Single Technology Appraisal

Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

Committee Papers

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Single Technology Appraisal

Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** AstraZeneca

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. British Liver Trust
   b. Warwick Evidence

3. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 25 February 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Overall comments on the draft guidance** • We would like to thank NICE for the comprehensive summary of the evidence that was considered in the evaluation of durvalumab with tremelimumab (Single Tremelimumab Regular Interval Durvalumab, 'STRIDE') for untreated advanced or unresectable hepatocellular carcinoma (HCC) and the recommendations and requests for follow-on analyses made by the committee.

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	• We are however disappointed that the committee decided to not recommend STRIDE for this indication. There was a clear consensus during the committee meeting that "*…advanced or unresectable HCC has a severe effect on both quality and length of life*" and that "*People with HCC often feel frustrated by the limited treatment options, particularly because existing options may not be suitable for them or have unmanageable side effects*". We agree with the committee that atezolizumab plus bevacizumab is used most commonly in this population because of its superior efficacy to TKIs. However, the committee also noted that people with untreated advanced or unresectable HCC would welcome an alternative effective first-line treatment option. • With our response to the draft guidance below, we provide the following to support the committee in their decision making: o A revised company base-case utilising the committee's preferred time-dependent approach for utility values (Table 1 and Table 5 in the Appendix) o A scenario where the OS for atezolizumab plus bevacizumab is equivalent to STRIDE (requested by the committee) o A scenario assuming a ratio between TTD and PFS for atezolizumab plus bevacizumab and lenvatinib o A scenario accounting for the costs of tremelimumab retreatment (requested by the committee) • We hope that the analyses support the committee in their decision-making during the next committee meeting. The analyses shows that **STRIDE still strongly dominates the primary comparator, atezolizumab plus bevacizumab, in the revised Company base case and provides a positive net health benefit at both the £20,000 and £30,000 willingness-to-pay thresholds**. In a scenario requested by the Committee, setting OS equivalent between STRIDE and atezolizumab plus bevacizumab, STRIDE provides cost savings of [redacted].
2	**The HIMALAYA trial provides the longest follow-up (5-years for OS) for an immunotherapy treatment in advanced or unresectable HCC, reducing the level of uncertainty in the long-term clinical outcomes and extrapolation of the STRIDE data. Other treatments have not published data with mature follow-up, making comparisons challenging.** • The draft guidance does not reference the 5-year published OS for STRIDE, which provides more certainty in the long term clinical outcomes and demonstrates a statistically significantly improved OS compared to sorafenib (HR: 0.76 [0.65-0.89]).[1] • Data from IMBrave150 (atezolizumab plus bevacizumab) and REFLECT (lenvatinib) has not provided a similar length of follow-up, making treatment comparisons in the long-term challenging. Using the published data available for the relevant comparators, a methodologically robust NMA was conducted and presented in the submission, following the NICE DSU Guidelines ('the Company NMA').[2] The results of this NMA were broadly aligned with previous NMAs, including Vogel 2023.[3] The committee have expressed a preference for using the hazard ratios derived from the Vogel NMA. • The primary difference between the Vogel NMA and the Company NMA was the use of different definitions across studies for PFS. The Company NMA used a consistent definition of PFS across studies, that is PFS assessed per investigator. The rationale behind this decision is as follows:

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	○ PFS per investigator was a secondary endpoint in HIMALAYA. PFS as assessed by blinded independent review (BICR) was an exploratory endpoint only at interim analysis 1 (patients with 32 weeks of follow-up). ○ Similarly, in REFLECT, PFS per BICR was a post-hoc analysis, whilst PFS per investigator was a secondary endpoint.[4] It is not clear whether Vogel used PFS per INV or PFS per BICR in their NMA. • The committee said that they preferred the PFS per BICR outcome measure over investigator-assessed PFS because it is a more objective measure with less risk of bias, however, no commentary is provided of using differing outcome definitions, or outcomes that are exploratory rather than secondary. It is also notable that the Vogel study did not identify these differences in definition across studies and failed to comment on the differences and limitations of their approach. (i.e., use of mixed definitions without providing commentary). • The Company NMA also used the most recent 5-year data for OS from HIMALAYA OS.[1] • For these reasons, the Company NMA represents the best evidence base for the indirect treatment comparison. This has been retained in the Company base case. • When applying the results of the NMA in the economic analysis, the committee's preference also disregards the finding that the proportional hazards assumption does not hold within the REFLECT trial. For both PFS and OS, the time-varying analysis of RELFECT shows the hazard ratio for lenvatinib vs. sorafenib trends towards or exceeds unity in all models tested. For OS, given that the REFLECT trial is a non-inferiority trial for OS reporting that lenvatinib was statistically non-inferior to sorafenib, the HR is set to 1 for OS in the company base case.[4] Assuming a constant HR of [redacted] as calculated in the Company NMA in the long-term is optimistic and inconsistent with published evidence. For PFS, the calculated HR from the NMA is used, but this is considered as a conservative assumption. • The application of a HR of 1 for lenvatinib therefore represents the most appropriate approximation of the long-term relationship between lenvatinib and sorafenib for OS, consistent with the non-inferiority findings of the REFLECT study. This has been retained in the Company base case.
3	**Rationale for selecting generalised gamma over the 1-knot hazard curve for modelling sorafenib OS has not been provided** • In the Company base case, a spline-based model was considered justified for sorafenib OS given the time-varying hazards observed in the HIMALAYA trial. After following the NICE DSU guidance including consideration of the goodness-of-fit statistics, visual inspection of the extrapolated vs. KM curves, and external validation to understand the suitability of the extrapolations, the Company considered the hazard 1-knot model to provide the best extrapolation of OS in the base case. In one-to-one interviews with 7 UK clinical experts, clinicians advised that the scenario predicting the lowest survival expectations (hazard 1-knot) would represent the most clinically plausible one, noting that all extrapolations may be overestimating survival for sorafenib.[5] The generalised gamma model represented a slightly more optimistic extrapolation and was tested in a scenario analysis; this was demonstrated to have a minor impact on the ICER.

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	• The rationale for the EAG's preference for generalised gamma over hazard 1-knot is unclear, particularly when the two models provide very similar extrapolations. Similarly, the committee have said they prefer the EAG approach but have not provided justification. • Given the omission of a rationale for preferring the generalised gamma, we have retained the hazard 1-knot model in our revised base case. This is further motivated by the generalised gamma providing slightly more optimistic predications in the long-term.
4	**A scenario setting equivalent OS hazard rate functions between atezolizumab plus bevacizumab and STRIDE from the time point at which they cross is not supported by data and considered a highly conservative assumption** • The committee requested further scenarios including updated OS modelling that has equal hazard rate functions from the time point at which the atezolizumab plus bevacizumab and STRIDE curves cross. • The atezolizumab plus bevacizumab and STRIDE OS curves cross because STRIDE is modelled using an independently fit curve to the data whilst atezolizumab plus bevacizumab is estimated by applying a HR calculated through the Company NMA to the sorafenib arm in the model. This approach was justified because the proportional hazards assumption was considered to not hold for STRIDE vs. sorafenib in HIMALAYA whereas it was considered to hold for atezolizumab plus bevacizumab vs. sorafenib in IMBRAVE150. The same conclusion was drawn about the IMBrave150 OS data in the TA666 submission.[6,7] • Furthermore, as noted in the committee papers, the clinical experts present during the committee meeting considered it plausible to observe a durable treatment effect with the STRIDE regimen given the mechanism of action of termelimumab, which may explain the crossing of OS curves. This is aligned with observations that delayed separation or crossing of survival curves is observed in other IO RCTs, driven by the distinct mode of action of such regimens.[8] • Therefore, this scenario is not supported by data or clinical opinion. It is a highly conservative scenario as it inflates the long-term benefit from atezolizumab plus bevacizumab, which is inconsistent with the modelling approach and is not supported by published data. Despite this, we considered the point at which the treatment arms crossed. STRIDE initially starts above atezolizumab plus bevacizumab until falling below in week 3. Atezolizumab plus bevacizumab then sits above STRIDE until week 341 (~6.5 years), where it crosses back over to sit beneath STRIDE. • Given the curves cross at two points, we considered a pragmatic solution to be to implement the assumption from the start of the model. The results of this analysis are provided in the Appendix Table 2. The incremental QALYs under this scenario are zero. STRIDE is cost saving compared to atezolizumab plus bevacizumab (incremental costs for STRIDE vs. atezolizumab plus bevacizumab are [redacted]). This finding is similar to the cost comparison provided in the Company submission Document B, Table 72.
5	**Whilst we recognise the Committee's preference for a consistent approach to modelling treatment duration, setting TTD equivalent to PFS for the STRIDE regimen does not reflect observed data from the HIMALAYA clinical trial and is inconsistent with approaches taken in previous technology appraisals**

