

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

[The final scope and final stakeholder list are on the NICE website.](#)

- 1. Company submission from AstraZeneca:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
 - c. Submission addendum
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. British Association for the Study of the Liver, *endorsed by Professor Tim Meyer, Consultant in Medical Oncology – clinical expert nominated by British Association for the Study of the Liver*
 - b. British Liver Trust, *endorsed by the patient expert Monica Walsh – nominated by British Liver trust*
- 4. Expert personal perspectives from:**
 - a. Dr David Pinato, Consultant Medical Oncologist – clinical expert nominated by AstraZeneca
- 5. External Assessment Report** prepared by Warwick Evidence
- 6. External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma

[ID2725]

Document B

Company evidence submission

30th September 2024

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Company evidence submission template for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the [user guide](#).

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Abbreviations

Abbreviations	Definition
AE	Adverse event
AFP	Alpha-fetoprotein
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
APC	Antigen presenting cell
AST	Aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
BGR	Brook–Gelman–Rubin
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BSG	British Society of Gastroenterology
CR	Complete response
CI	Confidence interval
CrI	Credible interval
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computerised tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DBP	Diastolic blood pressure
DCO	Data cut-off
DCR	Disease control rate
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSU	Decision Support Unit
EASL	Eastern Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
EGD	Esophagogastroduodenoscopy
EHS	Extrahepatic spread
EMA	European Medicines Agency

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Abbreviations	Definition
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
EQ	EuroQol
FACT-G	Functional Assessment of Cancer Therapy - General
FAS	Full analysis set
FE	Fixed effects
FWER	Family-wise error rate
GHS	Global Health Status
HBcAb	Hepatitis B surface antigen
HBV	Hepatic B virus
HCC	Hepatocellular carcinoma
HCRU	Healthcare resource utilisation
HCV	Hepatic C virus
HDV	Hepatic D virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
INR	International normalised ratio
INV	Investigator-assessed
IO	Immuno-oncology
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IWRS	Interactive web response system
LY	Life year
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MASLD	Metabolic dysfunction-associated steatotic liver disease
MCMC	Markov Chain Monte Carlo
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging

Abbreviations	Definition
MTP	Multiple testing procedure
mTTO	Median time to onset
mTTR	Median time to resolution
MVI	Macrovascular invasion
NCI	National Cancer Institute
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
RDI	Relative dose intensity
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazard
PHA	Proportional hazard assumption
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
Q4W	Every four weeks
QALY	Quality-adjusted life year
QLQ-C30	Core Quality of Life questionnaire
QLQ-HCC18	Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module
RCT	Randomised controlled trial
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
RWE	Real world evidence
SAE	Serious adverse event
SAS	Safety analysis set

Abbreviations	Definition
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMQs	Standardised MedDRA queries
STA	Single technology appraisal
STRIDE	Single Tremelimumab Regular Interval Durvalumab
TA	Technology appraisal
TACE	Transarterial chemoembolisation
TBL	Total bilirubin
TCR	T cell receptor
TEM	Treatment effect modifier
TIP	Tumour and immune cell positivity
TKI	Tyrosine kinase inhibitor
TRAE	Treatment-related adverse event
Treg	T regulatory cell
TSD	Technology Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
ULN	Upper limit normal
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
VBA	Visual Basis for Applications
VEGF	Vascular endothelial growth factor
WTP	Willingness to pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The objective of this evaluation is to determine the clinical and cost-effectiveness of durvalumab (1,500 mg; every four weeks [Q4W]) in combination with tremelimumab (300 mg; single dose), hereafter referred to as STRIDE, within its full marketing authorisation for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).^{1, 2}

First-line treatment options in the United Kingdom (UK) for adults with advanced or unresectable HCC comprise atezolizumab + bevacizumab (the current standard of care [SoC]), and sorafenib or lenvatinib as alternative first-line therapies.³ Advanced or unresectable HCC is associated with a significant clinical, humanistic and economic burden, imposing a negative impact on patients and caregivers, in addition to the healthcare system and workforce productivity in the UK. This submission explores the unmet need associated with currently available treatments and describes how STRIDE represents an alternative first-line option to address these. By leveraging mature clinical data from the pivotal HIMALAYA trial, conducting indirect treatment comparisons (ITCs) to assess the comparative efficacy of STRIDE vs. comparators followed by an economic analysis, this submission demonstrates the clinical and cost-effectiveness of STRIDE for the treatment of patients with advanced or unresectable HCC in the UK.⁴

The decision problem addressed within this submission is broadly consistent with the National Institute of Health and Care Excellence (NICE) final scope for this evaluation, and any differences between the decision problem addressed within this submission and the NICE final scope are clearly outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced or unresectable HCC	Individuals with advanced or unresectable HCC who are ineligible for locoregional therapy and have not undergone systemic therapy	The population largely aligns with the NICE final scope and incorporates additional specifications to match the eligibility criteria of the HIMALAYA trial (see Section B.2.3.1). Importantly, all individuals have HCC that is either advanced, meaning it has spread extensively, or unresectable, meaning it cannot be surgically removed (see Section B.1.3.2). The patient population of interest must also be ineligible for locoregional therapies. ⁵
Intervention	Durvalumab plus tremelimumab	STRIDE: durvalumab (1,500 mg Q4W) and a single dose of tremelimumab (300 mg)	The intervention is in line with the final scope. In the HIMALAYA trial, patients were randomised into one of four treatment arms, with one of these arms supporting the licensed dose for STRIDE. ^{1, 6}
Comparator(s)	• Atezolizumab + bevacizumab • Lenvatinib • Sorafenib • SIRT including SIR-Spheres and TheraSphere • QuerumSphere (subject to ongoing NICE evaluation at the time the final scope was published) • BSC	• Atezolizumab + bevacizumab • Lenvatinib • Sorafenib	The comparators considered within this submission align with current UK clinical practice for the treatment of patients with advanced or unresectable HCC who are ineligible for locoregional therapy.³ The selection of these comparators was validated through interviews with HCC specialists based in the UK⁷: • In line with BSG guidelines and clinical expert opinion, atezolizumab + bevacizumab is considered the SoC in first-line NHS clinical practice based on its superior efficacy to sorafenib and lenvatinib.³ Therefore, it represents the primary comparator within this evaluation. • When individuals are contraindicated to atezolizumab + bevacizumab, or would prefer to receive an oral treatment instead of IV therapy, lenvatinib and sorafenib are the recommended alternative first-line

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			options as per the BSG guidelines.^{3, 8-10} - Although SIRT is included in the NICE final scope, it is not a relevant comparator in this evaluation. As described above, the patient population relevant to this submission consists of individuals who are not candidates for locoregional therapy. This may be as a result of their tumour burden, level of liver function, and/or vascular invasion, among other factors.³ Since SIRT falls under the category of locoregional therapies, it may not be used in the patient population of interest to this evaluation, rendering SIRT an irrelevant comparator. Recent interviews with clinicians confirmed that only individuals ineligible for SIRT will be considered for STRIDE, further emphasising that SIRT is not a relevant comparator.⁷ - With regards to BSC, patients with advanced or unresectable HCC should be referred to palliative care services alongside their active cancer treatment. Therefore, palliative care should be administered alongside systemic treatment rather than considered as a comparator.³ Patients who receive BSC alone would only do so because they are ineligible for active therapy, and therefore standalone BSC is not considered a relevant comparator.
Outcomes	The outcome measures considered: - OS - PFS	The outcome measures considered: - OS - PFS	In line with the NICE final scope

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	- TTP - Response rates - AEs - HRQoL	- TTP - Response rates, specifically ORR, DoR and DCR - AEs - HRQoL, including EORTC QLQ-C30, EORTC QLQ-HCC18 and EQ-5D-5L	
Economic analysis	- The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. - If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. - The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. - Costs will be considered from an NHS and Personal Social Services perspective. - The availability of any	- A cost-effectiveness analysis was expressed in terms of QALYs and has been conducted in Microsoft Excel® to estimate the incremental costs of STRIDE vs the relevant comparators. - The time horizon for assessing costs was set to 40 years, which is sufficiently long to capture the majority of costs and effects associated with the use of STRIDE. - Costs were considered from an NHS and PSS perspective. - Publicly available commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. - The availability and cost of biosimilar and generic products will be taken into account.	In line with the NICE final scope

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	No subgroups analyses were recommended in the NICE scope.	Cost-effectiveness evidence has been provided for the full licensed patient population for STRIDE. Clinical efficacy subgroup analyses have been presented in Section B.2.7 to demonstrate the efficacy of STRIDE across HCC aetiologies, ECOG PS and the presence of MVI, among other patient characteristics.	In line with the NICE final scope
Special considerations including issues related to equity or equality	N/A	N/A	N/A

Abbreviations: AE: adverse events; BSC: best supportive care; BSG: British Society of Gastroenterology; ECOG PS: European Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels; HCC: hepatocellular carcinoma; HRQoL: health-related quality of life; IV: intravenous; MVI: macrovascular invasion; N/A: not applicable; QLQ-HCC18: Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PSS: personal social services; Q4W: every four weeks; QALY: quality-adjusted life year; QLQ-C30: Core Quality of Life questionnaire; SIRT: selective internal radiation therapies; SoC: standard of care; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTP: time-to-progression; UK: United Kingdom.

B.1.2 Description of the technology being evaluated

A description of the mechanism of action, marketing authorisation status, costs and administration requirements associated with each component of STRIDE (durvalumab [IMFINZI®] in combination with tremelimumab [IMJUDO®]), for the treatment of advanced or unresectable HCC, is provided in Table 2. The summary of product characteristics (SmPC) is presented in Appendix C.

Table 2: Technology being appraised

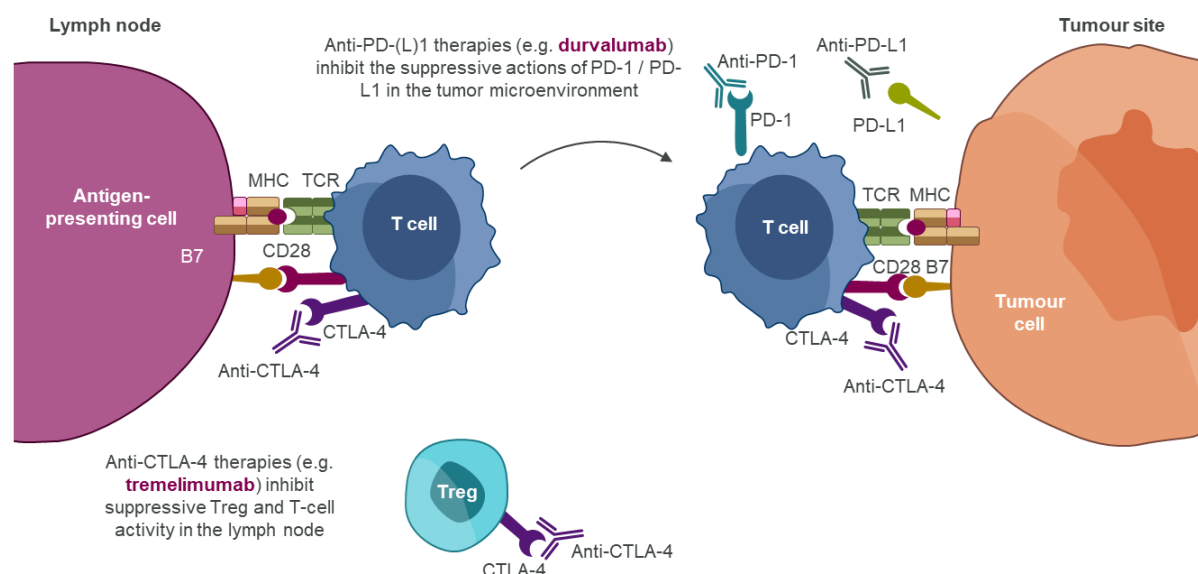
UK approved name and brand name	IMFINZI® (durvalumab) and IMJUDO® (tremelimumab)
Mechanism of action	STRIDE is composed of two IO therapies: durvalumab and tremelimumab. The mechanism of action of each IO therapy, as well as their combined effects, are outlined below and in Figure 1. Durvalumab is a high-affinity, human, recombinant IgG1k monoclonal antibody that is a potent inhibitor of human PD-L1.¹¹ PD-L1 is a transmembrane protein expressed on APCs which binds to PD-1 or CD80 receptors on activated T cells. This blocks T-cell function, resulting in reduced cellular activity, proliferation and cytokine production.⁶ PD-L1 is upregulated in HCC, protecting cancer cells from attack by cytotoxic T cells.¹²⁻¹⁴ Through binding to PD-L1, durvalumab inhibits the suppressive action of PD-1 and PD-L1 in the tumour microenvironment, allowing the immune system to exert a cytotoxic T-cell response against PD-L1-expressing tumour cells.^{6, 15} Tremelimumab is a fully human, IgG1k monoclonal antibody that binds to CTLA-4.¹⁶ CTLA-4 is expressed primarily on activated T cells and, when bound to CD80/CD86, acts to inhibit their activation.¹⁷ Tremelimumab therefore blocks the interaction between CTLA-4 and CD80/CD86, enabling CD28 to bind to CD80/CD86. This enhances the co-stimulatory signal required for T cell activation and function, resulting in increased release of cytokines from T cells and peripheral blood mononuclear cells.^{18, 19} Pre-clinical and clinical evidence suggests that the anti-tumour activity following PD-L1 blockade by durvalumab is strengthened by the inhibition of CTLA-4 by tremelimumab, demonstrating the benefit of combining the distinct mechanisms of action of durvalumab and tremelimumab.^{11, 15, 20-23} This distinct combination of two IO therapies is expected to result in complementary, long-lasting immune effects, enhanced anti-tumour activity and ultimately, improved patient outcomes.²⁴
Marketing authorisation/CE mark status	Durvalumab in combination with tremelimumab received EMA marketing authorisation for first-line treatment of adult patients with advanced or unresectable HCC on the 15th December 2022.² MHRA marketing authorisation was granted on the 6th June 2023.²⁵
Indications and any restriction(s) as described in the SmPC	The licensed indication for durvalumab in combination with tremelimumab is for the first-line treatment of adults with advanced or unresectable HCC. Contraindications include hypersensitivity to the active substances or excipients listed below:^{1, 6} • Histidine • Histidine hydrochloride monohydrate • Trehalose dihydrate

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UK approved name and brand name	IMFINZI® (durvalumab) and IMJUDO® (tremelimumab)
	• Disodium edetate dihydrate • Polysorbate 80 • Water for injections
Method of administration and dosage	Tremelimumab is administered as a single 300 mg priming dose in combination with durvalumab at Cycle 1/Day 1, followed by 1,500 mg durvalumab monotherapy Q4W. Both are administered as separate IV infusions. ^{1, 6}
Additional tests or investigations	No additional tests or investigations are required to determine eligibility for durvalumab in combination with tremelimumab in NHS clinical practice.
List price and average cost of a course of treatment	Durvalumab (120 mg/2.4 ml concentrate for solution for infusion vials) is available at a list price of £592.00 for the 120 mg/2.4 ml vial, and £2,466.00 for the 500 mg/10 ml vial. Tremelimumab (300 mg/15 ml concentrate for solution for infusion vials) is available at a list price of £20,610.00. The average cost of a course of treatment at list price for both durvalumab and tremelimumab is £28,652.02 for the first month, and £8,042.02 for subsequent months.
Patient access scheme (if applicable)	A confidential commercial access agreement is in place for durvalumab that provides a discount of [REDACTED] [REDACTED] The average cost of a course of durvalumab and tremelimumab treatment, when including the confidential commercial access agreement for durvalumab, [REDACTED]

Abbreviations: APC: antigen presenting cell; CTLA-4: cytotoxic T-lymphocyte antigen 4; EMA: European Medicines Agency; HCC: hepatocellular carcinoma; IgG1κ: immunoglobulin G1 kappa; IO: immuno-oncology; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; PAS: patient access scheme; PASLU: Patient Access Schemes Liaison Unit; PD-L1: programmed death ligand 1; Q4W: every four weeks; SmPC: summary of product characteristics; VAT: value added tax.

Figure 1: Mechanism of action: PD-L1 and CTLA-4 blockade



Abbreviations: CD-28: cluster of differentiation 28; CTLA-4: cytotoxic T-lymphocyte antigen-4; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; MHC: major histocompatibility complex; TCR: T cell receptor; Treg: T regulatory cell.

