)	Aligns with NICE final scope
Comparators	• Atezolizumab + bevacizumab • Lenvatinib • Sorafenib • SIRT including SIR-Spheres and TheraSphere • QuerumSphere • BSC	• Atezolizumab + bevacizumab • Lenvatinib • Sorafenib	Narrower than NICE's final scope. EAG agrees that BSC is complementary treatment and should not be a main comparator. Locoregional therapy is typically administered before systemic therapy, whereas the HIMALAYA trial included patients who were ineligible for locoregional therapy.
Outcomes	OS,PFS, TTP, Response rates, AEs, HRQoL	OS, PFS, TTP, Response rates (ORR, DoR and DCR), AEs, HRQoL	Aligns with NICE final scope

Abbreviations: AE, adverse events; DCR, Disease control rate; DoR, Duration of response; EAG, external assessment group; HCC, Hepatocellular carcinoma; ORR, objective response rate; OS, overall survival ; PFS, progression free survival ; TTP, Time to progression; Q4W, Every four weeks

Model structure

A partition survival model was developed to analyse cost-effectiveness

- Cost-effectiveness analysis was conducted using a partitioned survival model.
- Three health states used to measure key TTE endpoints (OS and PFS)
- This model aligns with previous NICE evaluations in HCC (TA551, TA474, TA666)
- Individuals enter the model in PF state and move to alternative health states according to OS and PFS curves from HIMALAYA



Simplified model schematic: Company submission, Figure 2

Abbreviations: OS, overall survival ; PFS, progression free survival ; TTE, Time to event;

Efficacy inputs use in company and EAG model

Variable	Company's Value	EAG's value
Overall survival		
STRIDE	Splines and knots: Normal - 1 knot	Constant HR: HR vs sorafenib=0.7816 (95% CrI: 0.66, 0.93)
Sorafenib	Splines and knots: Hazard - 1 knot	Generalized Gamma model (based on HIMALAYA trial)
Lenvatinib (HR vs. sorafenib)	1.00	Constant HR: HR vs sorafenib= 0.92 (95%CrI: 0.78, 1.08)
Atezolizumab + bevacizumab (HR vs. Sorafenib)	[redacted]	Constant HR: HR vs sorafenib= 0.68 (95%CrI: 0.42, 1.10)
PFS		
STRIDE	Splines and knots: Hazard - 3 knots	Constant HR: HR vs sorafenib=0.9041 (95%CrI: 0.62, 1.35)
Sorafenib	Splines and knots: Hazard - 2 knots	Company's approach accepted
Lenvatinib (HR vs. sorafenib)	[redacted]	Constant HR: HR vs sorafenib= 0.6535 (95%CrI: 0.44, 1)
Atezolizumab + bevacizumab (HR vs. Sorafenib)	[redacted]	Constant HR: HR vs sorafenib= 0.66 (95%CrI: 0.27, 1.59)
TTD		
STRIDE	One piece (Separately fitted): Weibull	Equivalent to STRIDE's PFS
Sorafenib	One piece (Separately fitted): Log-normal	Equivalent to Sorafenib's PFS
Lenvatinib	Constant HR (1.00) vs. PFS	Equivalent to Lenvatinib's PFS
Atezolizumab + bevacizumab	Constant HR (1.00) vs. PFS	Equivalent to EAG model of atezolizumab + bevacizumab's PFS

NICE Abbreviations: HR, hazard ratio; PFS, progression free survival; TTD, time to treatment discontinuation

Company base case PFS parametric survival extrapolations

Abbreviations: PFS, progression free survival;

EAG base case PFS parametric survival extrapolations

Abbreviations: PFS, progression free survival;

TTD modelling

Comparison of company's modelling of TTD for STRIDE and for atezolizumab + bevacizumab.

The figure shows the impact of the different approaches used by the company to model TTD for STRIDE vs atezolizumab + bevacizumab

Abbreviations: TTD, time-to-discontinuation