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	• As highlighted in the draft guidance, time to treatment discontinuation (TTD) data from the HIMALAYA study was used to model the treatment duration for STRIDE and sorafenib as it was considered the most accurate representation of treatment duration. • In the absence of TTD data for atezolizumab plus bevacizumab and lenvatinib, the Company base case assumed that TTD is equal to PFS for these comparators. As atezolizumab plus bevacizumab is recommended until loss of clinical benefit or unacceptable toxicity, and lenvatinib can be used until loss of ongoing clinical benefit or unacceptable toxicity, treatment beyond progression is permissible in clinical practice, making this assumption arguably conservative. This is supported by the draft guidance which notes that equating PFS with TTD is considered flawed and not reflective of clinical practice, potentially underestimating TTD for these treatments. • Whilst we recognise that the committee prefer a consistent across comparators, the proposed scenario is inconsistent with approaches adopted in previous appraisals. Of particular note, TA666 utilised observed TTD data for atezolizumab plus bevacizumab and sorafenib as TTD data were available from the IMBrave150 trial; meanwhile, PFS was used as a TTD proxy for lenvatinib due to the absence of TTD data (Company Submission pg 108). • Enforcing this assumption for STRIDE and sorafenib is inconsistent with the evidence from the HIMALAYA trial. Figure 1 in the Appendix shows the PFS curves sit below the TTD curves for both treatments initially; for sorafenib, this continues in the latter part of the KM curves and in the extrapolations, but for STRIDE, the KM curves converge at the end of the trial and the extrapolations cross. Based on this, we assert that the approach taken in the company base case is the most suitable given the available data. Nonetheless, we provide an alternative approach in a scenario, applying a consistent methodology across comparators, to address the committee's preference. • Given the relationship between TTD and PFS observed for STRIDE and sorafenib in HIMALAYA (Figure 1) we present a scenario whereby a ratio between the curves is calculated and assumed to apply to atezolizumab plus bevacizumab and lenvatinib. For atezolizumab plus bevacizumab, this is based on the STRIDE TTD vs. PFS relationship, and for lenvatinib, this is based on the sorafenib TTD vs. PFS relationship. Given the visual evidence of non-proportionality between these curves (particularly for STRIDE), this ratio was captured at annual timepoints based on the modelled curves for STRIDE and sorafenib for PFS and TTD from 1 year to 6 years. From 6-years onwards the relationship between the modelled TTD and PFS curves were observed to be stable in both arms in HIMALAYA. This calculated ratio is captured in Table 9 and Table 10; for STRIDE the TTD vs. PFS ratio ranges between [redacted] and [redacted], for sorafenib the range is much narrower between [redacted] and [redacted]. These ratios are then applied to the atezolizumab plus bevacizumab extrapolated PFS curve (values from Table 9) and the lenvatinib extrapolated PFS curve (values from Table 10). • The results of this scenario are provided in the Appendix Table 3 and Table 7. Compared to the revised Company base case, STRIDE remains dominant compared to atezolizumab plus bevacizumab. For the comparison to the TKIs, the pairwise ICER does not change relative to sorafenib, and it decreases by 9% compared to lenvatinib.
6	**Including tremelimumab retreatment costs is inconsistent with the marketing authorisation and anticipated use in clinical practice**

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	• STRIDE received EMA and MHRA marketing authorisation for first-line treatment of adult patients with advanced or unresectable HCC.[9] • In the HIMALAYA trial, a small proportion of participants (8%) in the STRIDE arm received retreatment with one additional dose of tremelimumab. The economic model did not include the additional cost of retreatment since tremelimumab retreatment is not permitted under its MHRA regulatory license, meaning this would not occur in practice. The committee expressed concern that incorporating the clinical benefits of tremelimumab retreatment without accounting for the additional costs could bias the cost-effectiveness results for STRIDE. There is no reason to believe that there is meaningful bias in the survival extrapolations for STRIDE given the small proportion of patients. • Despite this, we have provided the results of this in the Scenarios in the Appendix. There is minimal impact to the ICER (an increase of 2-3% in the TKI ICERs). In this scenario, the tremelimumab retreatment proportion displaces other subsequent treatments, with the distribution of the remaining subsequent treatments being evenly adjusted, maintaining the same relative proportions as in the Company submission.
7	**Benefits not captured in the QALY calculations** The draft guidance noted that NICE will consider various aspects including uncaptured health benefits in their assessment of a technology as an effective use of NHS resources. However, they have not been captured in detail in the draft guidance. Therefore, we believe it's important to emphasize the meaningful additional benefits associated with STRIDE that are not reflected in the QALY but are fundamental to the decision-making process. **Patients and caregivers' benefits** These benefits, particularly those that impact patient lives, are important qualitative considerations for decision making: HCC in conjunction with liver disease has been found to disproportionately affect the poorest in society, with higher incidence and inferior survival associated with socioeconomic deprivation.[10] This characteristic of liver disease cannot be overlooked when considering beyond the QALY benefits of STRIDE as: • **Impact on caregivers and family members:** It is estimated that approximately 15% of the total health cost of HCC across European countries, including UK, is due to informal care.[11] Having access to innovative treatment such as STRIDE could alleviate this financial and psychological strain, enabling caregivers to resume their professional lives and societal contributions • **Patient experience:** Durvalumab is administered every 4 weeks schedule, whilst atezolizumab plus bevacizumab is delivered more frequently (every 3 weeks), meaning less frequent trips to the hospital. Furthermore, there is no need for an endoscopy, and as there is no increased risk of bleeding there is a reduced burden of extra monitoring.[12] This facilitates a better patient experience, especially for patients with complex lives, disadvantaged backgrounds or in more remote locations who are unable to attend frequent hospital appointments. • **Option Value** the value of living longer to see future novel therapies, is a way patients and their loved ones perceive the impact of survival outcomes, which helps maintain hope, allowing them to better deal with the burden of the disease.[13] HIMALAYA 5-year follow-up reinforces the certainty around the long-term survival provided by STRIDE, giving the

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	patients the hope of live enough to being able to access the novel agents that are in development.
	References 1. Rimassa L, Sangro B, Lau G, et al. Five-year overall survival (OS) and OS by tumour response measures from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC). In: ; 2024. 2. Dias S, Welton N, Sutton A, Ades A. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials*.; 2011. https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf 3. Vogel A, Finn RS, Blanchet Zumofen MH, et al. Atezolizumab in Combination with Bevacizumab for the Management of Patients with Hepatocellular Carcinoma in the First-Line Setting: Systematic Literature Review and Meta-Analysis. *Liver Cancer*. 2023;12(6):510-520. doi:10.1159/000533166 4. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *The Lancet*. 2018;391(10126):1163-1173. doi:10.1016/S0140-6736(18)30207-1 5. AstraZeneca Data on File. *HIMALAYA Clinician Validation Interviews*.; 2024. 6. NICE. TA666 Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma. December 16, 2020. Accessed May 10, 2024. https://www.nice.org.uk/guidance/ta666 7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745 8. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2019;381(16):1535-1546. doi:10.1056/NEJMoa1910836 9. Medicines and Healthcare products Regulatory Agency (MHRA). IMJUDO 20 mg/ml concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). Accessed February 24, 2025. https://www.medicines.org.uk/emc/product/14841/smpc#gref 10. Cancer Research UK. Liver cancer incidence statistics by deprivation. Cancer Research UK. May 15, 2015. Accessed February 24, 2025. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/incidence 11. Digestive Cancers Europe. The Costs of Liver Cancer - Factsheet. 2021. Accessed February 24, 2025. https://digestivecancers.eu/publication/the-costs-of-liver-cancer-factsheet/ 12. Suddle A, Reeves H, Hubner R, et al. British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults. *Gut*. Published online April 16, 2024. doi:10.1136/gutjnl-2023-331695