Source: Figure adapted from Buchbinder, E. et al. (2016).²³ (Figure 4, pg5)

B.1.3 Health condition and position of the technology in the treatment pathway

Summary of health condition and position of STRIDE in the treatment pathway

Disease overview

- HCC is the most common form of primary liver cancer, accounting for ~50% of all liver cancer cases²⁶ (Section B.1.3.1)
- The National Cancer Registration statistics for England report that 3,557 adults (age 20 and older) were diagnosed with liver cancer (excluding intrahepatic cholangiocarcinoma) in 2021.²⁷ In a study projecting cancer incidence and mortality in the UK until 2035, liver cancer is among the fastest increasing cancers in both incidence and mortality²⁸
- Major risk factors for the development of HCC comprise drivers of cirrhosis, including infection with hepatitis B (HBV) or hepatitis C virus (HCV), chronic alcohol consumption, obesity and diabetes^{29, 30}
- Approximately 41% of cases are identified as advanced or unresectable HCC at first diagnosis.^{27, 29} This is partly due to HCC being generally asymptomatic or presenting with non-specific symptoms in the early stages of the disease (Section B.1.3.1)

Disease burden

- Survival for patients with HCC is poor; the five-year survival for HCC in the UK remains below 10%, dropping to 2% in metastatic HCC, representing a significant clinical burden for patients and their families.^{3, 29, 31, 32} For patients with advanced or unresectable HCC, average life expectancy is less than two years with treatments currently available in the UK³³ (Section B.1.3.3.1)
- HCC often presents with non-specific symptoms such as loss of appetite, weight loss, and malaise, similar to symptoms of cirrhosis.^{34, 35} Additionally, underlying liver disease and high portal hypertension in advanced or unresectable HCC patients increases the risk of gastrointestinal (GI) bleeding, which means some individuals may not be eligible to receive systemic treatment regimens containing anti-angiogenic agents^{7, 36} (Section B.1.3.3.1)
- Disease symptoms in individuals with advanced or unresectable HCC have profound

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humanistic and health-related quality of life (HRQoL) impacts.³⁷ As such, individuals report significantly lower physical wellbeing and overall HRQoL than the general population, patients with chronic liver disease, and patients with other cancers²⁹ (Section B.1.3.3.2)

- Advanced or unresectable HCC also poses a significant economic burden on both individual patients, caregivers and the National Health Service (NHS).^{37, 38} Indirect costs associated with HCC are primarily driven by sick leave, long-term disability days, workers' compensation and disability among employees.³⁹ Furthermore, unpaid family members caring for individuals with advanced or unresectable HCC face significant economic and HRQoL burdens, often resigning from their jobs, losing income, depleting savings and experiencing stress from supporting with their family member's receipt of specialised care⁴⁰ (Section B.1.3.3.2 and B.1.3.3.3)

Treatment pathway

- There are no curative treatment options for advanced or unresectable HCC, with systemic therapy being the only current treatment option^{29, 37} (Section B.1.3.4)
- Atezolizumab + bevacizumab is the current first-choice SoC treatment for patients with advanced or unresectable HCC^{3, 10, 41, 42} (Section B.1.3.4.1)
- For those who have contraindications or would prefer oral therapy, sorafenib and lenvatinib are alternative first-line therapies³ (Section B.1.3.4.2)

Unmet need in advanced or unresectable HCC

- The five-year survival for metastatic HCC in the UK is 2%, with an average life expectancy of less than two years despite current treatments.^{31, 33} This highlights the significant unmet clinical need for individuals with advanced or unresectable HCC^{3, 29, 31, 32} (Section B.1.3.4.4)
- There is a considerable unmet need for a treatment that can alleviate the humanistic burden associated with HCC, with patients emphasising the need for improved OS (Section B.1.3.4.4)
- Many patients with advanced or unresectable HCC have a high risk of bleeding and are therefore contraindicated to atezolizumab + bevacizumab.⁴³ For these individuals, there is a significant unmet need for a treatment that can extend survival without increasing toxicity²⁹ (Section B.1.3.4.4)
- Treatment with atezolizumab + bevacizumab also requires an endoscopy ahead of initiation, which increases the NHS resource burden and may introduce a delay to patients receiving life-extending therapy^{7, 44} (Section B.1.3.4.4)

Proposed positioning of STRIDE

- STRIDE (Single Tremelimumab Regular Interval Durvalumab) represents a novel treatment option with a favourable administration schedule for patients with advanced or unresectable HCC. The HIMALAYA trial provided unprecedented and highly mature overall survival (OS) data, including an exploratory five-year analysis, representing the longest follow-up for an immunotherapy treatment in this setting. The primary analyses showed a statistically and clinically significant benefit of STRIDE over sorafenib for OS (Section B.1.3.4.5)
- STRIDE also demonstrated an acceptable toxicity profile in HIMALAYA, with no meaningful increase in liver toxicity and no treatment-related gastrointestinal or oesophageal varices haemorrhage events observed.⁴⁵ The favourable safety profile is particularly beneficial when compared to the currently SoC, atezolizumab + bevacizumab³ (Section B.1.3.4.5)
- Based on expert clinician feedback, the British Society of Gastroenterology (BSG) guidelines and data from the HIMALAYA trial, STRIDE is proposed to be positioned as a first-line treatment option for patients with advanced or unresectable HCC in the UK who are ineligible for locoregional therapy³ (Section B.1.3.4)

B.1.3.1 Advanced or unresectable hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for ~50% of all liver cancer cases.²⁶ The National Cancer Registration statistics for England report that 3,557 adults (age 20 and older) were diagnosed with liver cancer (excluding intrahepatic cholangiocarcinoma) in 2021.²⁷ These figures have increased substantially since the 1970s, and Company evidence submission template for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

in a study projecting cancer incidence and mortality in the UK until 2035, liver cancer is among the fastest increasing cancers in both incidence and mortality.²⁸

Cirrhosis, regardless of its cause, is a primary factor contributing to HCC.³⁷ Accordingly, major risk factors for the development of HCC comprise drivers of cirrhosis, including infection with HBV or HCV, chronic alcohol consumption, obesity and diabetes.^{29, 30} Many of these causes are related to lifestyle, an issue recognised by the UK government, leading to the implementation of national policies to limit alcohol intake and encourage healthy living.^{3, 46}

During the early stages of disease, HCC is generally asymptomatic or presents with non-specific symptoms. These include fatigue, weakness, loss of appetite, weight loss, nausea and vomiting, pain around the liver area and malaise.^{34, 35} Despite improvements in the screening of patients with known HCC risk factors, including cirrhosis, age and geographic region,³⁶ patients often receive a delayed diagnosis.³⁴ Approximately 41% of cases are identified as advanced or unresectable at first diagnosis, whilst 30–50% of patients undergoing surgery experience disease recurrence within two years.^{27, 29, 47} For individuals with advanced or unresectable HCC, including those at the intermediate stage who are ineligible for locoregional therapy, systemic therapy remains the only treatment option.⁴⁷ As a result, despite potentially curative outcomes for early-stage patients, overall prognosis for patients with HCC remains poor, with the five-year survival remaining below 10% in the UK.^{3, 29, 32, 48} For patients with advanced or unresectable HCC, average life expectancy is less than two years with treatments currently available in the UK.³³

B.1.3.2 Classification of hepatocellular carcinoma

Diagnosis of HCC comprises imaging and pathological components, such as computerised tomography (CT), MRI (magnetic resonance imaging), ultrasounds, positron emission tomography (PET), biopsies and blood tests.⁴⁹ Once a patient has been diagnosed with HCC, their disease is classified via a process known as staging, which facilitates appropriate treatment selection.^{50, 51} The key factors for staging in HCC include tumour characteristics (size, number of tumours, growth rate, spread), liver function and patient health.^{50, 51}

The most widely used system to assess disease stage and treatment options in the UK is the Barcelona Clinic Liver Cancer (BCLC) classification.^{3, 52, 53} The BCLC staging system assesses the number and size of liver tumours, HCC clinical features (Okuda score), patient health and fitness (Eastern Cooperative Oncology Group [ECOG] performance status [PS]), and liver function (Child-Pugh score).⁵¹ These criteria are used to classify patients, starting from Stage 0 (very early HCC) to Stage D (terminal HCC).⁵¹ The patient populations considered within this evaluation are individuals in Stage B (intermediate HCC) who are ineligible for locoregional therapy, and Stage C (advanced or unresectable HCC). The Cancer Registration Statistic identified that approximately 41% of individuals have advanced or unresectable HCC at the time of diagnosis. This aligns with a prospective study involving 591 individuals in the UK who underwent BCLC stage assessment at diagnosis revealed that around 40% were classified as having advanced or unresectable HCC at the time of diagnosis (Table 3).⁴⁷

Table 3. BCLC classification for HCC

Stage	Number / size of tumours	Okuda score	ECOG PS ^a	Child-Pugh score ^b	Prevalence ^c (N=591) n (%)
Stage 0 (Very early HCC)	A single tumour ≤2 cm without MVI or extrahepatic spread	I	0	A	78 (13.2)
Stage A (Early HCC)	A single tumour irrespective of size or a multifocal HCC up to 3 nodules (none of them >3 cm), without MVI, extrahepatic spread	I–II	0	A/B	
Stage B (Intermediate HCC)	Multifocal HCC (exceeding BCLC-A criteria)	I–II	0	A/B	128 (21.7)
Stage C (Advanced or unresectable HCC)	Tumour with MVI or extrahepatic spread	I–II	1–2	A/B	234 (39.6)
Stage D (Terminal HCC)	Any	III	1–2	C	151 (25.5)

Footnotes: Stage B and C are bolded as it is the stage relevant to this evaluation; ^aECOG PS ranges from PS 0 (fully active) to PS 4 (complete care necessary);⁵¹ ^bThe Child-Pugh system assesses five markers (total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy) which are used to classify patients from class A (normal liver function) to class C (severe liver damage);⁵¹ ^cPrevalence refers to the number of individuals at each BCLC stage at diagnosis in the Haq et al. publication who were not undergoing active surveillance.⁴⁷

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; PS: performance score.

Sources: Reig, M. et al. (2022).⁵⁴ Collette, S. et al. (2008).⁵⁵ Haq, M. et al (2021).⁴⁷ (Table 3, pg6).

B.1.3.3 Burden of disease

B.1.3.3.1 Clinical burden

Patients with advanced or unresectable HCC experience a profound clinical burden, from both the symptoms of their condition, the therapies they are treated with, and the dismal survival prospects associated with this disease.

When symptomatic, HCC is generally associated with non-specific complaints, such as loss of appetite, weight loss and malaise, which are often comparable to symptoms of cirrhosis.^{34, 35} Symptoms with increased specificity to HCC are the onset of fluid in the abdomen (ascites), damage to the brain (encephalopathy), skin and eyes turning yellow (jaundice), or variceal bleeding in the GI tract.³⁴ In certain cases of advanced or unresectable HCC, patients may present with acute onset of severe abdominal pain and distension, low blood pressure (hypotension), tumour rupture and bleeding within the peritoneal cavity (intraperitoneal).³⁴

HCC is a highly fatal cancer, often diagnosed late, with an incidence to mortality ratio approaching one.³ Despite there being several treatment options available the median OS for patients with late-stage HCC on systemic therapies is 8–19 months.²⁹ The five-year survival from HCC in the UK remains below 10%, dropping to 2% in individuals with metastatic disease, highlighting the significant unmet clinical need particularly for individuals with advanced or unresectable HCC.^{3, 29, 31, 32}

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There is an additional clinical burden associated with systemic therapies currently available to patients with advanced or unresectable HCC. Firstly, the currently available treatments are associated with toxicities that not only decrease HRQoL but also result in treatment interruptions and dose reductions, which can potentially decrease treatment efficacy.⁵⁶ Secondly, the underlying liver disease and high likelihood of portal hypertension in patients with advanced or unresectable stage HCC results in an elevated risk of GI bleeding, particularly with treatments that include anti-angiogenic agents (such as bevacizumab), which inhibit the growth of new blood vessels.⁵⁷ Recent interviews with UK HCC clinicians found that some patients are being prescribed atezolizumab + bevacizumab at the discretion of their physician, despite the associated heightened bleeding risk which would typically be a contraindication. Physicians must then monitor patients for bleeding risk while they are on atezolizumab + bevacizumab, as there are no safer alternative systemic treatment options available with comparable efficacy. This highlights the need for alternative, efficacious treatment options that do not heighten the risk of bleeding.⁷ Thirdly, given the aforementioned bleeding risks, patients with HCC who are treated with atezolizumab + bevacizumab are required to receive an endoscopy prior to starting treatment to assess their bleeding risk. This procedure can be unpleasant for patients and may delay treatment initiation (further detail is given in Section B.1.3.4.1).^{57, 58}

B.1.3.3.2 Humanistic burden

Patients with HCC experience a substantial humanistic burden and report significantly lower physical wellbeing and overall HRQoL than the general population, patients with chronic liver disease, and patients with other cancers.²⁹ In a meta-analysis of 16 studies evaluating HRQoL of HCC patients using the 36-Item Short Form Survey (SF-36), individuals with HCC report substantially poorer scores in several domains: general health (38.2 vs. 70.1), mental health (45.2 vs. 75.2), physical functioning (36.2 vs. 83.0), role—emotional (37.7 vs. 77.9), role—physical (37.7 vs. 77.9), social functioning (38.7 vs. 83.6), and vitality (42.1 vs. 57.0) when compared to the age-adjusted general public.⁵⁹ Lower HRQoL scores are associated with a range of liver- and tumour-related factors, with worse Child-Pugh class and increased tumour burden being independently associated with lower HRQoL levels.²⁹ Wellbeing challenges include poor energy, troubles with sleep, difficulties digesting food, appetite loss, increased pain, decline in physical mobility, decreased ability to perform usual activities and poor mental health and social functioning.⁵⁶ Symptoms of diarrhoea, fatigue, skin toxicities and appetite loss are reported to have the largest impact on patients' HRQoL.³⁷

Whilst there is limited research into HRQoL in patients with advanced or unresectable HCC specifically, these patients report that the most severe symptoms at diagnosis are fatigue and distress, and 90% of patients report pain during and after treatment.⁶⁰⁻⁶² The abdomen and lower back were the most common sites of pain.⁶⁰ Following treatment, fatigue remained the most serious symptom, followed by sleep disturbance, distress, sadness, and lack of appetite.⁶² Symptoms of upper GI distress and liver function impairment also remained after treatment.⁶²

Improved patient HRQoL, in particular involvement in life situations involving family, partner relationship, work or household chores, may be independently associated with improved survival in patients with advanced or unresectable HCC.²⁹ Specifically, a multivariate analysis of the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (QLQ-C30) and clinical variables found that higher scores in the physical functioning domain ($p=0.0034$; hazard ratio [HR] for 10 point decrease=0.911) and the role functioning domain ($p=0.0383$; HR for 10 point decrease=0.944) were associated with longer survival.⁶³ Furthermore, poor HRQoL has been shown to be an independent prognostic factor of

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all-cause mortality among advanced stage HCC patients, highlighting that treatment strategies that maintain HRQoL may in turn help to improve survival.^{29, 59}

Patients with advanced or unresectable HCC often require informal caregiving to manage daily living; this is often provided by unpaid family members.⁴⁰ A systematic literature review (SLR) conducted by Woodrell et al. investigated the physical and emotional stressors for patients with advanced liver disease and their families.⁴⁰ The study found that liver diseases carry a considerable burden, with physiological, psychological, and social complexities posing a threat to the HRQoL experienced by both patients and family caregivers.⁴⁰

B.1.3.3 Economic burden

HCC imposes a significant economic burden on both individuals and the NHS. A study evaluating the impact of secondary and tertiary healthcare provision for 15,684 individuals diagnosed with HCC in England between 2010 to 2016 determined a total cost of approximately £245 million. Per patient, the median expenditure over a two-year period was £9,065, with an interquartile range of £1,965 to £20,491.³⁸ Individuals with compensated cirrhosis incurred significantly greater healthcare costs than those with decompensated cirrhosis (£14,038 vs £7,744; $p < 0.001$), highlighting the critical need for effective care and management of those with liver damage. Furthermore, healthcare expenditure for this condition is projected to increase as a result of the continuing upward trend in HCC incidence, as described above.²⁸

HCC is also associated with indirect costs as a result of lost productivity due to morbidity and premature mortality experienced by patients with the disease. As such, indirect costs associated with HCC are driven by sick leave, long-term disability days, workers' compensation and disability among employees.³⁹ Furthermore, caregivers experience financial burdens from caregiving responsibilities, with carers of patients with end-stage liver disease reported resigning from their job, losing income, and depleting savings in the last six months of a patient's life. Carers additionally report stress associated with travel for specialised care, including upheaval of everyday life and a financial impact.⁴⁰