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	13. Should We Consider Including a Value for "Hope" as an Additional Benefit Within Health Technology Assessment? *Value Health*. 2022;25(9):1619-1623. doi:10.1016/j.jval.2022.03.006 14. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evid*. 2022;1(8). doi:10.1056/EVIDoa2100070 15. Liver Cancer United Kingdom (UK). Stages of HCC. Liver Cancer UK. 2022. Accessed February 24, 2025. https://livercanceruk.org/liver-cancer-information/types-of-liver-cancer/hcc/treating-hcc/stages-of-hcc/ 16. Calculating severity shortfall for nice evaluations. July 23, 2024. Accessed February 25, 2025. https://www.sheffield.ac.uk/nice-dsu/tsds/severity-shortfall-tsd

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Updated base-case and scenario analysis results

In line with our response to the draft guidance above, we have updated the Company's base-case analysis accepting the use of the committee-preferred time-dependent approach for utility values. In the Company submission, utilities were modelled as being treatment-dependent because it was considered to be the most robust way of capturing the impact of adverse events due to TKIs on patients.[14,15] In response to the EAG clarification questions, the Company provided a time-to-death utility approach, which resulted in minor changes to the company submitted base case ICERs. Given the committee preference for this approach, this has been accepted in the revised Company base case.
Additionally, the following scenarios are presented:

- A scenario where the OS for atezolizumab plus bevacizumab is equivalent to STRIDE
- A scenario assuming a ratio between TTD and PFS for atezolizumab plus bevacizumab and lenvatinib
- A scenario accounting for the costs of tremelimumab retreatment (requested by the committee)

In the CEM submitted in the ACD response, these settings can be located on the 'Main Menu' worksheet.

The committee agreed that, according to clinical expert opinion and data from NHS England, atezolizumab plus bevacizumab is used most commonly in this population, and that a pairwise comparison with atezolizumab plus bevacizumab was an appropriate presentation of results. Therefore, as this is the primary comparator, we have presented these results first using a severity modifier of 1.

The committee also acknowledged that lenvatinib and sorafenib are taken by some people. This population generally consists of those who are not suitable for treatment with atezolizumab plus bevacizumab, with clinicians estimating that approximately 25% are contraindicated due to bleeding risk and other comorbidities.[5] We have therefore presented these pairwise results and fully incremental analysis in separate tables, retaining the x1.2 severity modifier, which was recalculated following the change to the Company base case. This approach is aligned with NICE methods guidance and DSU TSD23 which state it is appropriate to apply different severity modifier weights in different patient groups receiving different comparator treatments.[16]

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Comparison to atezolizumab plus bevacizumab

Table 1: Updated deterministic base-case results (pairwise analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Atezolizumab + bevacizumab	£244,087	3.02	2.43	[redacted]	[redacted]	[redacted]	STRIDE is dominant	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 2: Scenario setting OS equivalent between atezolizumab plus bevacizumab and STRIDE – a cost comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-
Atezolizumab + bevacizumab	£244,286	3.06	2.44	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

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Table 3: Scenario using a consistent approach towards TTD for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Atezolizumab + bevacizumab	£263,878	3.02	2.43	[redacted]	[redacted]	[redacted]	STRIDE is dominant	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 4: Scenario including the cost of tremelimumab retreatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Atezolizumab + bevacizumab	£263,878	3.02	2.43	[redacted]	[redacted]	[redacted]	STRIDE is dominant	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

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Comparison to TKIs

Table 5: Deterministic base-case results (pairwise analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Sorafenib	£36,799	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	£48,445	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab. *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 6: Deterministic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*
Sorafenib	£36,799	1.92	1.53	-	-	-	-
Lenvatinib	£48,445	1.92	1.53	-	-	-	Strictly Dominated
STRIDE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab. *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

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Table 7: Scenario using a consistent approach towards TTD for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Sorafenib	£36,799	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	£53,161	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab; *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 8: Scenario including the cost of tremelimumab retreatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Sorafenib	£36,799	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	£53,161	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab; *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Appendix: Figures and tables

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Figure 1 Kaplan Meier curves for PFS and TTD from the HIMALAYA trial

Table 9 STRIDE calculated ratio between modelled TTD and PFS

Month	Modelled PFS	Modelled TTD	Absolute Difference	Ratio of hazards (TTD vs. PFS)	Applied to A+B PFS between months:
12	21%	[redacted]	[redacted]	[redacted]	0-<12
24	13%	[redacted]	[redacted]	[redacted]	>12-< 24
36	10%	[redacted]	[redacted]	[redacted]	>24-<36

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48	8%		[redacted]			[redacted]			>36 - <48
60	6%		[redacted]			[redacted]			>48 - <60
72	6%		[redacted]			[redacted]			>60

Table 10 Sorafenib calculated ratio between modelled TTD and PFS

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Liver Trust

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	The British Liver Trust has received the following income from the Pharma and comparators in the last 12 months. All of these were hands off grants in which the companies had no input or involvement in the strategy, concepts, work programme, or content of the activities. Astra Zeneca: three grants for core work totalling £24,054. Boston Scientific (TheraSphere) £8000 Pfizer (bevacizumab) £25,153 Roche (atezolizumab, bevacizumab) 15,000
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The British Liver Trust has consulted widely with patients and is concerned that this recommendation will mean that this new treatment option will not be made available. A diagnosis of liver cancer is devastating and the prognosis is very poor (only 13% of patients live for 5 years) and there are very limited treatment options currently available – particularly if patients have varices (see below). Any new treatment that may prolonged their life and provided them with a real chance of survival is desperately needed for these patients

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2	The current first line treatment can be challenging if the patient has varices. We believe that this combination treatment addresses a key unmet need for an effective treatment that leads to improved survival for patients with advanced or unresectable HCC as it does not have the same bleeding risk. It also provides an alternative immunotherapy option for patients with other co-morbidities who would otherwise not be eligible for immunotherapy.
3	Patients 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 to put in order before death. The HIMALAYA study reports 5-year overall survival data which shows long-term survival benefits of STRIDE for clinicians and patients to make an informed decision about treatment. This survival data is the most mature available for a systemic therapy in HCC, since follow-up studies for atezo-bev and lenvatinib are limited.
4	Liver disease and liver cancer disproportionally affect the poorest in society. Our understanding is that this new treatment combination does not require a compulsory endoscopy before treatment, and that there are less frequent infusions in comparison to atezo-bev. We therefore believe it may represent a treatment option for patients that frees up patient time / money for travel to appointments. These patients are often relatively young have to balance many hospital appointments with work and family life.
5	HCC profoundly impacts patients' quality of life not only from physical but also from psychological and social perspectives, particularly due to the fact that HCC could be associated with lifestyle and personal choices and is often stigmatized. Widening the treatment options that these patients can access, can give patients hope and positively impact their QoL

Insert extra rows as needed

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Warwick Evidence

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No conflicts of interest to declare.
Name of commentator person completing form:	Warwick Evidence

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Comment on the company's modelling of overall survival** The company generated a parametric model of overall survival for STRIDE and sorafenib arms of HIMALAYA using Rimassa et al., 2024 Kaplan-Meier data. Each arm (sorafenib and STRIDE) was modelled separately under a non-proportional hazards procedure, thus the hazard ratio between arms was time varying. The company then applied the time-

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invariant hazard ratio from its network meta-analysis to the sorafenib arm model to obtain an overall survival model for the major comparator atezolizumab plus bevacizumab.
In this company procedure the models for STRIDE and for atezolizumab plus bevacizumab overall survival has been developed differently; for STRIDE there is a time-varying hazard ratio versus. sorafenib, but for the atezolizumab plus bevacizumab there is a time-invariant hazard ratio versus sorafenib.
The evidence assessment group considers that company models for the two competing interventions have not been processed equitably.
The best fit parametric overall survival models for Rimassa et al., based on Akaike and Bayesian information criteria were generalised gamma models. When generalised gamma models are fit to Rimassa et al., reconstructed Kaplan-Meier data under proportional hazards procedure and non-proportional hazards procedure the results differ (Figure 1). Note that the STRIDE model under proportional hazards is inferior to that under the company's a non-proportional hazards procedure and that the gain for STRIDE over sorafenib is reduced under the proportional hazards procedure versus the non-proportional hazards procedure