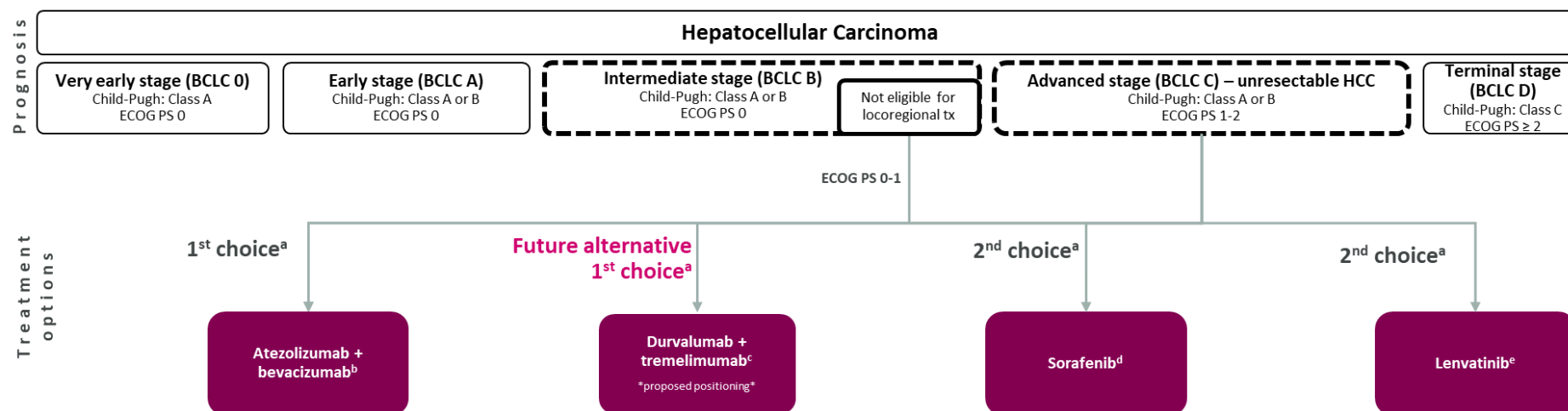
B.1.3.4 Clinical pathway of care

The BSG have recently published guidelines with recommendations for the management of patients with HCC, which, alongside NICE recommendations,^{8-10, 64, 65} are expected to guide clinical practice within the UK.³ They were developed by UK-based liver cancer experts, including hepatologists, liver surgeons, radiologists, pathologists, oncologists, palliative care physicians and clinical nurse specialists. Input was also provided by patients who have been diagnosed with and treated for liver cancer.

According to the BSG guidelines, at the early stages of HCC, treatments include surgical resection, liver transplantation and ablation.³ As the cancer progresses, locoregional therapy is considered for patients who are ineligible for surgery, or as a bridging therapy to reduce tumour size and number to maintain eligibility criteria for transplantation whilst on the waiting list.³ However, for individuals at the advanced or unresectable stage, curative treatment is not possible.⁶⁶ Currently, systemic therapy is the only treatment option for individuals within the patient population considered in this evaluation, with the goal of extending survival and maintaining patients' HRQoL for as long as possible.^{3, 67}

In the UK, the treatment pathway for patients with advanced or unresectable HCC who are ineligible for locoregional therapy, as outlined by the BSG and NICE guidance, is presented in Figure 2. The diagram presents first line systemic options that are currently available to patients. This treatment pathway was further validated during subsequent validation interviews with UK HCC clinical experts.⁷

Figure 2: Treatment pathway for patients with advanced or unresectable HCC who are ineligible for locoregional therapy



Footnotes: ^aBSG positioning recommendations³; ^bFirst-choice SoC treatment option as per Suddle 2024 and clinician interviews;^{3, 7} ^cProposed positioning of STRIDE as per Suddle 2024 and clinician interviews;^{3, 7} ^{d,e}Alternative first-line treatment options as per Suddle 2024 and clinician interviews.^{3, 7}

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; STRIDE: Single Tremelimumab Regular Interval Durvalumab; tx: treatment.

Source: Suddle, A. et al. (2024)³; NICE TA666 (2020).¹⁰ NICE TA474 (2017).⁹ NICE TA551 (2018).⁸

B.1.3.4.1 Atezolizumab + bevacizumab

Atezolizumab + bevacizumab is the current first-line SoC treatment for patients with advanced or unresectable HCC in the UK, following its NICE recommendation in December 2020 (TA666).^{3, 10, 41, 42} This combination is administered intravenously (IV) every three weeks (Q3W) until loss of clinical benefit as assessed by the investigator or until unacceptable toxicity. Both atezolizumab and bevacizumab are monoclonal antibodies, with atezolizumab targeting programmed death-ligand 1 (PD-L1) and bevacizumab targeting vascular endothelial growth factor (VEGF). Clinical evidence supporting atezolizumab + bevacizumab for the treatment of advanced or unresectable HCC was evaluated in the open-label, Phase III IMbrave150 randomised controlled trial (RCT) vs. sorafenib.⁴⁴

Despite becoming the first-line SoC for patients with advanced or unresectable HCC, there are limitations associated with this treatment. Firstly, the IMbrave150 trial only provided a median follow up of 15.6 months (range: 0–28.6), which increases the uncertainty in the long-term efficacy and safety of this treatment.³³ Secondly, atezolizumab + bevacizumab may not be suitable for a considerable proportion of patients, with clinicians estimating that approximately 25% are contraindicated due to bleeding risk and other comorbidities.⁷ As discussed in Section B.1.3.3.1, patients with advanced or unresectable HCC are at an increased risk of GI bleeding, particularly those with cirrhosis.^{3, 7, 44} This risk can be exacerbated by anti-angiogenic agents such as bevacizumab. Consequently, an endoscopy is required for all individuals prior to initiation of treatment with atezolizumab + bevacizumab to assess patients for the presence and treatment of oesophageal varices, increasing the NHS resource burden.^{57, 68} Furthermore, the need to undergo an endoscopy may not only be distressing for patients but may also delay patients' initiation of this systemic therapy and subsequently the receipt of any treatment benefit.

B.1.3.4.2 Sorafenib and lenvatinib

For patients who have a contraindication to atezolizumab + bevacizumab, or otherwise decline IV therapy in favour of oral therapy, sorafenib and lenvatinib are alternative first-line therapies recommended by NICE for advanced or unresectable HCC.^{8, 9} Additionally, both therapies are recommended by the BSG HCC guidelines as second-line therapies for patients who have previously been treated with atezolizumab + bevacizumab in the first-line.³ This recommendation is also supported by the BlueTeq criteria.⁶⁹ Given the non-inferiority of OS for lenvatinib compared with sorafenib, the BSG guidelines advocate that the decision on which of these to use might be influenced by consideration of secondary endpoints such as response rate and progression-free survival (PFS), in addition to toxicity profile.³

Sorafenib is an orally administered multi-receptor tyrosine kinase inhibitor (TKI) that exerts anti-angiogenic and anti-proliferative effects through the inhibition of multiple protein kinases.⁷⁰ It was recommended by NICE in 2017 (TA474) for the treatment of advanced HCC in patients with Child-Pugh class A liver impairment.⁹ Treatment with sorafenib is associated with high toxicity, limited long-term survival and worse clinical outcomes for patients with poor liver function, which is common to patients with advanced or unresectable HCC.^{71, 72}

Lenvatinib is an alternative, orally administered multi-receptor TKI which was recommended by NICE in 2018 (TA551).⁸ Whilst lenvatinib and sorafenib have comparable OS, lenvatinib has demonstrated increased PFS relative to sorafenib (NCT01761266).⁷³ Similar to sorafenib, treatment with lenvatinib is associated with high toxicity.⁷³

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B.1.3.4.3 Selective internal radiation therapies

Selective internal radiation therapy (SIRT) is an intra-arterial therapy option involving the injection of small radioactive beads into the liver's blood supply. The beads lodge themselves within the vessels that supply the tumour and emit localised radiation to kill tumour cells.⁷⁴ SIRT requires close coordination between nuclear medicine, interventional radiology and oncology, and demands specific equipment and expertise. It is therefore only available in 11 NHS centres in the UK due to its specialised nature.⁷⁵

Two types of SIRT, SIR-Spheres and SIRT TheraSphere, were recommended by NICE in March 2021 as an option for treating unresectable advanced HCC in patients with Child-Pugh class A.⁷⁶ Subsequently, SIRT QuiremSphere was also recommended by NICE in TA985 for unresectable advanced HCC.⁷⁷ All three treatments have been proposed as potential comparators to STRIDE in the NICE final scope.⁷⁸ However, as described in Table 1, the patient population for this submission excludes candidates eligible for locoregional therapy due to the nature of their liver disease, which renders locoregional therapy unsuitable as a possible result of their tumour burden, liver function, vascular invasion, among other factors.⁵ Therefore, since SIRT is a locoregional therapy, it is not considered a relevant comparator for this population. Recent interviews with clinician experts in the UK have reinforced this perspective.⁷ They indicated that patients with advanced or unresectable HCC are only considered for systemic therapy if they are no longer eligible for SIRT or other locoregional treatments, or if SIRT is not available to them.⁷ Furthermore, clinicians have raised concerns on the limited clinical evidence on SIRT therapies as well as the ambiguous guidelines on when SIRT therapies should be used.⁷

As mentioned above, available clinical evidence on the efficacy of SIRT treatments in HCC is weak. Studies such as SIR-TACE (comparing SIR-Spheres to TACE) and the PREMIER and Kulik et al. studies (comparing TheraSphere to TACE) did not demonstrate statistically significant improvements in outcomes, nor improved overall survival, and were associated with high levels of uncertainty due to small sample sizes and a high risk of bias.⁷⁶ Furthermore, the SARAH and SIRveNIB trials comparing SIR-Spheres with systemic therapy showed no survival advantage over sorafenib.^{79, 80}

The DOSISPHERE open-label Phase II study, which investigated TheraSphere in patients with large solitary tumours (≥ 7 cm), found that SIRT could be beneficial for patients with large solitary tumours who are not eligible for TACE or systemic therapy.⁸¹ However, this evidence is associated with significant uncertainty, including imbalances in baseline characteristics and the lack of a direct comparison of SIRT to a current first-line treatment option (e.g., sorafenib).⁷⁶ UK HCC clinicians interviewed supported the use of SIRT exclusively for patients with large solitary tumours ineligible for TACE or systemic therapy.⁷

The HEPAR Phase II study investigating the safety and efficacy of QuiremSphere in patients with HCC at BCLC stage B or C found that QuiremSphere has a manageable safety and tolerability profile.⁸² As such, NICE have approved QuiremSphere for use based on a cost comparison, with QuiremSphere considered equivalent in cost and efficacy to the other SIRT therapies, SIR-Spheres and TheraSphere.⁷⁷ However, there are a number of concerns regarding the robustness of QuiremSphere data, given the extremely limited evidence and the lack of high-quality, head-to-head comparisons, which hinder meaningful comparisons with other SIRT therapies. Furthermore, the existing comparative evidence is largely limited to retrospective studies that carry a high risk of bias due to imbalances in baseline characteristics between treatment arms and the absence of adjustments for confounding variables.^{83, 84}

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In conclusion, all three SIRT therapies are not considered a suitable comparator for individuals with advanced or unresectable HCC who are ineligible for locoregional therapy. In addition, the existing evidence on the survival benefits of SIRT in patients with advanced unresectable HCC who are eligible for locoregional treatment remains limited.

B.1.3.4.4 Unmet need in advanced or unresectable HCC

As noted above, atezolizumab + bevacizumab is the current SoC for the first-line treatment of patients with advanced or unresectable HCC in the UK, with lenvatinib and sorafenib offering alternative first-line treatment options.³ However, the limited long-term follow-up data limits the confidence in survival extrapolation.³³ Furthermore, treatment with atezolizumab + bevacizumab requires an endoscopy ahead of administration, which not only increases NHS resource use burden, but may also introduce a delay in patients receiving potentially life-extending therapy.^{7, 44} Furthermore, atezolizumab + bevacizumab may not be suitable for a considerable proportion of patients who are contraindicated to this regimen.^{3, 7, 44} Accordingly, there is a significant unmet need for a novel treatment that can extend survival without increasing bleeding risk.²⁹ There further remains a considerable unmet need for a treatment that can contribute to alleviating the humanistic burden associated with HCC, both for the individual and their carers.^{29, 85} Finally, advanced or unresectable HCC imposes a considerable economic cost on society, both directly and indirectly, hence alternative treatments that can help reduce this burden are paramount.^{37, 38}

B.1.3.4.5 STRIDE for advanced or unresectable HCC

STRIDE represents a novel treatment option for patients with advanced or unresectable HCC that aims to address the unmet need that exists for this condition. STRIDE has been evaluated in the randomised, open-label, multicentre, Phase III HIMALAYA study, in which statistically significant and clinically meaningful improvements in key clinical outcomes relative to sorafenib were observed.⁴⁵ Importantly, STRIDE provided the longest follow-up from a Phase III study in this setting, establishing itself as the only approved regimen to demonstrate a survival benefit after five years in an exploratory analysis. This analysis showed that STRIDE demonstrated a 19.6% probability of OS compared to 9.4% in sorafenib after 5 years.

This combination of two immuno-oncology (IO) therapies was hypothesised to result in complementary, long-lasting immune effects, enhanced anti-tumour activity and ultimately, improved patient outcomes, which is evidenced in the 5-year data cut from HIMALAYA.²⁴ Relatedly, the mechanism of action of STRIDE offers patients important advantages with regards to risk of bleeding. As described previously, patients with advanced or unresectable HCC are at increased risk of variceal bleeding as a result of conditions such as cirrhosis, portal hypertension and anticoagulant use, among others.⁸⁶ As such, treatment regimens that include anti-angiogenic agents may not be suitable for a considerable proportion of patients with advanced or unresectable HCC. No anti-angiogenic agents are included within the STRIDE regimen, making STRIDE suitable for all patients with advanced or unresectable HCC regardless of bleeding risk.

The administration frequency of STRIDE is also advantageous when compared to current SoC. Both treatment administration and laboratory tests for STRIDE occur every four weeks, whereas with the current SoC, atezolizumab + bevacizumab, these occur every three weeks. Therefore, STRIDE presents a less burdensome treatment pathway, requiring fewer hospital visits. This reduction in visit frequency not only alleviates the burden on the NHS but also contributes to improving HRQoL for patients by reducing the number of hospital visits required.

The BSG made a strong recommendation for the use of STRIDE in first-line advanced or unresectable HCC in their recent guidelines. This recommendation is underpinned by high-quality clinical evidence demonstrating improved survival compared to sorafenib, a manageable toxicity profile and a reduced risk of variceal bleeding.^{3, 78, 87} This recommendation is echoed by the BCLC guidelines, which highlight the superior survival outcomes with STRIDE over sorafenib as a key differentiator.⁸⁷ This aligns with the view of experts in the field, who concluded that STRIDE is a suitable first-line treatment. Furthermore, clinicians have highlighted that the unprecedented long-term efficacy data provides confidence in the regimen's lasting benefits, while also offering particular advantages for patients at risk of GI bleeding and with other comorbidities.⁸⁸

Furthermore, STRIDE is suitable for some patients with BCLC Stage B, corresponding to intermediate HCC. For individuals with intermediate disease who are ineligible for locoregional therapy or no longer qualify after receiving one or more rounds of locoregional therapy, systemic therapies are offered.³ STRIDE therefore represents a valuable treatment option for patients with unresectable intermediate HCC for patients who are not amenable to locoregional therapy.