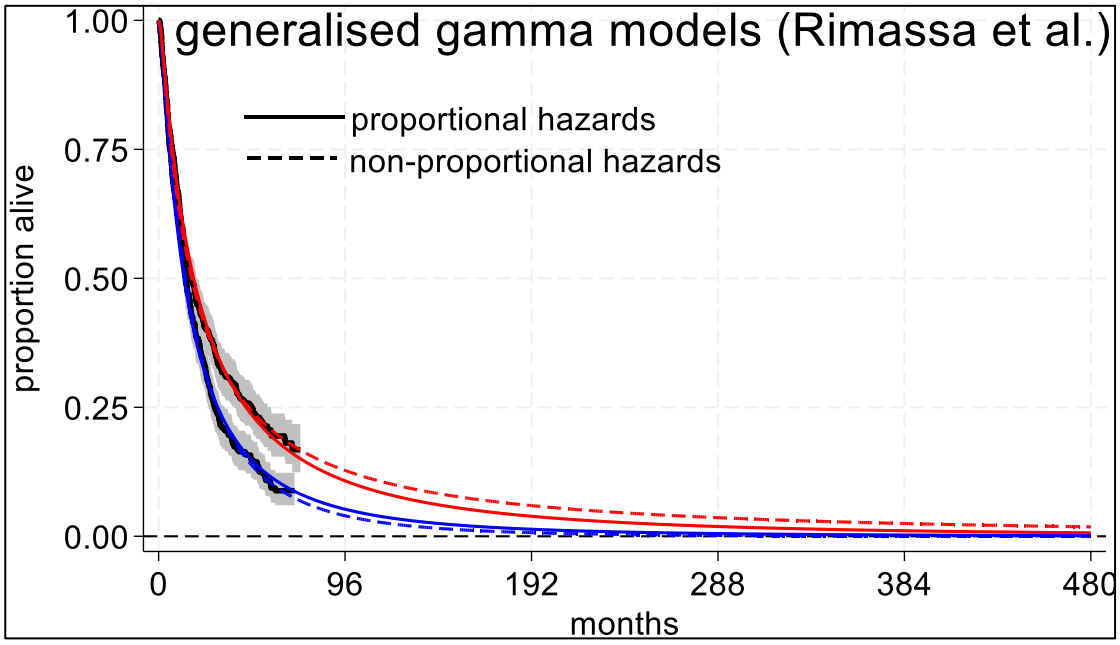

Figure 1: Reconstructed Kaplan Meier plots for STRIDE and Sorafenib derived from the Rimassa et al., and generalised gamma models under proportional (solid lines) and non-proportional hazards procedure (dashed lines)

The company's time invariant network meta-analysis hazard ratio for sorafenib versus atezolizumab plus bevacizumab ([redacted]) can be applied to either the proportional hazards sorafenib model (Figure 1, solid blue line) or to the a non-proportional hazards procedure sorafenib model (Figure 1 dashed blue line) to obtain different models for atezolizumab plus bevacizumab, and these models can be compared with proportional hazards and non-proportional hazards models for STRIDE (Figure 2).
Differing overall survival performance consequent of these two methods is shown in Figure 2A. With the company method (Figure 2A red line) STRIDE is strongly superior to atezolizumab plus bevacizumab over the first 78 months followed by superiority of

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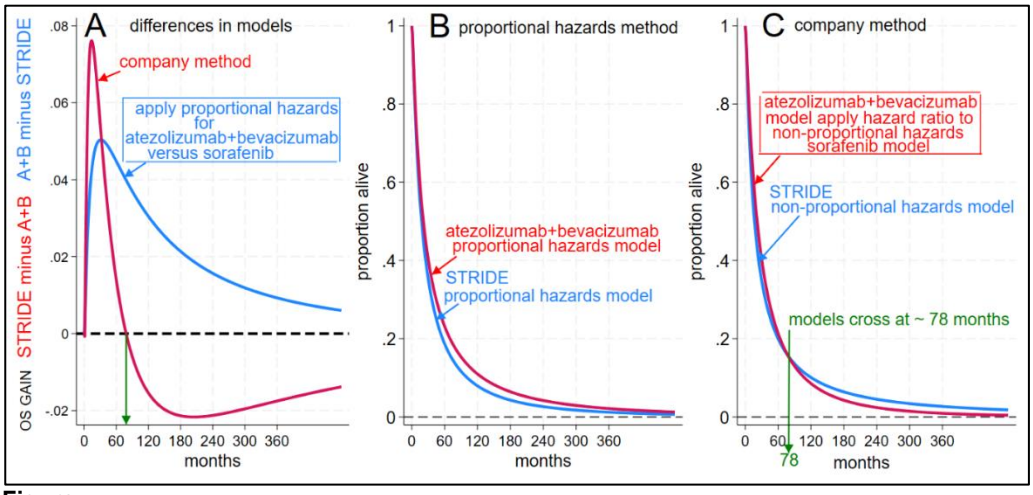
	atezolizumab plus bevacizumab in extrapolation; the end result is that over life time horizon overall survival in the two interventions is almost equal (*as seen in company submission document B Table 68, life-years gained: STRIDE =* [redacted]*; atezolizumab plus bevacizumab =* [redacted]); the reason for this can be seen in Figure 2C where STRIDE and atezolizumab plus bevacizumab models are seen to cross over at about 78 months due to inequitable handling of the two interventions (*as can be seen in company submission document B Figure 35)*. In contrast, when the same method is used for both treatments (Figure 2B) atezolizumab plus bevacizumab is superior to STRIDE across the life-time horizon (Figure 2A blue line). The evidence assessment group considers the company method over-estimates the performance of STRIDE relative to that of atezolizumab plus bevacizumab.  **Figure** **2A: difference between models (comparing atezolizumab plus bevacizumab with STRIDE) when the company method or proportion hazards methods are applied to obtain a model for atezolizumab plus bevacizumab.** **2B: STRIDE and atezolizumab plus bevacizumab models under proportional hazards method.** **2C: STRIDE and atezolizumab plus bevacizumab models under non-proportional hazards method.**
2	**Comment on the company's modelling of progression-free survival and of time to discontinuation of durvalumab treatment.** The company's modelling of progression-free survival followed the same procedure as for overall survival. As described above for overall survival this leads to inequitable procedures for STRIDE versus atezolizumab plus bevacizumab. As described in the evidence assessment group report a further problem arose from the use of a network meta-analysis hazard ratio for atezolizumab plus bevacizumab versus sorafenib that was a clear outsider relative to hazard ratios reported in many relevant published network meta-analyses. Since the company used progression-free survival as a proxy for these problems extend to time to treatment discontinuation of durvalumab.
3	**Comment on an alternative assumption for modelling overall survival** Proportional hazards may hold between recent interventions STRIDE and atezolizumab plus bevacizumab; this may seem more likely than between the older intervention

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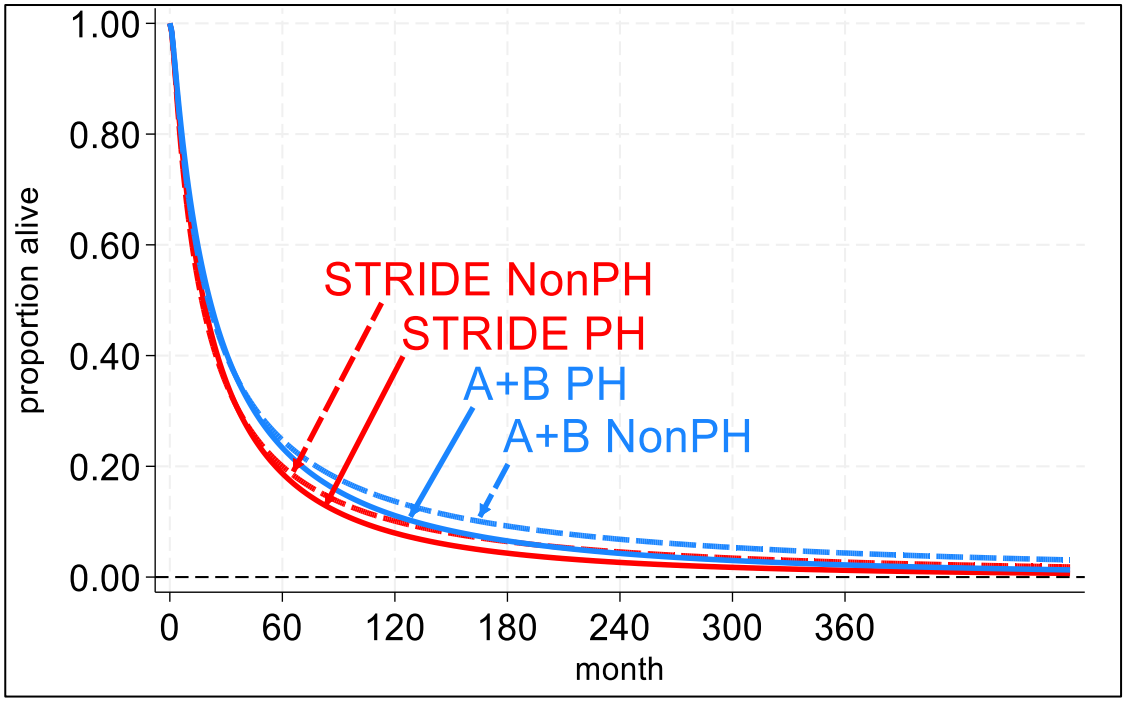
	sorafenib and the recent interventions STRIDE and atezolizumab plus bevacizumab. The company's network meta-analysis hazard ratio for atezolizumab plus bevacizumab versus STRIDE was approximately [redacted]. As illustrated in Figure 3 when this hazard ratio is applied to proportional hazards or to non-proportional hazards models of STRIDE the resulting atezolizumab plus bevacizumab models are superior to the STRIDE models across most of the lifetime horizon.  **Figure 3: STRIDE and atezolizumab and bevacizumab generalised gamma models under alternative assumption of proportional hazards hold between recent interventions atezolizumab and bevacizumab and STRIDE.**
4	**Conclusion** STRIDE and atezolizumab plus bevacizumab are both clearly superior interventions versus sorafenib, but the most important comparison is between STRIDE and atezolizumab plus bevacizumab. In the evidence assessment group's opinion the company's modelling methodology tends to bias in favour of STRIDE relative to atezolizumab plus bevacizumab. In consequence the company's overall survival modelling implies equal mortality and is slightly in favour of STRIDE versus atezolizumab plus bevacizumab, an inference that seems very unlikely in view of company's own network meta-analysis hazard ratio for atezolizumab plus bevacizumab versus STRIDE being less than one and in line with seven previously published network meta-analyses comparing first line treatments for advanced hepatocellular carcinoma listed below: **Meta-analysis author** — **Hazard ratio** *Vogel 2023 et al: Liver Cancer DOI: 10.1159/000533166:* — *0.87* *Fong 2023 et al: Liver Cancer 2023; 12: 7–18* — *0.81* *Wang 2024 et al: PLoS ONE 19(7): e0306869.* — *0.79*

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	Ding 2023 et al: Critical Reviews in Oncology/Hematology 2023; 184 103940	*0.84*
	Zhang 2023 et al: Annals of Medicine 2023; 55, (2):2242384	*0.85*
	Liu 2022 et al: Front. Immunol. 13:1103055. DOI: 10.3389	*0.85*
	Chen 2024 et al: J Clinical & Translational Hepatology 2024 12(1):15-24	*0.85*

5

Comment on the severity modifier

The evidence assessment group identifies a potential inconsistency between the new evidence on market share provided in Sections 1.2 and 3.2 and the committee's conclusion on severity, as presented in Section 3.12.

- **Section 1.2 (page 3)** states: *"Most people have atezolizumab plus bevacizumab."*
- **Section 3.2 (page 5)** states: *"The NHS England Cancer Drugs Fund lead confirmed that in the last year, around 69% of people with HCC had first-line treatment with atezolizumab plus bevacizumab. Around 16% of people with HCC had lenvatinib, and 15% had sorafenib."*
- **Section 3.12 (Severity, page 14)** states: *"The committee considered both approaches, but it did not reach a conclusion on whether a severity modifier should be applied for fully incremental analyses or pairwise comparisons between STRIDE and lenvatinib or sorafenib."*

The evidence assessment group's assessments demonstrate that, using the company's inputs, including age, sex distribution, and total quality adjusted life years for comparators and assuming that at least 28% of patients receive atezolizumab plus bevacizumab while 82% receive other comparators (sorafenib and lenvatinib), the proportional shortfall is estimated to be [redacted]%, with a quality adjusted life year weight of one. This result is confirmed when the treatment distribution is based on the data presented in Section 3.2 of the *Draft Guidance Consultation* document.

Accordingly, if it is assumed that 69% of people with hepatocellular carcinoma received first-line treatment with atezolizumab plus bevacizumab, while approximately 16% received lenvatinib and 15% received sorafenib, the proportional shortfall is calculated to be [redacted]%, with a quality adjusted weight of one.

Table 1: Severity weight assuming market share for people receiving treatment for hepatocellular carcinoma

% of hepatocellular carcinoma patients treated with atezolizumab plus	Weighted quality adjusted life years*	Absolute (proportional) shortfall	Quality adjusted life year weight

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	bevacizumab 0% [redacted] [redacted] x 1.2 10% x 1.2 20% x 1.2 25% x 1.2 27% x 1.2 28% x 1 29% x 1 35% x 1 50% x 1 69% x 1 80% x 1 100% x 1 *Calculated based on the percentage of HCC patients receiving each comparator, including atezolizumab plus bevacizumab, as well as other treatments, sorafenib and lenvatinib. Quality adjusted life years inputs come from company's base-case **Conclusion** The evidence assessment group concludes that if only 28% of people with hepatocellular carcinoma received first-line treatment with atezolizumab plus bevacizumab, then no modifier should be applied to any of the comparisons, including fully incremental analyses or pairwise comparisons.

Insert extra rows as needed

Checklist for submitting comments

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.	

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Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK	
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A	

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Name of commentator person completing form:	[redacted]	

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.	EAG responses
1	**Overall comments on the draft guidance** • We would like to thank NICE for the comprehensive summary of the evidence that was considered in the evaluation of durvalumab with tremelimumab (Single Tremelimumab Regular Interval Durvalumab, 'STRIDE') for untreated advanced or unresectable hepatocellular carcinoma (HCC) and the recommendations and requests for follow-on analyses made by the committee. • We are however disappointed that the committee decided to not recommend STRIDE for this indication. There was a clear consensus during the committee meeting that "*…advanced or unresectable HCC has a severe effect on both quality and length of life*" and that "*People with HCC often feel frustrated by the limited treatment options, particularly because existing options may not be suitable for them or have unmanageable side effects*". We agree with the committee that atezolizumab plus bevacizumab is used most commonly in this population because of its superior efficacy to TKIs. However, the committee also noted that people with untreated advanced or unresectable HCC would welcome an alternative effective first-line treatment option. • With our response to the draft guidance below, we provide the following to support the committee in their decision making: o A revised company base-case utilising the committee's preferred time-dependent approach for utility values (Table 1 and Table 5 in the Appendix)	The EAG thanks the company for acknowledging/agreeing with the committee that atezolizumab plus bevacizumab is the most used treatment for untreated advanced or unresectable hepatocellular carcinoma. The EAG has acknowledged receipt of the model, which comprised updated base-case results based on making a change to utilising the committee's preferred assumption of a time-dependent approach for utility values and an increase to the discount for durvalumab. Additionally, the EAG acknowledges receipt of the company's scenario analyses. With regards to the scenario recommended by the AC, 'A scenario where the OS for atezolizumab plus bevacizumab is equivalent to STRIDE', the EAG notes that this scenario does not reflect the request of the AC. However, the company has provided their rationale in point 4. Based on the models submitted and the analyses performed, the

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	○ A scenario where the OS for atezolizumab plus bevacizumab is equivalent to STRIDE (requested by the committee) ○ A scenario assuming a ratio between TTD and PFS for atezolizumab plus bevacizumab and lenvatinib ○ A scenario accounting for the costs of tremelimumab retreatment (requested by the committee) • We hope that the analyses support the committee in their decision-making during the next committee meeting. The analyses shows that **STRIDE still strongly dominates the primary comparator, atezolizumab plus bevacizumab, in the revised Company base case and provides a positive net health benefit at both the £20,000 and £30,000 willingness-to-pay thresholds**. In a scenario requested by the Committee, setting OS equivalent between STRIDE and atezolizumab plus bevacizumab, STRIDE provides cost savings of [redacted].	were able to replicate these results.
2	**The HIMALAYA trial provides the longest follow-up (5-years for OS) for an immunotherapy treatment in advanced or unresectable HCC, reducing the level of uncertainty in the long-term clinical outcomes and extrapolation of the STRIDE data. Other treatments have not published data with mature follow-up, making comparisons challenging.** • The draft guidance does not reference the 5-year published OS for STRIDE, which provides more certainty in the long term clinical outcomes and demonstrates a statistically significantly improved OS compared to sorafenib (HR: 0.76 [0.65-0.89]).[1] • Data from IMBrave150 (atezolizumab plus bevacizumab) and REFLECT (lenvatinib) has not provided a similar length of follow-up, making treatment comparisons in the long-term challenging. Using the published data available for the relevant comparators, a methodologically robust NMA was conducted and presented in the submission, following the NICE DSU Guidelines ('the Company NMA').[2] The results of this NMA were broadly aligned with previous NMAs, including Vogel 2023.[3] The committee have expressed a preference for using the hazard ratios derived from the Vogel NMA. • The primary difference between the Vogel NMA and the Company NMA was the use of different definitions across studies for PFS. The Company NMA used a consistent definition of PFS across studies, that is PFS	