B.1.4 *Equality considerations*

It is not anticipated that the provision (or non-provision) of STRIDE within its licensed indication would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary of clinical effectiveness

HIMALAYA trial design

- HIMALAYA is a randomised, multicentre, open-label, Phase III study that explored the efficacy and safety of STRIDE in patients with advanced or unresectable HCC vs. sorafenib⁴⁵ (Section B.2.2)
- Adult patients with confirmed advanced or unresectable HCC (Barcelona Clinic Liver Cancer [BCLC] stage B or C) were enrolled in the trial. Patients ineligible for receipt of locoregional therapy were included (Section B.2.3.1)
- The primary analysis took place on 27th August 2021, once 555 OS events had occurred in the STRIDE and sorafenib treatment arms combined (71% maturity).⁸⁹ Two additional exploratory OS data cut-offs (DCOs) took place on 23rd January 2023 and 1st March 2024, representing four and five years of follow up, respectively

Key primary and secondary endpoints

- HIMALAYA met its primary endpoint (DCO: 27th August 2021), with STRIDE demonstrating a statistically significant and clinically meaningful improvement in OS vs. sorafenib, with a survival rate of 30.7% for STRIDE vs. 20.2% for sorafenib (HR: 0.76; 95% confidence interval [CI]: 0.61–0.96) (Section B.2.6.1)
 - STRIDE consistently demonstrated an improvement in OS compared to sorafenib at all measured timepoints, including at 18, 24, 36 (the primary DCO), 48 and 60 months
 - At the exploratory five-year analysis, STRIDE demonstrated a survival rate of 19.6% compared to 9.4% for sorafenib⁹⁰
 - These clinically meaningful results are consistent with expectations for the distinct dual immunotherapy (IO) mechanism of action of STRIDE
 - The maturity of the HIMALAYA OS dataset is unparalleled, representing the longest OS follow-up period of any study in advanced or unresectable HCC to date, providing treating clinicians with confidence in the long-term efficacy of STRIDE
- At the primary DCO (27th August 2021), a greater proportion of patients were progression-free in the STRIDE treatment arm compared with the sorafenib arm (12.5% vs. 4.9%, respectively). The median PFS for STRIDE and sorafenib was comparable (HR: 0.90; 95% CI: 0.77–1.05)⁴⁵
 - This comparable result between arms aligns with the typical efficacy pattern observed with IO-IO therapies, whereby the indirect mechanism of action results in a delayed treatment effect.⁹¹ As a result, IO-IO therapies often show minor PFS benefits despite clinically significant improvements in OS. Existing literature and clinicians highlight that OS is considered the most reliable endpoint for patients with HCC, and reiterate that weak surrogacy exists between OS and PFS in advanced or unresectable HCC, particularly for treatment with IO-IO therapies^{3, 92-94} (Section B.2.6.2)
- A statistically significantly greater proportion of patients responded to STRIDE compared to sorafenib, with a four-fold increase in objective response rate (ORR), a secondary endpoint, in the STRIDE treatment arm compared to the sorafenib treatment arm (20.1% vs. 5.1%; OR: 4.69; 95% CI: 2.85–8.04; nominal $p < 0.0001$; primary DCO: 27th August 2021)^{45, 89} (Section B.2.6.2)

- Patients treated with STRIDE additionally had a longer median duration of response (DoR), a secondary endpoint (22.3 months vs. 18.4 months; primary DCO: 27th August 2021; Section B.2.6.2)⁴⁵
- The time to progression (TTP) and disease control rate (DCR) of STRIDE and sorafenib were also secondary endpoints assessed at the primary DCO (27th August 2021, as detailed in Section B.2.6.2)

HRQoL

- Patient-reported outcomes (PROs) demonstrated that patients receiving STRIDE maintained their HRQoL level for longer compared to patients receiving sorafenib, with a longer time to deterioration observed vs. sorafenib on measures of global health status (GHS)/quality of life (QoL), physical functioning, fatigue, appetite, nausea, abdominal pain and abdominal swelling⁹⁵ (Section B.2.6.3)
- EQ-5D-5L scores were [REDACTED] between treatment arms, with the score for patients in the STRIDE treatment arm remaining [REDACTED] mean scores over time vs. sorafenib (Section B.2.6.3)^{89, 96}

Summary of safety

- HIMALAYA demonstrated the favourable safety profile of STRIDE, with all AEs manageable according to toxicity management guidelines and no new signals observed beyond the established safety profiles^{4, 22} (Section B.2.10)
- STRIDE demonstrated lower rates of grade 3/4 treatment-related adverse events (TRAEs) and TRAEs leading to discontinuation compared with sorafenib^{4, 97} (Section B.2.10.3)
- Haemorrhagic-related TRAEs were more than twice as high in the sorafenib arm (4.8%) compared with the STRIDE arm (1.8%),⁹³ indicating that STRIDE is not associated with an increased bleeding risk (Section B.2.10.3)
- Additionally, hepatotoxicity and treatment-related hepatotoxicity were comparable between STRIDE and sorafenib, indicating that STRIDE does not increase liver toxicity⁸⁹ (Section B.2.10.3)

Indirect treatment comparison

- The clinical SLR identified 17 studies, which were assessed for inclusion in the network meta-analysis (NMA). Three studies, the HIMALAYA, IMbrave150 and REFLECT trials, were eligible and formed a network of evidence for both OS and PFS, connected via a common sorafenib treatment arm (Section B.2.9.2 and B.2.9.3)
- The appropriateness of performing an NMA was assessed. Overall, the trials were generally comparable in terms of study design and patient baseline characteristics (Section B.2.9.4). However, there was a significant disparity in the length of follow-up reported across all three trials, with HIMALAYA having materially longer follow-up compared to IMbrave150 in particular
- There was evidence of proportional hazard (PH) assumption violation for HIMALAYA and REFLECT for OS and PFS. Time-varying analyses for REFLECT showed that the HR for lenvatinib vs. sorafenib trended towards 1 over time for both PFS and OS, meaning that the results from an NMA may overpredict survival for lenvatinib. There was no evidence of PH violation for IMbrave150, and therefore the estimate from the NMA of atezolizumab + bevacizumab vs sorafenib was unlikely to be biased
- A Bayesian NMA was conducted for OS and PFS to provide estimates of the relative effectiveness of STRIDE, atezolizumab + bevacizumab, lenvatinib and sorafenib. Both fixed effects (FE) and random effects (RE) models were fitted with the most appropriate model selected using the deviance information criterion (Section B.2.9.6)
- For OS, the NMA used the updated analysis II (5-year) OS DCO from HIMALAYA. For STRIDE and atezolizumab + bevacizumab, the NMA showed improved OS compared with sorafenib, with similar point estimates to the trial results ([REDACTED])

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_____). However, CrI all crossed 1, indicating no statistically significant differences between all comparators and sorafenib in the RE model with informative prior. For lenvatinib, the NMA found that lenvatinib had a non-inferior OS compared with sorafenib, with a similar point estimate to trial results (_____)

- For investigator-assessed PFS, the NMA results found that all three comparators, atezolizumab + bevacizumab, lenvatinib and STRIDE, showed improved PFS compared with sorafenib (_____), reflecting point estimates from trial results, but no statistical differences were observed in the RE model with informative prior
- Overall, the NMA identified that STRIDE was associated with a comparable improvement in survival vs. sorafenib compared to atezolizumab + bevacizumab, the key comparator in this submission

Conclusions

- The HIMALAYA trial offered an unprecedented level of mature OS data, with STRIDE demonstrating a survival rate of 30.7% vs. 20.2% for sorafenib (HR: 0.76; 95% confidence interval [CI]: 0.61–0.96) at the primary analysis. Encouraging OS results were maintained at the exploratory five-year DCO, with 19.6% survival observed in the STRIDE treatment arm compared to 9.4% survival for sorafenib.
- The STRIDE regimen demonstrated a manageable safety profile, with no new safety signals identified, lower TRAEs, lower haemorrhagic-related TRAEs and comparable hepatotoxicity levels to sorafenib^{22, 89}
- In the NMA, the key area of uncertainty related to the differing lengths of follow-up between the trials included. For the key endpoint of interest, OS, the NMA found that STRIDE and atezolizumab + bevacizumab improved OS compared with sorafenib, with similar point estimates to the trial results, although these were not statistically significant. For lenvatinib, the NMA found that lenvatinib had a HR close to 1 compared to sorafenib, which is aligned with the REFLECT trial results demonstrating non-inferiority
- Overall, the robust, significant OS data for STRIDE, combined with a favourable benefit-risk profile, highlight that STRIDE fulfils the unmet need for a well-tolerated and effective treatment alternative that prolongs survival in patients with advanced or unresectable HCC in the UK

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify and synthesise relevant clinical evidence on the efficacy and safety of durvalumab in combination with tremelimumab (STRIDE regimen) and other first-line treatments in patients with advanced or unresectable HCC. The original SLR was conducted on 31st August 2020, and subsequently underwent updates on 26th October 2021 and 10th April 2024.

In the recent SLR update, following de-duplication of results, a total of 1,764 publications were screened at the title and abstract stage. Of these, 146 were reviewed at the full-text stage. After excluding publications that did not meet the eligibility criteria, 54 publications were included in the SLR from database searches. Supplementary searches retrieved an additional 16 articles, resulting in a total of 70 articles included from both the electronic database and supplementary searches. Following an evidence prioritisation step, in which studies of direct relevance to the submission decision problem were extracted, 14 of the 70 publications identified in the SLR update were extracted. Additionally, 26 articles were included from the original SLR and first update. Therefore, a total of 40 publications were ultimately extracted.

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An overview of the SLR methodology, including search strategy, study selection process, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, list of included/excluded studies at full text review, and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

Of the unique studies identified, only one trial (HIMALAYA) provided evidence for the clinical efficacy and safety of STRIDE in the patient population of interest for this evaluation (patients with advanced or unresectable HCC).

HIMALAYA

The clinical effectiveness and safety of durvalumab in combination with tremelimumab for patients with advanced or unresectable HCC was assessed in HIMALAYA, a randomised, multicentre, open-label, Phase III trial. This study considered patients with advanced or unresectable HCC who were not eligible for locoregional therapy and had not received prior systemic therapy for HCC.⁴

A total of four treatment arms were analysed:

- **STRIDE:** A single dose of tremelimumab (300 mg) and durvalumab (1,500 mg Q4W)
- Durvalumab 1,500 mg monotherapy Q4W
- **Sorafenib** (400 mg) twice daily (BID)
- T75+D: A dose of tremelimumab (75 mg Q4W) and durvalumab (1,500 mg Q4W)

For this submission, only the STRIDE and sorafenib arms are considered relevant (the other two regimens are not licensed nor anticipated to be licensed for the indication of relevance to this submission). Accordingly, results presented within the submission are for these two treatment arms only. Further information on the trial design can be found in Section B.2.3.2. An overview of HIMALAYA is included in Table 4, with the methodology and results of the trial presented in the sections that follow.

Table 4: Clinical effectiveness evidence

Study ID	HIMALAYA (NCT03298451)
Study design	A randomised, multicentre, open-label, Phase III study
Population	Adults (aged ≥18 years) with confirmed advanced or unresectable HCC (BCLC stage B or C), who are ineligible for locoregional therapy and had not received prior systemic therapy
Intervention	STRIDE: A single dose of tremelimumab (300 mg) and durvalumab (1,500 mg Q4W) (n=393)
Key comparator	Sorafenib (400 mg) BID (n=389)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A

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Study ID	HIMALAYA (NCT03298451)
Reported outcomes specified in the decision problem	Primary endpoint: - OS Secondary endpoints: - OS at 18, 24 and 36 months - PFS, TTP, ORR, DCR, and DoR according to RECIST 1.1 using Investigator assessment - Time to deterioration in EORTC QLQ-C30 and EORTC QLQ-HCC18 Key exploratory endpoint: - EQ-5D-5L

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; BID: twice daily; DCR: disease control rate; EORTC: European Organisation for Research and Treatment of Cancer; HCC: hepatocellular carcinoma; ID: identification; ORR: objective response rate; OS: overall survival; OS18: OS at 18 months; OS24: OS at 24 months; PFS: progression-free survival; Q4W: every four weeks; QLQ-C30: Core Quality of Life questionnaire; QLQ-HCC18: Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module; RECIST: response evaluation criteria in solid tumours; TTP: time to progression; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Abou-Alfa, G. et al. 2022b.⁴

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial methodology

A summary of the HIMALAYA methodology can be found in Table 5.

Table 5: Summary of HIMALAYA methodology

Study ID	HIMALAYA (NCT03298451)
Study design	Randomised, multicentre, open-label, Phase III study
Study locations	181 sites across 170 study centres in 16 countries: Brazil, Canada, France, Germany, Hong Kong, India, Italy, Japan, South Korea, Russian Federation, Spain, Taiwan, Thailand, Ukraine, USA and Vietnam
Population	Adults (aged ≥18 years) with confirmed advanced or unresectable HCC (BCLC stage B or C), who are ineligible for locoregional therapy and had not received prior systemic therapy
Key inclusion criteria	- Patients who had histologically-confirmed HCC - Patients aged ≥18 years and weighed >30 kg at the time of screening - Patients must not have received prior systemic therapy for HCC - Patients must have been deemed ineligible for locoregional therapy for advanced or unresectable HCC. For patients who had experienced disease progression following prior receipt of locoregional therapy, the locoregional therapy must have been completed at least 28 days prior to baseline screening - BCLC stage B (and ineligible for locoregional therapy) or C - Child-Pugh class A

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Study ID	HIMALAYA (NCT03298451)
	• ECOG-PS of 0 or 1 at enrolment • Patients with HBV, characterised by positive HBsAg and/or anti-HBcAb with detectable HBV DNA and must be treated with antiviral therapy, and remain on antiviral therapy until six months after the last dose of study treatment • Patients with HCV • ≥ 1 measurable lesion that had not been previously irradiated, which was ≥ 10 mm in the longest diameter at baseline (≥ 15 mm in the short axis for lymph nodes) and was deemed suitable for accurate repeated measurements. This could include lesions that had progressed after previous TACE or ablation • Adequate organ and bone marrow function, which could not be met with blood transfusions, infusions or growth factor administered within 14 days of starting the first dose a) Haemoglobin ≥ 9 g/dL b) Absolute neutrophil count $\geq 1,000$ /μL c) Platelet count $\geq 75,000$ /μL d) TBL $\leq 2.0 \times$ ULN e) AST and ALT $\leq 5 \times$ ULN f) Albumin ≥ 2.8 g/dL g) INR ≤ 1.6. Note: INR prolongation due to anticoagulants for prophylaxis (e.g., atrial fibrillation) in patients without liver cirrhosis could be an exception h) Calculated creatinine clearance ≥ 50 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24 hr urine creatinine clearance • Postmenopausal status, or negative urinary or serum pregnancy test for female premenopausal patients • Life expectancy of ≥ 12 weeks
Key exclusion criteria	• Patients with a known allergy or hypersensitivity to any of the study treatment excipients • Patients with unresolved toxicity (as defined by an NCI CTCAE grade of ≥ 2) (certain exceptions are included in the clinical study report) • Patients with receipt of concurrent chemotherapy or biological/hormonal therapy for cancer treatment • Patients with radiotherapy with a wide field of radiation, or with irradiation of $>30\%$ of the bone marrow, within 28 days of the first dose of study treatment • Patients with exposure to an investigational product within 28 days of the first dose of study treatment • Patients who had undergone a major surgical procedure within 28 days of the first dose of study treatment • Active or prior documented GI bleeding (e.g., oesophageal varices or ulcer bleeding) within 12 months. Note: For patients with a history of GI bleeding for more than 12 months or assessed as high

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Study ID	HIMALAYA (NCT03298451)
	risk for oesophageal varices by the Investigator adequate endoscopic therapy according to institutional standards was required • Current symptomatic or uncontrolled hypertension defined as DBP >90 mmHg or SBP >140 mmHg • Patients with confirmed coinfection with both HBV and HCV • Pregnant or lactating women
Treatment arms	Patients were randomised into the following treatment arms in a 1:1:1:1 ratio using IWRS and treated until they experienced confirmed disease progression, unacceptable toxicity or met any of the trial discontinuation criteria:^a • STRIDE (a single dose of tremelimumab [300 mg] + durvalumab [1,500 mg] Q4W [T300+D]): 393 patients • Sorafenib (400 mg) BID: 389 patients • Durvalumab monotherapy (1,500 mg Q4W): 389 patients^b • T75+D (tremelimumab [75 mg] Q4W for four doses + durvalumab [1,500 mg] Q4W): 153 patients^c
Stratification factors	Patients were stratified by the following factors: • Presence of MVI (Yes vs. No) • Aetiology of liver disease (Confirmed HBV vs. Confirmed HCV vs. Other) • ECOG PS (0 vs. 1)
Method of study drug administration	A single dose of tremelimumab (300 mg) was administered as a priming dose at the start of treatment, and durvalumab (1,500 mg) was administered Q4W (n=393). Both treatments were administered via IV infusion. Sorafenib was administered orally BID.
Duration of study and follow-up	Treatment continued until progression, unacceptable toxicity, consent withdrawal, or other discontinuation criteria were met. Patients could continue treatment after progression if the investigator assessed that they were benefiting from treatment and they met criteria for continuation after progressive disease.
Primary objective	Primary endpoint: • OS
Secondary objectives relating to the STRIDE regimen^d	Secondary endpoints: • OS at 18, 24 and 36 months • PFS, TTP, ORR, DCR, and DoR according to RECIST 1.1 using Investigator assessment • Time to deterioration in EORTC QLQ-C30 and EORTC QLQ-HCC18
Key exploratory endpoint related to the STRIDE regimen	Key exploratory endpoint • EQ-5D-5L

Footnotes: ^aIn certain cases, patients with confirmed PD could continue to receive their assigned intervention if the study investigator deemed that they were continuing to receive benefit from the treatment; ^bFollowing a benefit-risk assessment based on the results of the pre-planned analysis of Phase II Study 22, recruitment in the T75+D treatment arm was closed due to non-meaningful differentiation from durvalumab monotherapy, and thereafter patients were randomised in a 1:1:1 ratio to three remaining treatment groups; ^cDurvalumab monotherapy was found to be non-inferior but not superior to sorafenib in terms of OS, as such results for the durvalumab

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monotherapy treatment arm are not considered a relevant comparator in this evaluation; ^dOnly secondary objectives relating to the comparison of interest (STRIDE vs. sorafenib) are presented.

Abbreviations: ADAs: anti-drug antibodies; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; BID: twice daily; CTCAE: common terminology criteria for adverse event; DBP: diastolic blood pressure; DCR: disease control rate; DNA: deoxyribonucleic acid; DoR: duration of response; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30: EORTC core quality of-life questionnaire; EORTC QLQ-HCC18: EORTC Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HRQoL: health-related quality of life; ID: identification; INR: international normalised ratio; IV: intravenous; IWRS: interactive web response system; MVI: macrovascular invasion; NCI: National Cancer Institute; ORR: overall response rate; OS: overall survival; OS18: overall survival at 18 months; OS24: overall survival at 24 months; OS36: overall survival at 36 months; PFS: progression-free survival; Q4W: every 4 weeks; RECIST: response evaluation criteria in solid tumours; SBP: systolic blood pressure; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TACE: transarterial chemoembolisation; T75+D: tremelimumab 75 mg × 4 doses + durvalumab 1,500 mg Q4W; TBL: total bilirubin; TTP: time to progression; ULN: upper limit normal; USA: United States of America.

Source: Abou-Alfa, G. et al. 2022b.⁴ AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ Sangro, B. et al. 2022.⁹⁵

B.2.3.2 Trial design

The trial initially planned to screen approximately 1,600 patients and randomly assign 1,200 patients across each of the four treatment arms in a 1:1:1:1 ratio using an interactive web response system (IWRS).^{4, 22} The protocol was altered after the T75+D treatment arm was closed following a risk-benefit assessment. This decision was based on results from a pre-planned analysis evaluating tolerability and clinical activity in a Phase II trial (Study 22; NCT02519348), in which the efficacy data for the T75+D regimen did not differentiate from the durvalumab monotherapy arm.²² As a result, there was insufficient clinical activity observed in Study 22 to warrant continuation of enrolment in the T75+D arm in the HIMALAYA study. Consequently, the planned sample size was increased from 1,200 to 1,310 patients. This included 385 patients allocated to the STRIDE, durvalumab monotherapy and sorafenib arm, as well as 155 to T75+D arm, who were randomly assigned before enrolment closure.⁴

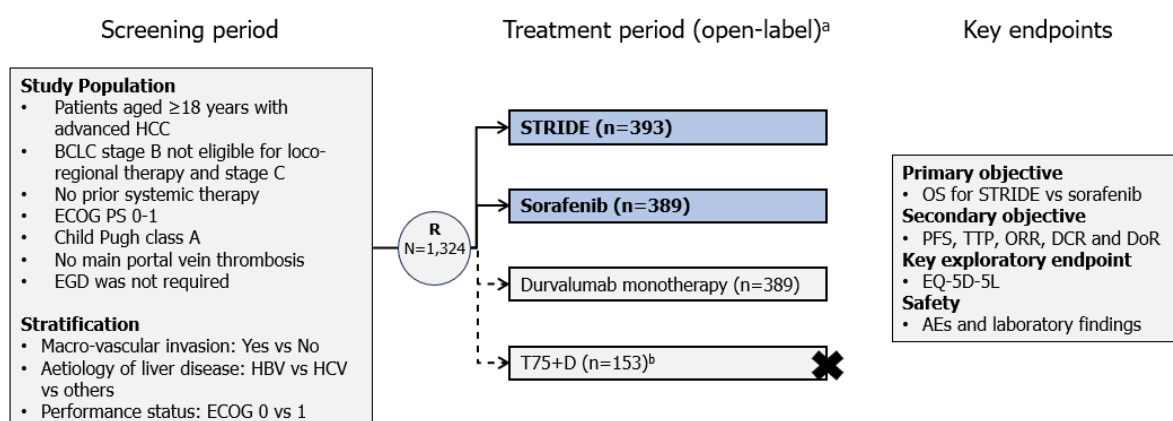
The key inclusion and exclusion criteria are outlined in Table 5. The following stratification factors were applied during randomisation: MVI (Yes or No), aetiology of liver disease (HBV vs. HCV vs. others) and ECOG performance status (0 or 1). Patients continued their assigned treatment arm until confirmed disease progression, unacceptable toxicity or met any of the trial discontinuation criteria. However, patients with confirmed progressed disease (PD) who, in the Investigator's opinion, continued to receive benefit from their assigned treatment and met the criteria for treatment in the setting of PD, could continue to receive their assigned treatment regimen.

The finalised distribution of patients and methodology of drug administration across treatment arms are below, with the two treatment arms relevant to this submission marked in **bold** (Figure 3):

- **STRIDE** (a single dose of tremelimumab [300 mg] + durvalumab [1,500 mg] Q4W [T300+D]): 393 patients
- **Sorafenib** (400 mg) BID: 389 patients
- Durvalumab monotherapy (1,500 mg) Q4W: 389 patients
- T75+D (tremelimumab [75 mg] Q4W for four doses + durvalumab [1,500 mg] Q4W): 153 patients

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Figure 3: Trial design of HIMALAYA



Footnote: ^aPatients continue study treatment until confirmed PD, unacceptable toxicity, or any discontinuation criteria were met. However, patients with confirmed PD who, in the Investigator's opinion, continued to receive benefit from their assigned treatment and met the criteria for treatment in the setting of PD, could continue to receive their assigned treatment regimen. ^bOngoing patients continue despite trial arm closure. Blue boxes denote the treatment arms that are relevant for this submission.

Abbreviations: AE: adverse event; BCLC: Barcelona Clinic Liver Cancer; DCR: diseases control rate; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; EGD: esophagogastroduodenoscopy; EORTC: European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30: EORTC core quality of-life questionnaire; EORTC QLQ-HCC18: EORTC Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module; HBV: hepatic B virus; HCC: hepatocellular carcinoma; HCV: hepatic C virus; HRQoL: health-related quality of life; ORR: objective response rate; T75+D: durvalumab in combination with tremelimumab (75 mg); TTP: time to progression; PD: progressed disease; PFS: progression-free survival; R: randomised; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Abou-Alfa, G. et al. 2022b.⁴ Sangro B. et al. 2023.⁹⁷ (slide 5).

B.2.3.3 Data cut-offs

Data cut-offs

The key analyses conducted for the HIMALAYA study relevant for this submission are:

- **Primary analysis:** The primary analysis was performed once 555 OS events occurred in the STRIDE and sorafenib arms combined (representing 71% maturity), 47 months after the first patient was randomised (DCO: 27th August 2021). This is the DCO considered for all secondary endpoints^{4, 89}
- **Updated analysis I:** The updated analysis evaluated the OS and safety of STRIDE vs. sorafenib with 4 years of follow-up (DCO: 23rd January 2023)⁹⁸
- **Updated analysis II:** Additional five-year OS analysis has been conducted for STRIDE vs. sorafenib, representing the longest follow up to date in Phase III studies in advanced or unresectable HCC (DCO: 1st March 2024)

It should be noted that the primary analysis was powered for statistical analysis. The updated analyses were exploratory endpoints intended to assess the long-term effectiveness of STRIDE, thus capturing the high level of maturity within the dataset, but they were not powered for statistical analysis.

B.2.3.4 Trial endpoints

Key primary, secondary, and safety endpoints of HIMALAYA are summarised in Table 6.

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Table 6: Key endpoints of HIMALAYA

Objectives	Endpoint Description	Assessment	Results Section
Primary	To assess the efficacy of STRIDE vs. sorafenib OS		Section B.2.6.1
Secondary: Efficacy	To assess the efficacy of STRIDE vs. sorafenib: - OS18, OS24 and OS36 - PFS, TTP, ORR^a, DCR, and DoR^b	PFS, TTP, ORR, DCR and DoR according to RECIST 1.1 using Investigator assessment	Section B.2.6.2
Secondary: PROs	To assess disease-related symptoms, impacts and HRQoL in STRIDE vs. sorafenib: - Time to deterioration in global health status/QoL, functioning (physical), multi-term symptom (fatigue), single-item symptoms (appetite loss, nausea) - Time to deterioration in single-item symptoms (shoulder pain, abdominal pain, abdominal swelling)	Questionnaire-assessed using the EORTC QLQ-C30 and EORTC QLQ-HCC18	Section B.2.6.3
Key exploratory: PROs	To assess physician-reported patient outcomes in STRIDE vs. sorafenib: EQ-5D-5L	EQ-5D-5L were collected in the trial and were cross-walked to the EQ-5D-3L for the economic model, following NICE's recommendation and Hernández-Alava et al.'s methods ⁹⁹ (Section B.3.4.5)	Section B.2.6.3
Safety	To assess the safety and tolerability profile of STRIDE vs. sorafenib AEs and laboratory findings	Endpoint variables include categories of AEs, most frequently reported AEs, serious AEs, fatal AEs, AEs leading to discontinuation of study treatment, other AEs, AEs of special interest and immune-related AEs	Section B.2.10

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Footnote: ^aORR was evaluated based on Investigator assessment. ^bFor patients who have not progression, the most recent RECIST assessment will be used to calculate DoR. However, in cases where progression has led to death, DoR will be calculated with death as the endpoint.

Abbreviations: AE: adverse event; BICR: blinded central independent review; BID: twice daily; DCR: disease control rate; DoR: duration of response; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30: EORTC core quality of-life questionnaire; EORTC QLQ-HCC18: EORTC Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module; FAS: full analysis set; HCC: hepatocellular carcinoma; HRQoL: health-related quality of life; ORR: Overall Response Rate; OS: overall survival; OS18: overall survival at 18 months; OS24: overall survival at 24 months; OS36: overall survival at 36 months; PROs: patient-reported outcomes; Q4W: every 4 weeks; PFS: progression-free survival; QoL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumours; TTP: time to progression.

Source: Abou-Alfa, G. et al. 2022b.⁴

B.2.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The statistical methods used in HIMALAYA are outlined in Table 7.

Table 7: Statistical methods in HIMALAYA

Trial name	HIMALAYA (NCT03298451)
Statistical analysis	OS was analysed using a stratified log-rank test, adjusted for the aetiology of liver disease (confirmed HBV, confirmed HCV vs. others), ECOG PS (0 vs. 1), and MVI (yes vs. no). The effect of STRIDE vs. sorafenib was estimated using a stratified Cox proportional hazards model, adjusting for the stratification factors, with a corresponding CI and P value. Kaplan-Meier plots visually represented survival times, enabling a comprehensive overview of treatment efficacy across arms. The assumed treatment effect size was an average HR of 0.70.
Sample size, power calculation	The final analysis was to be performed when approximately 515 events had occurred in the STRIDE and sorafenib arms combined (~67% maturity). This number of OS events will provide at least 97% power to demonstrate a statistically significant difference in OS at a two-sided 4.25% significance level. Ultimately, the final analysis took place once 555 OS events occurred in the STRIDE and sorafenib arms combined (71% maturity).^{4, 89} To control for type 1 error in multiple testing procedures, the primary objective OS (STRIDE vs. sorafenib) was tested at 4.9%. This is because 0.1% of the alpha level was spent on the IA1 ORR and DoR analysis (IA1), with the remaining 4.9% alpha level spent on all OS analyses (using the Lan DeMets approach).^{89, 100, 101} This approach will control for the FWER at the 5% level (2-sided). The endpoints PFS, TTP, ORR, DCR, DoR were not included in the multiple testing procedure, and as such they were not controlled for multiplicity. Statistical testing was performed at a nominal 5% significance level.
Patient discontinuation	Patients could discontinue the assigned treatment regimen at any time, or at the discretion of the Investigator(s), and were to be discontinued in the event of any of the following:⁸⁹ • Withdrawal of consent from further treatment with the assigned treatment regimen • Any AE that, in the opinion of the Investigator or AstraZeneca, contraindicated further dosing • Any AE that met criteria for discontinuation as defined in the toxicity management guidelines or as defined in the local prescribing information for sorafenib 400 mg BID • Pregnancy or intent to become pregnant

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Trial name	HIMALAYA (NCT03298451)
	- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warranted withdrawal from the assigned treatment regimen (e.g., refusal to adhere to scheduled visits) - Initiation of alternative anticancer therapy, including another investigational agent - Clinical progression, i.e. the Investigator determined that the patient was no longer benefiting from the assigned treatment regimen, with or without radiological progression by RECIST 1.1
Patient withdrawal	Withdrawal protocol:⁸⁹ - Patients were free to withdraw from the study at any time, without prejudice to further treatment. Patients were asked about their reason(s) for withdrawal and the presence of any AEs, which were followed-up by the Investigator outside the study. Survival follow-up was to continue until the end of the study unless the patient expressly withdrew their consent - If a patient had actively withdrawn consent to processing of their personal data, the survival status of the patient was to be obtained by site personnel from publicly available death registries (if available) where permitted under applicable local laws to obtain a current survival status

Abbreviations: AEs: adverse events; BID: twice daily; CI: confidence interval; DCO: data cutoff; DCR: disease control rate; DoR: duration of response; FAS: full analysis set; FWER: family-wise error wise; HR: hazard ratio; IA1: first interim analysis; IDMC: Independent Data Monitoring Committee; ORR: objective response rate; OS: overall survival; PFS: progression free survival; RECIST: response evaluation criteria in solid tumours; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTP: time to progression.

Source: Abou-Alfa, G. et al. (2022b).⁴ AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹

Analysis sets

All efficacy analyses were carried out on the full analysis set (FAS), which included all randomised patients. In general, assessment was carried out by the trial investigator, and tumour status was assessed according to RECIST 1.1.¹⁰²

A summary of the key analysis sets from HIMALAYA that are presented in this document are presented in Table 8.

Table 8: Analysis sets in HIMALAYA

Analysis Set	Description	Number of patients	Outcomes Analysed
FAS	ITT population; all patients randomised to a treatment arm (including those who do not subsequently receive treatment)	STRIDE: n=393 Sorafenib: n=389	Efficacy
SAS	All patients who received at least one treatment dose	STRIDE: n=388 Sorafenib: n=374	Safety and tolerability

Abbreviations: DCO: data cut-off; FAS: full analysis set; IA1: interim analysis 1; ITT: intention-to-treat; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab; T75+D: tremelimumab 75 mg × 4 doses + durvalumab 1,500 mg Q4W.