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	assessed per investigator. The rationale behind this decision is as follows: ○ PFS per investigator was a secondary endpoint in HIMALAYA. PFS as assessed by blinded independent review (BICR) was an exploratory endpoint only at interim analysis 1 (patients with 32 weeks of follow-up). ○ Similarly, in REFLECT, PFS per BICR was a post-hoc analysis, whilst PFS per investigator was a secondary endpoint.[4] It is not clear whether Vogel used PFS per INV or PFS per BICR in their NMA. • The committee said that they preferred the PFS per BICR outcome measure over investigator-assessed PFS because it is a more objective measure with less risk of bias, however, no commentary is provided of using differing outcome definitions, or outcomes that are exploratory rather than secondary. It is also notable that the Vogel study did not identify these differences in definition across studies and failed to comment on the differences and limitations of their approach. (i.e., use of mixed definitions without providing commentary). • The Company NMA also used the most recent 5-year data for OS from HIMALAYA OS.[1] • For these reasons, the Company NMA represents the best evidence base for the indirect treatment comparison. This has been retained in the Company base case. • When applying the results of the NMA in the economic analysis, the committee's preference also disregards the finding that the proportional hazards assumption does not hold within the REFLECT trial. For both PFS and OS, the time-varying analysis of RELFECT shows the hazard ratio for lenvatinib vs. sorafenib trends towards or exceeds unity in all models tested. For OS, given that the REFLECT trial is a non-inferiority trial for OS reporting that lenvatinib was statistically non-inferior to sorafenib, the HR is set to 1 for OS in the company base case.[4] Assuming a constant HR of [redacted] as calculated in the Company NMA in the long-term is optimistic and inconsistent with published evidence. For PFS, the calculated HR from the NMA is used, but this is considered as a conservative assumption. • The application of a HR of 1 for lenvatinib therefore represents the most appropriate approximation of the long-term relationship between lenvatinib and sorafenib for OS, consistent with the non-inferiority findings of the	

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	REFLECT study. This has been retained in the Company base case.	
3	**Rationale for selecting generalised gamma over the 1-knot hazard curve for modelling sorafenib OS has not been provided** • In the Company base case, a spline-based model was considered justified for sorafenib OS given the time-varying hazards observed in the HIMALAYA trial. After following the NICE DSU guidance including consideration of the goodness-of-fit statistics, visual inspection of the extrapolated vs. KM curves, and external validation to understand the suitability of the extrapolations, the Company considered the hazard 1-knot model to provide the best extrapolation of OS in the base case. In one-to-one interviews with 7 UK clinical experts, clinicians advised that the scenario predicting the lowest survival expectations (hazard 1-knot) would represent the most clinically plausible one, noting that all extrapolations may be overestimating survival for sorafenib.[5] The generalised gamma model represented a slightly more optimistic extrapolation and was tested in a scenario analysis; this was demonstrated to have a minor impact on the ICER. • The rationale for the EAG's preference for generalised gamma over hazard 1-knot is unclear, particularly when the two models provide very similar extrapolations. Similarly, the committee have said they prefer the EAG approach but have not provided justification. • Given the omission of a rationale for preferring the generalised gamma, we have retained the hazard 1-knot model in our revised base case. This is further motivated by the generalised gamma providing slightly more optimistic predications in the long-term.	**EAG comments on the modelling of OS** In the EAG's critique of the company's overall survival (OS) modelling of STRIDE and sorafenib, we reconstructed OS KM data from Rimassa et al and fitted several standard models. We found that the best fitting parametric model to the reconstructed KM OS data was the generalised gamma models assessed by the information criteria. Following the NICE DSU guidance about selecting the most appropriate curve (AIC/BIC statistics, visual inspection and external validation) we selected the generalised gamma in our base-case. As noted by the company, the generalised gamma produced similar extrapolation OS results to the company's spline model with 1-knot. In the EAG's modelling of OS, we re-constructed KM data under proportional hazards and non-proportional hazard procedures, which led to different results (see Figure 1)  Figure 1: Reconstructed Kaplan Meier plots for STRIDE and Sorafenib derived from the Rimassa et al., and generalised gamma models under proportional (solid lines) and non-proportional hazards procedure (dashed lines).

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		The company's models of OS for STRIDE and sorafenib arms of HIMALAYA used Rimassa et al., 2024 Kaplan-Meier data. Each arm (sorafenib and STRIDE) was modelled separately under a non-proportional hazards procedure, thus the hazard ratio between arms was time varying. The company applied the time-invariant hazard ratio ([redacted]) from its network meta-analysis to the sorafenib arm model to obtain its overall survival model for atezolizumab plus bevacizumab (A+B). The company OS models for STRIDE and for A+B have been developed differently; for STRIDE there is a time-varying hazard ratio versus sorafenib, but for the A+B there is a time-invariant hazard ratio versus sorafenib. The EAG considers that the company models for the two interventions have been processed inequitably introducing bias in favour of STRIDE. This inequitable procedure means the company's OS models for STRIDE and A+B imply superiority for STRIDE for the first 78 months, then the models cross over implying superiority for A+B. The consequence is that the life-time OS gain for the two is almost equal. If equitable time invariant HRs versus sorafenib ([redacted] for STRIDE and [redacted] for A+B) are applied to the sorafenib model then A+B OS is superior to, or as good as, STRIDE OS over the whole life-time horizon and models do not cross. NOTE: AstraZeneca and Vogel et al., OS HRs for STRIDE versus sorafenib and A+B versus sorafenib align closely.

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		AZ Vogel A+B vs sorafenib [redacted] 0.68 STRIDE vs sorafenib [redacted] 0.78
4	**A scenario setting equivalent OS hazard rate functions between atezolizumab plus bevacizumab and STRIDE from the time point at which they cross is not supported by data and considered a highly conservative assumption** • The committee requested further scenarios including updated OS modelling that has equal hazard rate functions from the time point at which the atezolizumab plus bevacizumab and STRIDE curves cross. • The atezolizumab plus bevacizumab and STRIDE OS curves cross because STRIDE is modelled using an independently fit curve to the data whilst atezolizumab plus bevacizumab is estimated by applying a HR calculated through the Company NMA to the sorafenib arm in the model. This approach was justified because the proportional hazards assumption was considered to not hold for STRIDE vs. sorafenib in HIMALAYA whereas it was considered to hold for atezolizumab plus bevacizumab vs. sorafenib in IMBRAVE150. The same conclusion was drawn about the IMBrave150 OS data in the TA666 submission.[6,7] • Furthermore, as noted in the committee papers, the clinical experts present during the committee meeting considered it plausible to observe a durable treatment effect with the STRIDE regimen given the mechanism of action of termelimumab, which may explain the crossing of OS curves. This is aligned with observations that delayed separation or crossing of survival curves is observed in other IO RCTs, driven by the distinct mode of action of such regimens.[8] • Therefore, this scenario is not supported by data or clinical opinion. It is a highly conservative scenario as it inflates the long-term benefit from atezolizumab plus bevacizumab, which is inconsistent with the modelling approach and is not supported by published data. Despite this, we considered the point at which the treatment arms crossed. STRIDE initially starts above atezolizumab plus bevacizumab until falling below in week 3. Atezolizumab plus bevacizumab then sits above STRIDE until week 341 (~6.5 years), where it crosses back over to sit beneath STRIDE. • Given the curves cross at two points, we considered a pragmatic solution to be to implement the assumption from the start of the model. The results of this analysis are provided in the Appendix Table 2. The incremental QALYs under this scenario are zero. STRIDE is cost	The EAG considers that the company's approach results in inequitable modelling of atezolizumab + bevacizumab and STRIDE. Following AC1, the committee requested a scenario analysis that sets the equivalent OS hazard rate functions between atezolizumab plus bevacizumab and STRIDE from the timepoint at which they cross. However, it was unclear to the EAG the committee's preference in using the OS curve for STRIDE or atezolizumab plus bevacizumab from the timepoint at which they crossed. Hence, we undertook two scenarios using the STRIDE OS survival curve from the timepoint the curves crossed and the atezolizumab plus bevacizumab OS survival at the timepoint the curves crossed. Additionally, the EAG considered the company's approach of assuming equivalence between STRIDE and atezolizumab plus bevacizumab (using the STRIDE OS model only). Another scenario was considered, using the company's approach in modelling OS and PFS for STRIDE and sorafenib (i.e., using IPD from HIMALAYA trial), and the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the OS and PFS of atezolizumab plus bevacizumab, and lenvatinib. An alternative approach that could be considered is to assume that the proportional hazard assumption is more likely to hold between recent interventions. The EAG thinks proportional hazards is more