Source: AstraZeneca Data on File - HIMALAYA CSR, Jan 2022.⁸⁹ Abou-Alfa, G. et al. 2022b.⁴ (Table 3, pg9)

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B.2.4 Patient characteristics

The demographic and key baseline characteristics of the overall population of patients included in the HIMALAYA trial are presented in Table 9. The treatment arms were balanced in terms of demographic and baseline characteristics.⁴ In addition, the stratification factors comprising aetiology of liver disease (determined by virology laboratory assessments at screening), MVI and ECOG PS were also balanced across treatment arms.⁴

Both arms of this trial are representative of patients with advanced or unresectable HCC in the UK, as evidenced by a recent prospective, multicentre audit of 361 patients with advanced HCC in the UK.¹⁰³ The audit involved 11 UK centres providing specialist care to liver cancer patients, and reported comparable baseline characteristics to the HIMALAYA trial, including a similar percentage of male participants (82%), average age (68, range 21–87), Child-Pugh scores (5 and 6 in 75% and 25% of individuals, respectively) and baseline alpha-fetoprotein (AFP; ≥ 400 ng/mL in 37% of individuals).¹⁰³ The alignment between the HIMALAYA trial and the UK population was validated through clinician interviews. Slight deviations were noted in the baseline populations; for example, a higher incidence of non-viral HCC aetiology is observed in the UK compared to HIMALAYA. This is attributed to increased rates of metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol consumption, particularly in UK cities. Nonetheless, clinicians expected these variations and still considered this dataset to be generalisable to UK clinical practice.⁷

Table 9: Demographic and other baseline characteristics reported in HIMALAYA (FAS)

Parameter	STRIDE (n=393)	Sorafenib (n=389)
Median age (range), years	65.0 (22-86)	64.0 (18-88)
Male sex, n (%)	327 (83.2)	337 (86.6)
Race, n (%)		
White	██████	██████
Black or African American	████	████
Asian	██████	██████
Native Hawaiian or other Pacific Islander	████	█
American Indian or Alaska Native	█	█
Other	████	████
Missing	████	████
Total	██████	██████
Ethnic group, n (%)		
Hispanic or Latino	████	████
Not Hispanic or Latino	██████	██████
Missing	█	████
Total	██████	██████
Weight group (kg), n (%)		
<70	██████	██████
≥ 70 –<90	██████	██████
≥ 90	██████	██████

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Parameter	STRIDE (n=393)	Sorafenib (n=389)
BMI group (kg/m ²), n (%)		
<18.5	██████	██████
≥18.5—<25.0	██████	██████
≥25.0—<30	██████	██████
≥30.0	██████	██████
Region, n (%)		
Asia (excluding Japan)	156 (39.7)	156 (40.1)
Rest of world (including Japan)	237 (60.3)	233 (59.9)
Alcohol use, n (%)		
Never	██████	██████
Current	██████	██████
Former	██████	██████
Missing	████	█
PD-L1 status, n (%)		
Positive	148 (37.7)	148 (38.0)
Negative	189 (48.1)	181 (46.5)
Missing	52 (13.2)	45 (11.6)
Fibrosis score, n (%)		
F0	██████	██████
F1	██████	██████
Missing	██████	██████
Prior disease-related radiotherapy, n (%)	48 (12.2)	37 (9.5)
ECOG performance status score, n (%)		
0	244 (62.1)	241 (62.0)
1	148 (37.7)	147 (37.8)
Child-Pugh class/score, n (%)		
A/5	295 (75.1)	277 (71.2)
A/6	92 (23.4)	102 (26.2)
B/7	4 (1.0)	10 (2.6)
Other	2 (0.5)	0
BCLC stage, n (%)		
B	77 (19.6)	66 (17.0)
C	316 (80.4)	323 (83.0)
Aetiology, n (%)		
HBV	122 (31.0)	119 (30.6)
HCV	110 (28.0)	104 (26.7)
Nonviral	161 (41.0)	166 (42.7)
Macrovascular invasion, n (%)	103 (26.2)	100 (25.7)
Extrahepatic spread, n (%)	209 (53.2)	203 (52.2)

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Parameter	STRIDE (n=393)	Sorafenib (n=389)
AFP ≥400 ng/ml, n (%)	145 (36.9)	124 (31.9)

Footnotes: ^aBaseline is the last assessment prior to the intake of the first dose of any study treatment. ^bPD-L1 expression level is based on the TIP score method as: PD-L1 positive (TIP ≥1%) or PD-L1 negative (TIP <1%). ^cBaseline PD-L1 results are not available for patients who were randomised but not treated. ^dMissing PD-L1 may be due to the following reasons: screening sample not tested, screening sample not evaluable for TIP score, or screening sample not provided by site.

Abbreviations: AFP: alpha-fetoprotein analysis; BCLC: Barcelona Clinic Liver Cancer; BMI: body mass index; DCO: data cutoff; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; Max: maximum; Min: minimum; N: number of patients in treatment group; n: number of patients included in analysis; PD-L1: programmed cell death ligand 1; S: sorafenib 400 mg twice daily; SD: standard deviation; TIP: Tumour and Immune Cell Positivity; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Abou-Alfa, G. et al. 2022b.⁴ (Table 1, pg5). AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 15, pg125 and Table 16, pg127).

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment conducted for all clinical trials included in the SLR is presented in Appendix D. Overall, the results of the HIMALAYA trial may be considered at a low risk of bias. A summary of the quality assessment conducted for the HIMALAYA trial is provided in Table 10.

Table 10: Quality assessment conducted for HIMALAYA

Study Question	Grade (risk)
Was randomisation carried out appropriately?	Low risk: Randomisation IxRS
Was the allocation adequately concealed?	Unclear: No details provided
Were the care providers, participants, and outcome assessors blind to treatment allocation?	High risk: Open label and investigator assessed
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Low risk: Similar baseline results
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Low risk: Some disparity between rates of death between arms, with more people lost in the sorafenib arm, but this is to be expected
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: All prespecified outcomes were reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk: Not explicitly specified but the intention-to-treat population was likely used
Details of study funding	AstraZeneca funded the study
Further quality assessment notes	None

Abbreviations: IxRS: Interactive Voice/Web Response System

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 Primary endpoint: overall survival

Overall survival is defined as the time from the date of randomisation until death due to any cause, regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy. Any patient not known to have died at the DCO date was censored based on the last recorded date on which the patient was known to be alive. If the last known date alive or if the date of death was after the DCO date, patients were censored at the DCO date.

HIMALAYA met its primary endpoint (DCO: 27th August 2021), with STRIDE demonstrating a statistically significant and clinically meaningful improvement in OS vs. sorafenib, with a median survival of 16.43 months (95% CI: 14.16–19.58) vs. 13.77 months (95% CI: 12.25–16.13; Appendix M). In the exploratory 4-year updated analysis I (DCO: 23rd January 2023), STRIDE maintained improved OS results, with survival probabilities of 25.2% for STRIDE compared to 15.1% for sorafenib (Appendix M).¹⁰⁴ Most recently, in the exploratory 5-year (DCO: 1st March 2024) updated analysis II, the survival probabilities were 19.6% for STRIDE compared to 9.4% for sorafenib (Table 11). This represents the most mature OS dataset available for a systemic therapy in advanced or unresectable HCC, thereby enabling clinicians to have confidence in the long-term survival benefits of STRIDE for their patients.¹⁰⁴

Table 11: Summary of HIMALAYA OS results (updated analysis II;^a FAS) (DCO: 1st March 2024)

	STRIDE (n=393)	Sorafenib (n=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS, mo (95% CI) ^b	16.43 (14.16–19.58)	13.77 (12.25–16.13)
HR ^c (95% CI)	0.76 (0.65–0.89)	
Median follow-up duration in all patients (95% CI), mo ^d	62.49 (59.47–64.79)	59.86 (58.32–61.54)

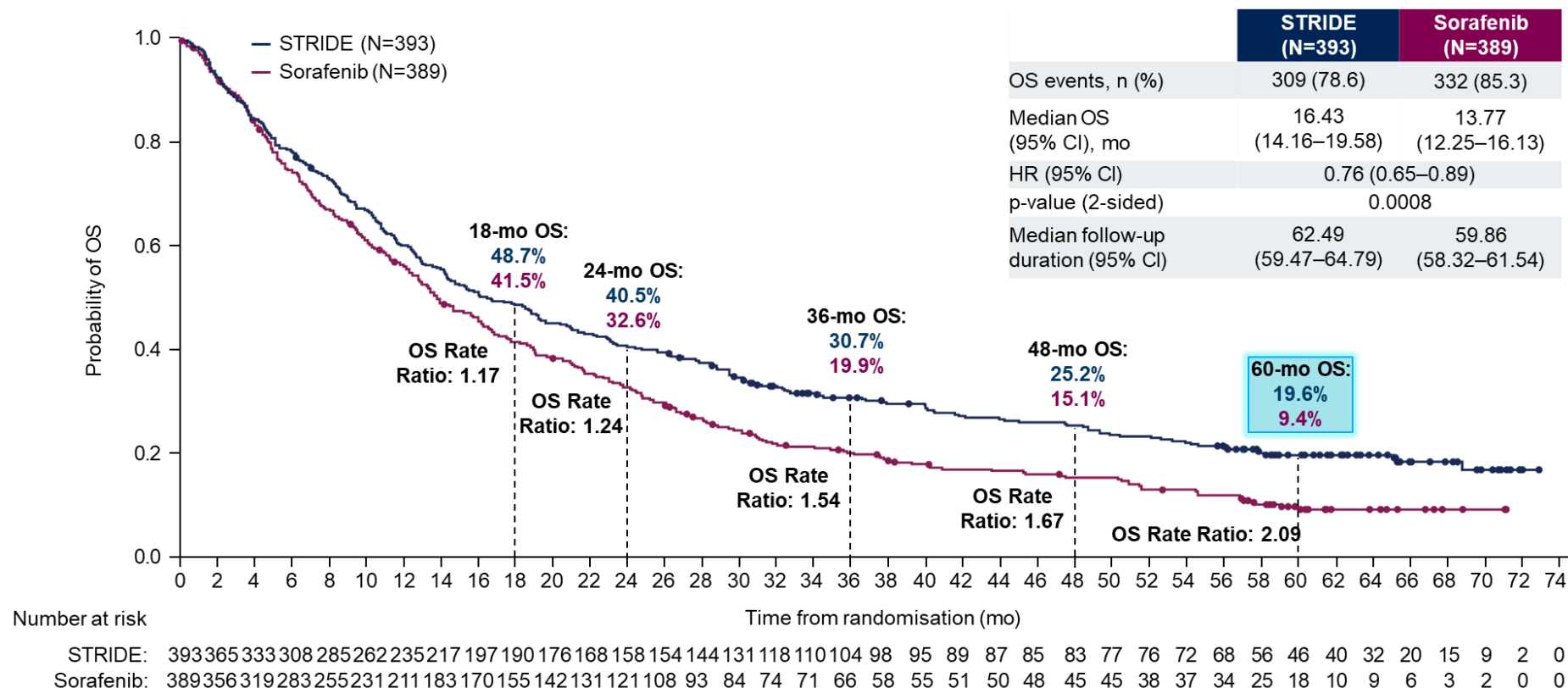
Footnotes: ^aThe updated analysis II was not powered for statistical analysis; ^bCalculated using the reverse Kaplan-Meier technique (with censor indicator reversed); ^cHazard ratio stratified by factors based upon the categories used in the randomisation system HR stratified by factors based upon the categories used in the randomisation system; ^dp-value from a stratified log-rank test.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; OS: overall survival; SD: standard deviation; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Rimassa 2024⁹⁰

The Kaplan-Meier plot for OS separated approximately four months after randomisation, demonstrating the rapid onset of treatment effect associated with STRIDE compared to sorafenib. This separation was sustained, with a greater number of patients alive in the STRIDE treatment arm compared with the sorafenib treatment arm at all recorded timepoints (Figure 4).⁹⁸ This pattern aligns with the expected mechanism of action of STRIDE, where the dual IO-IO regimen leads to a strong stimulation of the immune response to attack cancer cells (see Section B.1.2).

Figure 4: Kaplan-Meier plot of HIMALAYA OS results (updated analysis II:^a FAS) (DCO: 1st March 2024)



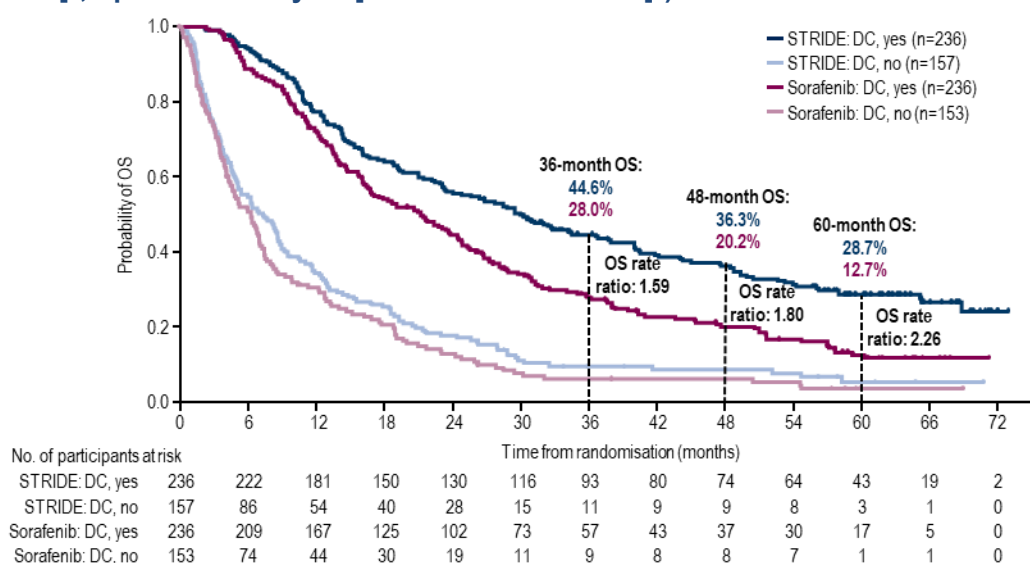
Footnote: ^aThe updated analysis II was not powered for statistical analysis.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Rimassa 2024⁹⁰

Furthermore, STRIDE demonstrated benefits over sorafenib in patients who achieved disease control; OS rates were 44.6% at 3 years, 36.3% at 4 years and 28.7% at 5 years in participants who achieved disease control with STRIDE, vs. 28.0%, 20.2% and 12.7% in participants who achieved disease control with sorafenib, respectively (**Error! Not a valid bookmark self-reference.**).^{90, 105} Of patients who achieved disease control with STRIDE, over 1 in 4 patients were alive at 5 years (28.7%). These results reinforce the sustained long-term OS benefit of STRIDE vs. sorafenib.

Figure 5: Summary of HIMALAYA OS results by disease control at 3, 4 and 5 years (primary analysis [DCO: 27th August 2021]^a, updated I analysis [DCO: 23rd January 2023]^b, updated II analysis [DCO: 1st March 2024]^b)



Footnote: ^aThe primary analysis was powered for statistical analysis; ^bThe updated analysis I and II were not powered for statistical analysis; Responses were based on investigator assessment according to RECIST 1.1. Disease control was defined as the sum of the number of patients who achieved CR, the number of patients who achieved PR, and the number of patients who experienced SD.

Abbreviations: CR: complete response; DC: disease control; DCO: data cut-off; DCR: disease control rate; mo: months; NE: not evaluable; OS: overall survival; PR: partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD: stable disease; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Rimassa 2024⁹⁰

The HIMALAYA outcomes for OS are highly promising for patients with advanced or unresectable HCC in the UK. The mature dataset, which includes three-year primary analysis data along with four and five-year OS exploratory analyses, demonstrates a statistically significant and clinically meaningful improvement in survival relative to sorafenib over the longest follow-up duration observed in this setting. The availability of an alternative therapy that enhances survival compared to current therapies will be of significant value to patients with advanced or unresectable HCC and their families.

B.2.6.2 Secondary endpoints: efficacy

Five key secondary endpoints were used to assess the efficacy of STRIDE compared to sorafenib in patients with advanced or unresectable HCC. These included PFS, TTP, ORR, DoR and DCR. At the primary DCO (27th August 2021), all five endpoints are assessed in all individuals in the FAS according to RECIST 1.1 by Investigator assessment.