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	saving compared to atezolizumab plus bevacizumab (incremental costs for STRIDE vs. atezolizumab plus bevacizumab are [redacted]). This finding is similar to the cost comparison provided in the Company submission Document B, Table 72.	likely to hold between recent interventions (atezolizumab + bevacizumab and STRIDE) than between recent interventions and sorafenib (introduced about 15 years ago). Under this scenario using the company's NMA HRs the EAG found that STRIDE OS was inferior to atezolizumab + bevacizumab OS across the whole life-time horizon (EAG Figure B, solid lines). [redacted] Figure 2: Atezolizumab + bevacizumab and STRIDE generalised gamma models under assumption that proportional hazards hold between recent interventions A+B and STRIDE.
5	**Whilst we recognise the Committee's preference for a consistent approach to modelling treatment duration, setting TTD equivalent to PFS for the STRIDE regimen does not reflect observed data from the HIMALAYA clinical trial and is inconsistent with approaches taken in previous technology appraisals** • As highlighted in the draft guidance, time to treatment discontinuation (TTD) data from the HIMALAYA study was used to model the treatment duration for STRIDE and sorafenib as it was considered the most accurate representation of treatment duration. • In the absence of TTD data for atezolizumab plus bevacizumab and lenvatinib, the Company base case assumed that TTD is equal to PFS for these comparators. As atezolizumab plus bevacizumab is recommended until loss of clinical benefit or unacceptable toxicity, and lenvatinib can be used until loss of ongoing clinical benefit or unacceptable toxicity, treatment beyond progression is permissible in clinical practice, making this assumption arguably conservative. This is supported by the draft guidance which notes that equating PFS with TTD is considered	**EAG comments on the company scenario assuming a ratio between TTD and PFS for atezolizumab plus bevacizumab and lenvatinib** It is unfortunate that PFS was used as proxy for TTD because consistency of the relationship between these variables both within and between treatments is problematical. Although TTD for lenvatinib (generated by EAG for TA551) is in the public domain, the TTD for atezolizumab plus bevacizumab, although presented by the company for TA666, remains commercial-n-confidence. The company suggested a novel approach that estimated the TTD to PFS ratio for STRIDE and for sorafenib and have employed the annualised

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	flawed and not reflective of clinical practice, potentially underestimating TTD for these treatments. • Whilst we recognise that the committee prefer a consistent across comparators, the proposed scenario is inconsistent with approaches adopted in previous appraisals. Of particular note, TA666 utilised observed TTD data for atezolizumab plus bevacizumab and sorafenib as TTD data were available from the IMBrave150 trial; meanwhile, PFS was used as a TTD proxy for lenvatinib due to the absence of TTD data (Company Submission pg 108). • Enforcing this assumption for STRIDE and sorafenib is inconsistent with the evidence from the HIMALAYA trial. Figure 1 in the Appendix shows the PFS curves sit below the TTD curves for both treatments initially; for sorafenib, this continues in the latter part of the KM curves and in the extrapolations, but for STRIDE, the KM curves converge at the end of the trial and the extrapolations cross. Based on this, we assert that the approach taken in the company base case is the most suitable given the available data. Nonetheless, we provide an alternative approach in a scenario, applying a consistent methodology across comparators, to address the committee's preference. • Given the relationship between TTD and PFS observed for STRIDE and sorafenib in HIMALAYA (Figure 1) we present a scenario whereby a ratio between the curves is calculated and assumed to apply to atezolizumab plus bevacizumab and lenvatinib. For atezolizumab plus bevacizumab, this is based on the STRIDE TTD vs. PFS relationship, and for lenvatinib, this is based on the sorafenib TTD vs. PFS relationship. Given the visual evidence of non-proportionality between these curves (particularly for STRIDE), this ratio was captured at annual timepoints based on the modelled curves for STRIDE and sorafenib for PFS and TTD from 1 year to 6 years. From 6-years onwards the relationship between the modelled TTD and PFS curves were observed to be stable in both arms in HIMALAYA. This calculated ratio is captured in Table 9 and Table 10; for STRIDE the TTD vs. PFS ratio ranges between [redacted], for sorafenib the range is much narrower between [redacted]. These ratios are then applied to the atezolizumab plus bevacizumab extrapolated PFS curve (values from Table 9) and the lenvatinib extrapolated PFS curve (values from Table 10). • The results of this scenario are provided in the Appendix Table 3 and Table 7. Compared to the revised Company base case, STRIDE remains	life-time extrapolated results to develop a TTD estimate for atezolizumab plus bevacizumab (and also for lenvatinib). In this the company used extrapolated modelled data for both arms of HIMALAYA for both PFS and TTD rather than Kaplan-Meier ("observed") data. The company state: *"for STRIDE the TTD vs. PFS ratio ranges between [redacted] and [redacted], for sorafenib the range is much narrower between [redacted] and [redacted]."* and annualised values for STRIDE and for sorafenib are presented in Tables 11 and 12. In EAG opinion it is preferable to use "observed" Kaplan-Meier data to develop TTD vs PFS ratios rather than to use "selected" and extrapolated parametric models. Also, EAG prefer a continuous graphical representation of TTD / PFS ratios to the tabulated annualised values presented by the company. Therefore, the EAG estimated TTD to PFS ratios using Kaplan-Meier data reported in the company's economic model. The ratios TTD to PFS for STRIDE and for sorafenib are shown EAG Figure A. [redacted] **EAG Figure A. TTD/PFS ratios calculated using Kalan-Meier**

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	dominant compared to atezolizumab plus bevacizumab. For the comparison to the TKIs, the pairwise ICER does not change relative to sorafenib, and it decreases by 9% compared to lenvatinib.	**data submitted in the company economic model** The results suggest more variation in the TTD/PFS ratio for sorafenib than for STRIDE in contrast to the company's tabulated annualised ratios that over extrapolation to a lifetime horizon suggest that *"for STRIDE the TTD vs. PFS ratio ranges between [redacted] and [redacted], for sorafenib the range is much narrower between [redacted] and [redacted]."* EAG's inference from Figure 1 is that the TTD/PFS ratios take contrasting forms and the results from the company approach may depend more on the use of selected parametric models and the extreme extrapolation to a lifetime horizon than on the "observed" Kaplan-Meier data from the HIMALAYA trial.
6	**Including tremelimumab retreatment costs is inconsistent with the marketing authorisation and anticipated use in clinical practice** • STRIDE received EMA and MHRA marketing authorisation for first-line treatment of adult patients with advanced or unresectable HCC.[9] • In the HIMALAYA trial, a small proportion of participants (8%) in the STRIDE arm received retreatment with one additional dose of tremelimumab. The economic model did not include the additional cost of retreatment since tremelimumab retreatment is not permitted under its MHRA regulatory license, meaning this would not occur in practice. The committee expressed concern that incorporating the clinical benefits of tremelimumab retreatment without accounting for the additional costs could bias the cost-effectiveness results for STRIDE. There is no reason to believe that there is meaningful bias in the survival extrapolations for STRIDE given the small proportion of patients. • Despite this, we have provided the results of this in the Scenarios in the Appendix. There is minimal impact to the ICER (an increase of 2-3% in the TKI ICERs). In this scenario, the tremelimumab retreatment proportion	The EAG has followed the company's approach regarding the inclusion of tremelimumab retreatment costs, assuming this is inconsistent with its marketing authorisation and clinical practice in the UK context. Based on the EAG's assessment, this has a small effect on the ICER. The EAG is happy with the AC and the company's approach in providing a scenario analysis to demonstrate the impact of including tremelimumab retreatment costs on incremental costs and ICERs in different pairwise comparisons.