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B.2.6.2.1 Progression-free survival

PFS is defined as the time from the date of randomisation until the date of objective progressive disease (PD) or death by any cause in the absence of PD, regardless of whether the patient withdrew from study treatment or received another anticancer therapy prior to progression. As PFS was not included in multiple testing procedure (MTP), it is not controlled for multiplicity and statistical testing was performed at a nominal 5% significance level (please see Table 7 for more detail on statistical analyses).^{89, 98}

At the primary analysis (DCO: 27th August 2021), the Kaplan-Meier estimate for median PFS was similar in both treatment arms. Median PFS was 3.78 months in the STRIDE treatment arm compared with 4.07 months in the sorafenib treatment arm (Table 12 and Figure 6).⁴ Despite this, a greater proportion of patients were progression-free at the primary analysis in the STRIDE treatment arm compared with the sorafenib arm (12.5% vs. 4.9%; Table 12).⁴

This finding of similarity in median PFS for STRIDE relative to sorafenib aligns with the typical efficacy pattern observed with IO-IO therapies, where the indirect mechanism of action, specifically, the inhibition of cellular pathways that down-regulate the immune response, subsequently allowing the upregulation of the immune system to target cancer cells (see Section B.1.2), often results in a delayed treatment effect.⁹¹ As a result, the observed PFS benefit is often minor with IO-IO therapies, whilst a clinically significant improvement in OS is observed.^{3, 92-94}

Recent interviews with UK HCC experts highlighted the importance of the prolongation of OS as a key outcome for patients with HCC and their carers, with one clinical expert emphasising that OS is the most important endpoint for decision-making in advanced or unresectable HCC. Supporting this, Huang et al. published a study in 2024 in which an SLR and meta-regression of Phase I–III clinical trials of IO therapies in unresectable HCC was performed. Meta-regression of OS and surrogate endpoints identified a particularly weak correlation between PFS and OS (R^2 : 0.352, 95% CI: 0.000–0.967) across Phase II and III trials, with the authors concluding that PFS has limited utility as a surrogate endpoint in unresectable HCC. Potential reasons for this offered by the authors were the role of pseudoprogression, in which the tumour may show local enlargement or the appearance of new lesions at the beginning of treatment, but then significant therapeutic effects can appear subsequently, in addition to the role of liver decompensation as a key risk factor for mortality in HCC.⁹⁴

The clinical experts consulted echoed the findings of this study, highlighting that firstly, the measurement of PFS is challenging, as radiologic progression is a subjective measurement prone to reading errors.¹⁰⁶ Secondly, it was also noted that patients are frequently eligible to continue treatment both within the trial setting and real-world setting even after disease progression.⁴ This is crucial for patients with limited subsequent treatment options, as is the case for advanced or unresectable HCC, however, it undermines PFS as a reliable prognostic marker for OS. Collectively, these findings indicate a weak surrogacy between PFS and OS in advanced or unresectable HCC, particularly when IO-IO therapies are used. Overall, OS is considered the most reliable endpoint for evaluation of efficacy in this setting by clinical experts.^{7, 93}

Table 12: Summary of HIMALAYA PFS results (primary analysis; FAS) (DCO: 27th August 2021)

	STRIDE (n=393)	Sorafenib (n=389)
Median PFS, months (95% CI)	3.78 (3.68–5.32)	4.07 (3.75–5.49)

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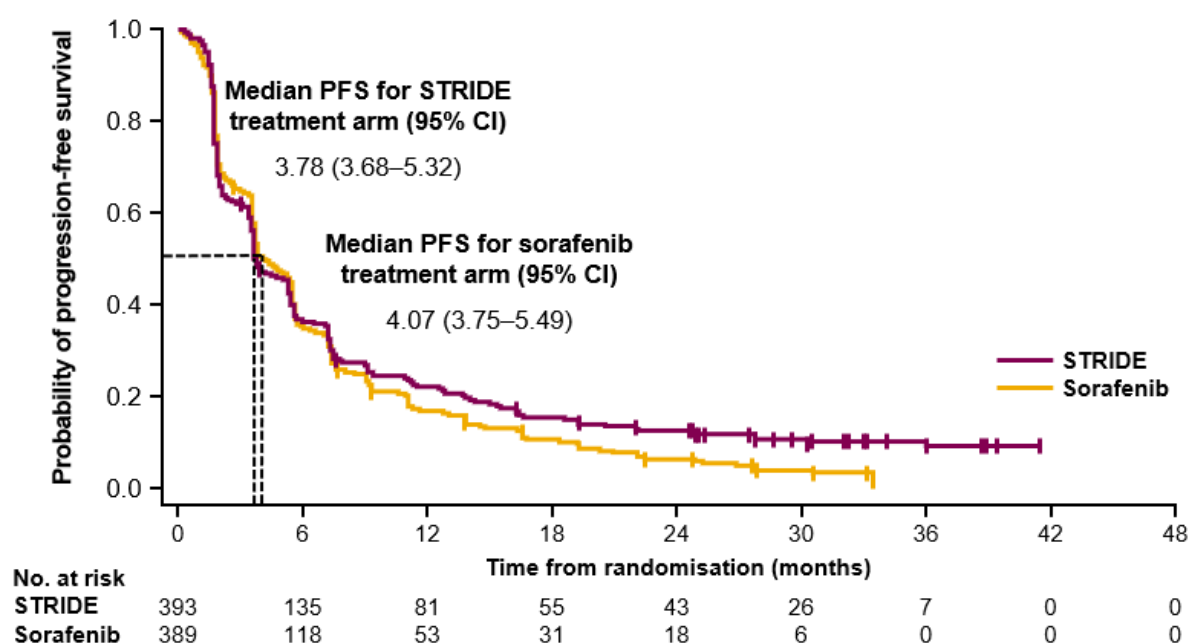
	STRIDE (n=393)	Sorafenib (n=389)
HR	0.90	
95% CI for HR	0.77–1.05	
2-sided p-value	[REDACTED]	
Progression-free, n (%)	[REDACTED]	[REDACTED]

Footnotes: ^aCalculated using the Kaplan-Meier technique.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Abou-Alfa, G. et al. 2022b.⁴⁵ (Figure 1B, pg6). AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 31, pg161).

Figure 6: Kaplan-Meier plot of HIMALAYA PFS results (primary analysis; FAS) (DCO: 27th August 2021)



Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

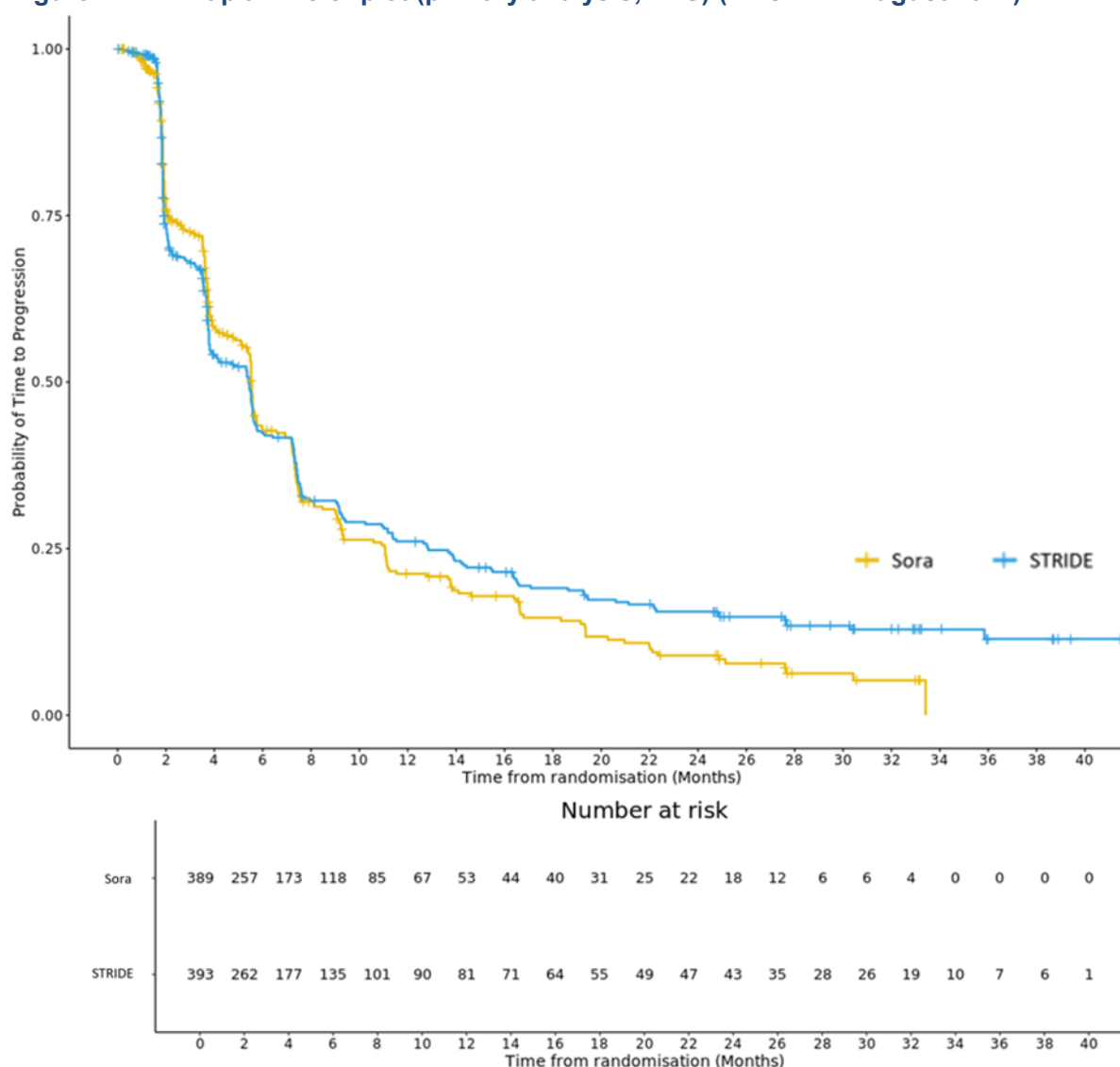
Source: Abou-Alfa, G. et al. 2022a.⁴⁵ (Slide 13).

B.2.6.2.2 Time to progression

TTP is defined as the time from randomisation until objective tumour progression in the absence of death. If a patient died without tumour progression, they were censored at the time of death.

At the primary analyses, the Kaplan-Meier estimate of median TTP was 5.4 months (95% CI: 3.8–5.6) in the STRIDE treatment arm and 5.6 months (95% CI: 5.1–5.8) in the sorafenib treatment arm (Figure 7).⁴

Figure 7: TTP Kaplan-Meier plot (primary analysis; FAS) (DCO: 27th August 2021)



Abbreviations: DCO: data cut-off; FAS: full analysis set; TTP: time-to-progression; sora: sorafenib; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Sources: Adapted from AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Figure 14.2.3.1, pg469).

B.2.6.2.3 Response rates

Upon receipt of cancer treatment, there are four categories of response level that can be achieved: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). ORR is defined as the percentage of patients with at least one unconfirmed visit response of CR or PR. Data obtained up until PD, or the last evaluable assessment in the absence of PD, was included in the assessment of ORR. Patients who discontinued the assigned treatment regimen without PD or received a subsequent therapy and then responded were not included as responders in the ORR.

At the primary analysis, the ORR based on Investigator assessment according to RECIST 1.1 for confirmed response was 20.1% for the STRIDE treatment arm, and 5.1% for the sorafenib treatment arm.⁴ Treatment with STRIDE had a nominally greater likelihood of response compared to sorafenib (████████████████████).⁸⁹ Confirmed CRs were only observed in patients in the STRIDE treatment arm (n=12/393, 3.1%), with no complete Company evidence submission for durvalumab with tremelimumab for untreated unresectable hepatocellular carcinoma [ID2725]

responses observed in the sorafenib arm.⁴ The significance of robust CR results in HCC has been reinforced by the above mentioned meta-regression analysis, which revealed a strong correlation between CR and OS ($R^2=0.905$, 95% CI: 0.728-1.000) in patients with unresectable HCC. Clinicians regard OS as the primary measure when evaluating HCC, thereby highlighting the importance of response rates as a meaningful outcome in this context.⁹⁴ Detailed ORR results are presented in Table 13.

Table 13: Summary of HIMALAYA ORR results (primary analysis; FAS) (DCO: 27th August 2021)

Proportion of patients / %	Treatment	
	STRIDE	Sorafenib
ORR	20.1	5.1
Response		
CR	3.1	0.0
PR	17.0	5.1
Non-response		
PD	████	████
SD ^a	39.9	55.5

Footnotes: Determined by Investigator assessment according to RECIST 1.1. ^aDefined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD (calculation: SD = 100 – disease control rate).

Abbreviations: CR: complete response; DCO: data cut-off; FAS: full analysis set; ORR: objective response rate; PD: progressive disease; PR: partial response; STRIDE: Single Tremelimumab Regular Interval Durvalumab; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.

Source: Abou-Alfa, G. et al. 2022b.⁴ (Table 2, pg7); AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 29, pg156).

B.2.6.2.4 Disease control rate

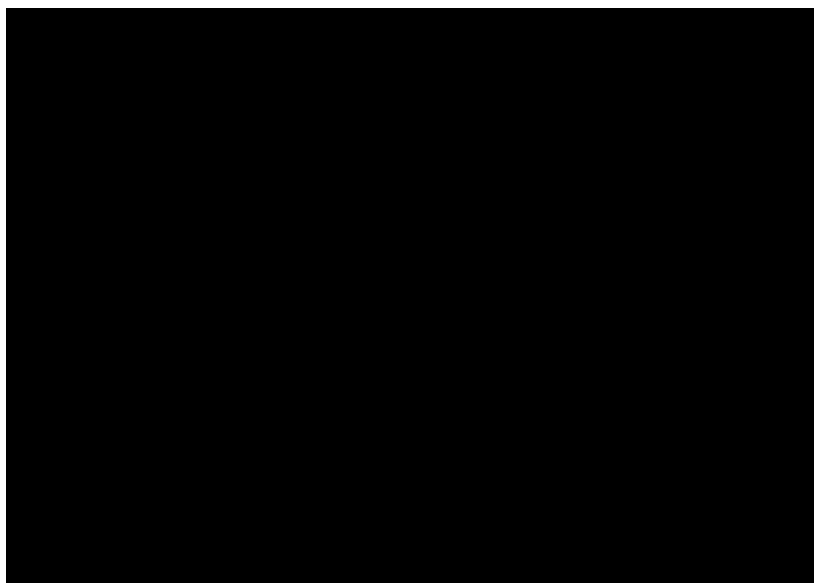
DCR is defined as the sum of the number of patients who achieved CR, PR or SD and was a key secondary endpoint explored in HIMALAYA.⁴ CR, PR and SD were defined based on Investigator assessment, according to RECIST 1.1.⁴ Two related secondary endpoints were also explored: █████, which measures the number of patients achieving █████, █████, and █████, which measures the corresponding variable for █████.⁸⁹ As previously mentioned, CR, a crucial element of DCR, strongly correlates with OS, considered by clinicians to be the primary outcome for evaluating new treatments in advanced or unresectable HCC.

At the primary analysis, a similar overall DCR was seen in both STRIDE and sorafenib treatment arms (60.1% vs. 60.7% respectively; DCO: 27th August 2021).⁴ These rates were maintained in updated analysis II (five years), as discussed in Section B.2.6.1 (and 28.7% at 5 years in participants who achieved disease control with STRIDE, vs. 28.0%, 20.2% and 12.7% in participants who achieved disease control with sorafenib, respectively (**Error! Not a valid bookmark self-reference.**)).^{90, 105} Of patients who achieved disease control with STRIDE, over 1 in 4 patients were alive at 5 years (28.7%). These results reinforce the sustained long-term OS benefit of STRIDE vs. sorafenib.

Figure 5). However, individuals in the STRIDE arm who achieved disease control (CR, PR or SD) demonstrated higher OS rates compared with those in the sorafenib arm (Section 2.6.1; Table 12).^{97, 98} An overview of the DCR results from HIMALAYA are presented in Figure 8.⁸⁹

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Figure 8: Summary of HIMALAYA DCR results (primary analysis; FAS) (DCO: 27th August 2021)



Footnotes: Percentage of patients who achieved complete response, partial response or stable disease (DCR); percentage of patients who achieved complete response, partial response or stable disease for 16 weeks (DCR-16w); percentage of patients who achieved complete response, partial response or stable disease for 24 weeks (DCR-24w).

Abbreviations: DCO: data cut-off; DCR: disease control rate; FAS: full analysis set.

Source: Abou-Alfa, G. et al. 2022b.⁴ (Table 2, pg7). AstraZeneca Data on File - HIMALAYA CSR, Jan 2022.⁸⁹ (Table 33, pg165).

B.2.6.2.5 Duration of response

DoR is defined as the time from the date of first documented response (CR or PR) until the first date of documented PD, or death in the absence of PD.

At the primary analysis, the median DoR from onset for patients with an objective response was found to be greater for patients in the STRIDE treatment arm (22.3 months) than for patients in the sorafenib treatment arm (18.4 months). At [REDACTED] following onset of response, the percentage of patients remaining in response was [REDACTED] for the [REDACTED] treatment arm compared with the [REDACTED] treatment arm ([REDACTED] vs. [REDACTED] respectively). This aligns with expectations of the STRIDE mechanism of action, in which a strong and durable stimulation of the immune system to attack cancer cells is elicited. However, it should be noted that the number of responders in the sorafenib treatment arm is low (20 patients achieving PR and no patients achieving CR), leading to uncertainty in the median estimate for this arm.^{4, 89} Detailed DoR results are presented in Table 14.

Table 14: Summary of HIMALAYA DoR results (primary analysis; FAS) (DCO: 27th August 2021)

	STRIDE (n=393)	Sorafenib (n=389)
Number of patients experiencing partial or complete response, n (%) ^a	79 (20.1)	20 (5.1)
Number of patients who subsequently progressed or died, n ^a	■	■
Median time to onset of response from randomisation, months	2.17	3.78
Median DoR from onset of response, months ^b	22.34	18.43
Percentage remaining in response, %		
After ■	■	■
After ■	■	■

Footnotes: ^aResponses include only confirmed responses; ^bCalculated using the Kaplan-Meier technique.