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	displaces other subsequent treatments, with the distribution of the remaining subsequent treatments being evenly adjusted, maintaining the same relative proportions as in the Company submission.	
7	**Benefits not captured in the QALY calculations** The draft guidance noted that NICE will consider various aspects including uncaptured health benefits in their assessment of a technology as an effective use of NHS resources. However, they have not been captured in detail in the draft guidance. Therefore, we believe it's important to emphasize the meaningful additional benefits associated with STRIDE that are not reflected in the QALY but are fundamental to the decision-making process. **Patients and caregivers' benefits** These benefits, particularly those that impact patient lives, are important qualitative considerations for decision making: HCC in conjunction with liver disease has been found to disproportionately affect the poorest in society, with higher incidence and inferior survival associated with socioeconomic deprivation.[10] This characteristic of liver disease cannot be overlooked when considering beyond the QALY benefits of STRIDE as: • **Impact on caregivers and family members:** It is estimated that approximately 15% of the total health cost of HCC across European countries, including UK, is due to informal care.[11] Having access to innovative treatment such as STRIDE could alleviate this financial and psychological strain, enabling caregivers to resume their professional lives and societal contributions • **Patient experience:** Durvalumab is administered every 4 weeks schedule, whilst atezolizumab plus bevacizumab is delivered more frequently (every 3 weeks), meaning less frequent trips to the hospital. Furthermore, there is no need for an endoscopy, and as there is no increased risk of bleeding there is a reduced burden of extra monitoring.[12] This facilitates a better patient experience, especially for patients with complex lives, disadvantaged backgrounds or in more remote locations who are unable to attend frequent hospital appointments. • **Option Value** the value of living longer to see future novel therapies, is a way patients and their loved ones perceive the impact of survival outcomes, which helps maintain hope, allowing them to better deal with the burden of the disease.[13] HIMALAYA 5-year follow-up	The EAG acknowledges the company's statements about the additional benefits that may not be captured in the QALY calculation.

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	reinforces the certainty around the long-term survival provided by STRIDE, giving the patients the hope of live enough to being able to access the novel agents that are in development.	
	References 1. Rimassa L, Sangro B, Lau G, et al. Five-year overall survival (OS) and OS by tumour response measures from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC). In: ; 2024. 2. Dias S, Welton N, Sutton A, Ades A. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials*.; 2011. https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf 3. Vogel A, Finn RS, Blanchet Zumofen MH, et al. Atezolizumab in Combination with Bevacizumab for the Management of Patients with Hepatocellular Carcinoma in the First-Line Setting: Systematic Literature Review and Meta-Analysis. *Liver Cancer*. 2023;12(6):510-520. doi:10.1159/000533166 4. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *The Lancet*. 2018;391(10126):1163-1173. doi:10.1016/S0140-6736(18)30207-1 5. AstraZeneca Data on File. *HIMALAYA Clinician Validation Interviews*.; 2024. 6. NICE. TA666 Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma. December 16, 2020. Accessed May 10, 2024. https://www.nice.org.uk/guidance/ta666 7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745 8. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2019;381(16):1535-1546. doi:10.1056/NEJMoa1910836	

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	9. Medicines and Healthcare products Regulatory Agency (MHRA). IMJUDO 20 mg/ml concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). Accessed February 24, 2025. https://www.medicines.org.uk/emc/product/14841/smpc#gref 10. Cancer Research UK. Liver cancer incidence statistics by deprivation. Cancer Research UK. May 15, 2015. Accessed February 24, 2025. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/incidence 11. Digestive Cancers Europe. The Costs of Liver Cancer - Factsheet. 2021. Accessed February 24, 2025. https://digestivecancers.eu/publication/the-costs-of-liver-cancer-factsheet/ 12. Suddle A, Reeves H, Hubner R, et al. British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults. *Gut*. Published online April 16, 2024. doi:10.1136/gutjnl-2023-331695 13. Should We Consider Including a Value for "Hope" as an Additional Benefit Within Health Technology Assessment? *Value Health*. 2022;25(9):1619-1623. doi:10.1016/j.jval.2022.03.006 14. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evid*. 2022;1(8). doi:10.1056/EVIDoa2100070 15. Liver Cancer United Kingdom (UK). Stages of HCC. Liver Cancer UK. 2022. Accessed February 24, 2025. https://livercanceruk.org/liver-cancer-information/types-of-liver-cancer/hcc/treating-hcc/stages-of-hcc/ 16. Calculating severity shortfall for nice evaluations. July 23, 2024. Accessed February 25, 2025. https://www.sheffield.ac.uk/nice-dsu/tsds/severity-shortfall-tsd	

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- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [redacted]' in turquoise, and all information submitted as '[redacted]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

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Updated base-case and scenario analysis results

In line with our response to the draft guidance above, we have updated the Company's base-case analysis accepting the use of the committee-preferred time-dependent approach for utility values. In the Company submission, utilities were modelled as being treatment-dependent because it was considered to be the most robust way of capturing the impact of adverse events due to TKIs on patients.[14,15] In response to the EAG clarification questions, the Company provided a time-to-death utility approach, which resulted in minor changes to the company submitted base case ICERs. Given the committee preference for this approach, this has been accepted in the revised Company base case.
Additionally, the following scenarios are presented:

- A scenario where the OS for atezolizumab plus bevacizumab is equivalent to STRIDE
- A scenario assuming a ratio between TTD and PFS for atezolizumab plus bevacizumab and lenvatinib
- A scenario accounting for the costs of tremelimumab retreatment (requested by the committee)

In the CEM submitted in the ACD response, these settings can be located on the 'Main Menu' worksheet.

The committee agreed that, according to clinical expert opinion and data from NHS England, atezolizumab plus bevacizumab is used most commonly in this population, and that a pairwise comparison with atezolizumab plus bevacizumab was an appropriate presentation of results. Therefore, as this is the primary comparator, we have presented these results first using a severity modifier of 1.

The committee also acknowledged that lenvatinib and sorafenib are taken by some people. This population generally consists of those who are not suitable for treatment with atezolizumab plus bevacizumab, with clinicians estimating that approximately 25% are contraindicated due to bleeding risk and other comorbidities.[5] We have therefore presented these pairwise results and fully incremental analysis in separate tables, retaining the x1.2 severity modifier, which was recalculated following the change to the Company base case. This approach is aligned with NICE methods guidance and DSU TSD23 which state it is appropriate to apply different severity modifier weights in different patient groups receiving different comparator treatments.[16]

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Comparison to atezolizumab plus bevacizumab

Table 1: Updated deterministic base-case results (pairwise analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Atezolizumab + bevacizumab	£244,087	3.02	2.43	[redacted]	[redacted]	[redacted]	STRIDE is dominant	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 2: Scenario setting OS equivalent between atezolizumab plus bevacizumab and STRIDE – a cost comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-
Atezolizumab + bevacizumab	£244,286	3.06	2.44	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

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Table 3: Scenario using a consistent approach towards TTD for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Atezolizumab + bevacizumab	£263,878	3.02	2.43	[redacted]	[redacted]	[redacted]	STRIDE is dominant	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 4: Scenario including the cost of tremelimumab retreatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Atezolizumab + bevacizumab	£263,878	3.02	2.43	[redacted]	[redacted]	[redacted]	STRIDE is dominant	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

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Comparison to TKIs

Table 5: Deterministic base-case results (pairwise analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Sorafenib	£36,799	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	£48,445	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab. *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 6: Deterministic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*
Sorafenib	£36,799	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	£48,445	1.92	1.53	[redacted]	[redacted]	[redacted]	Strictly Dominated
STRIDE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab. *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

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Table 7: Scenario using a consistent approach towards TTD for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Sorafenib	£36,799	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	£53,161	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab; *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Table 8: Scenario including the cost of tremelimumab retreatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER vs. baseline (£/QALY)*	INHB (£20,000 WTP)	INHB (£30,000 WTP)
STRIDE	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Sorafenib	£36,799	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	£53,161	1.92	1.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All results include the commercial access agreement in place for durvalumab; *includes x1.2 severity modifier
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness to pay.

Appendix: Figures and tables

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Figure 1 Kaplan Meier curves for PFS and TTD from the HIMALAYA trial

[redacted]

[redacted]	[redacted] PFS	[redacted] TTD	[redacted] Difference	[redacted] (TTD vs. PFS)	[redacted] between months:
12	21%	[redacted]	[redacted]	[redacted]	0-<12
24	13%	[redacted]	[redacted]	[redacted]	>12-< 24

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36	10%		[redacted]			[redacted]			>24-<36
48	8%		[redacted]			[redacted]			>36 - <48
60	6%		[redacted]			[redacted]			>48 - <60
72	6%		[redacted]			[redacted]			>60

Table 10 Sorafenib calculated ratio between modelled TTD and PFS

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

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