Abbreviations: DCO: data cut-off; DoR: duration of response; FAS: full analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Sources: Abou-Alfa, G. et al. 2022b.⁴ (Table 2, pg7). AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 30, pg159).

B.2.6.3 Patient-reported outcomes

B.2.6.3.1 EORTC QLQ-C30 and EORTC QLQ-HCC18

A secondary objective of the HIMALAYA study was to assess disease-related symptoms, impacts and HRQoL of the STRIDE regimen vs. sorafenib.^{89, 107} Two PRO instruments were used to measure patient HRQoL as a secondary objective in the HIMALAYA trial: the EORTC QLQ-C30 and EORTC QLQ-18-item HCC HRQoL questionnaire (EORTC QLQ-HCC18).¹⁰⁷

The EORTC QLQ-C30 is a 30-item self-administered questionnaire which reviews five functional scales, three symptom scales and a global health status. The EORTC QLQ-HCC18 is an 18-item self-administered questionnaire developed and validated specifically for HCC.

Baseline EORTC QLQ-C30 and EORTC QLQ-HCC18 were mostly comparable for patients in the STRIDE and sorafenib treatment arms, and scores were generally towards the higher end of the scale for physical functioning for STRIDE but reduced for GHS/QoL (Table 15). Additionally, there was a trend towards more severe symptoms at baseline in the sorafenib treatment arm, in particular for fatigue, appetite loss, abdominal pain, and shoulder pain.¹⁰⁷

Table 15: EORTC QLQ-C30 and EORTC QLQ-HCC18 PRO Scores at Baseline (primary analysis; FAS) (DCO: 27th August 2021)

Scale/Item	STRIDE (n=393)	Sorafenib (n=389)
EORTC QLQ-C30, n (SD)		
GHS/QoL	70.5 (18.89)	67.4 (19.94)
Functional—physical functioning	84.6 (16.54)	81.0 (20.52)
Functional—role	84.7 (21.69)	80.5 (26.91)
Multiple symptoms—fatigue	26.2 (20.73)	31.3 (25.65)

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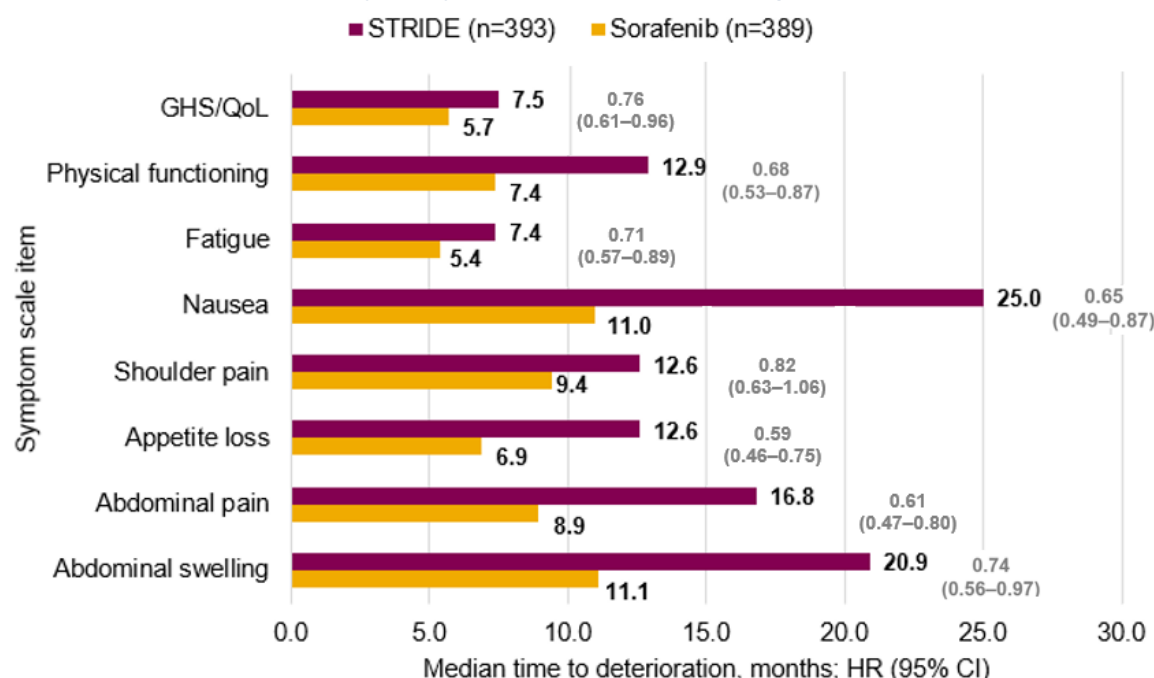
Scale/Item	STRIDE (n=393)	Sorafenib (n=389)
Single item—appetite loss	12.2 (21.02)	17.8 (25.61)
Single item—nausea	7.5 (17.84)	9.8 (21.24)
Single item—diarrhoea	6.0 (15.91)	7.6 (16.07)
EORTC QLQ-HCC18, n (SD)		
Single item—shoulder pain	14.1 (22.37)	18.0 (26.70)
Single item—abdominal pain	15.5 (21.45)	17.7 (24.70)
Single item—abdominal swelling	11.9 (21.49)	12.0 (21.07)
Multiple symptoms—jaundice	8.5 (14.18)	10.9 (16.14)

Abbreviations: EORTC: European Organization for Research and Treatment of Cancer; GHS: global health status; HCC: hepatocellular carcinoma; PRO: patient-reported outcome; QLQ-C30: 30-item Quality of Life Questionnaire; QLQ-HCC18: 18-item HCC health-related Quality of Life Questionnaire; QoL: quality of life; SD: standard deviation; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Sangro, B. et al. 2024b.¹⁰⁷ (Table 1, pg3)

Treatment with STRIDE resulted in a numerically longer median time to deterioration compared to sorafenib in all PRO measures except for jaundice, where sorafenib was numerically greater.¹⁰⁷ A summary of key EORTC QLQ-C30 and EORTC QLQ-HCC18 scores from HIMALAYA for STRIDE and sorafenib can be found in Figure 9. The assessments for EORTC QLQ-C30 and EORTC QLQ-C30 have demonstrated that the STRIDE regimen improves functioning and reduces symptom burden compared to sorafenib.⁹⁸

Figure 9: Comparison of HIMALAYA Time To Deterioration of EORTC QLQ-C30 and EORTC QLQ-HCC18 (primary analysis; FAS) (DCO: 27th August 2021)



Footnotes: Time to deterioration was defined as the time from randomisation to first clinically meaningful deterioration (worsening ≥10 points) confirmed at a subsequent visit or death.

Abbreviations: CI: confidence interval; DCO: data cut-off; EORTC: European Organisation for Research and Treatment of Cancer; FAS: full analysis set; GHS: global health status; HR: hazard ratio; QoL: quality of life; QLQ-C30: 30-item core quality of life questionnaire; QLQ-HCC18: 18-item hepatocellular cancer HRQoL questionnaire; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

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Source: Sangro, B. et al. 2024b.¹⁰⁷ (Figure 3A, pg6).

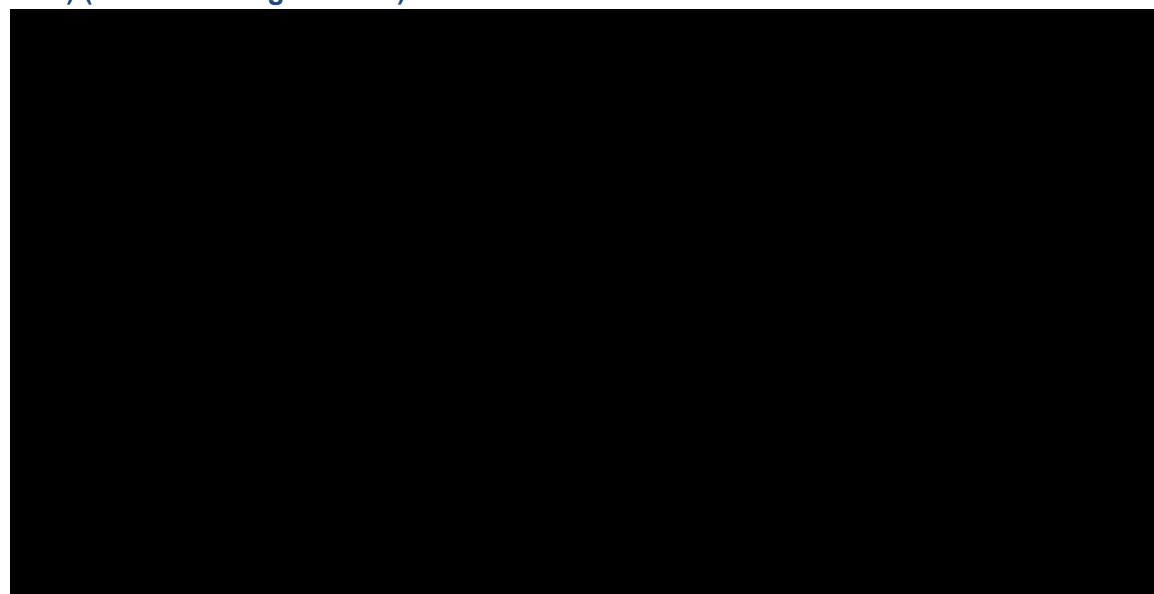
B.2.6.3.2 EQ-5D-5L

EQ-5D-5L data were also collected as an exploratory endpoint to provide insights into HRQoL. EQ-5D-5L is composed of an EQ-5D descriptive system and the EQ-visual analogue scale (EQ-VAS). The EQ-5D and EQ-VAS measurements were [REDACTED]

[REDACTED]

Post-hoc analyses of the HIMALAYA EQ-5D dSata were conducted to determine treatment specific health state utility values to the EQ-5D data from HIMALAYA (Figure 10), with a VAS summary of mean EQ-5D-5L scores presented in Figure 11. It should be noted that, since the pivotal study was open-label and PRO data were not the primary endpoint, the PRO data were not protected against multiplicity.

Figure 10: Mean EQ-5D-5L scores by treatment status in HIMALAYA (primary analysis; FAS) (DCO: 27th August 2021)

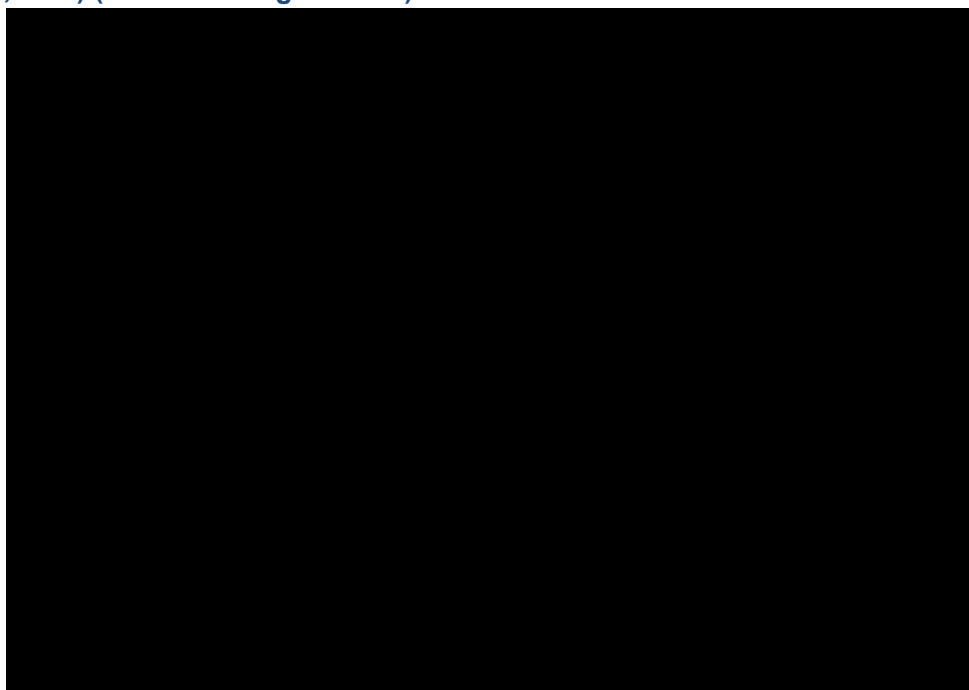


Footnotes: Baseline STRIDE: n=293; Baseline sorafenib: n=322; On treatment STRIDE: n=1,112; On treatment sorafenib: n=892; Off treatment STRIDE: n=260; Off treatment sorafenib: n=163. ^aThe EQ-5D-5L questionnaire comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. There are five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. An EQ-5D-5L score is derived from the scores provided for the different dimensions, ranging from 0 to 1, with a higher score indicating better health status.

Abbreviations: DCO: data cut-off; EQ-5D-5L: EuroQoL-5 Dimensions-5 Levels; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: AstraZeneca Data on File - IEMT201-HIMALAYA.⁹⁶ (Slide 29–30)

Figure 11: Summary of mean EQ-VAS scores by treatment status in HIMALAYA (primary analysis; FAS) (DCO: 27th August 2021)



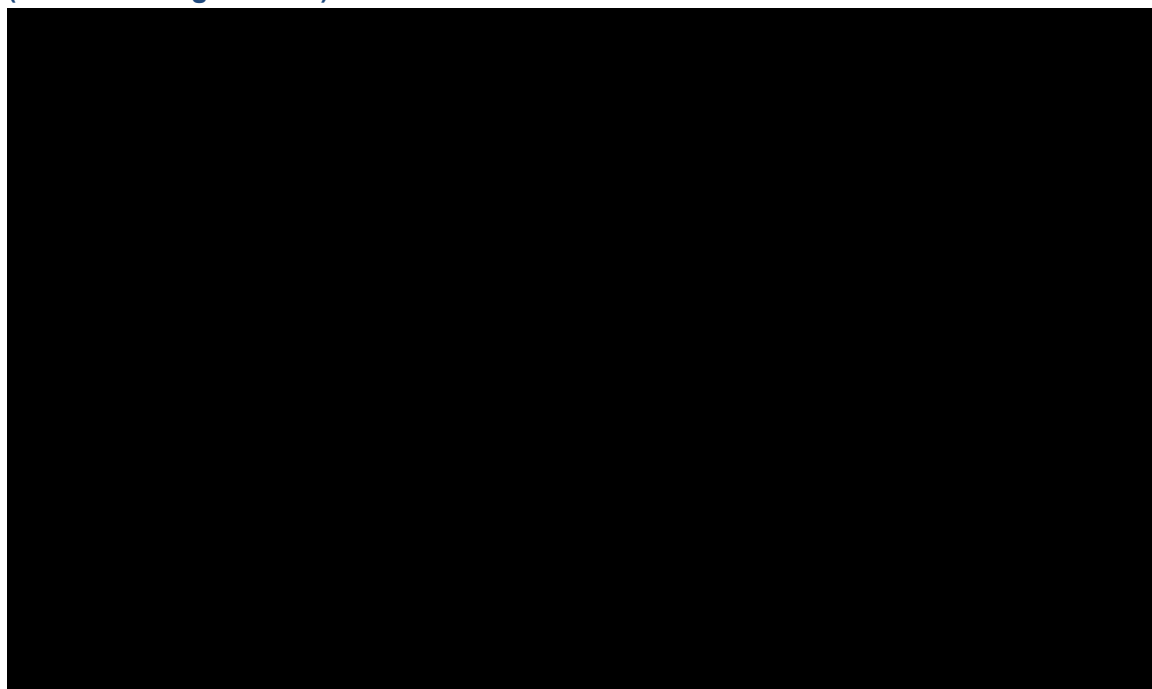
Footnotes: ^aThe EQ-VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine". These values range from 0 to 1, with a higher score indicating better health status.

Abbreviations: DCO: data cut-off; EQ-VAS: EuroQoL-Visual Analogue Scale; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: AstraZeneca Data on File - IEMT201-HIMALAYA.⁹⁶ (Slide 108)

The proportion of patients experiencing moderate to extreme problems in each domain of EQ-5D-5L was also explored, which [REDACTED] between the last visit prior to- and first visit post-discontinuation for both arms. The proportion of patients experiencing moderate to extreme problems was [REDACTED] with STRIDE compared to sorafenib for both on- and off-treatment, except [REDACTED] (Figure 12).¹⁰⁸

Figure 12: Proportion of patients in HIMALAYA with moderate to extreme problems before (on treatment) and after treatment discontinuation (off treatment) (primary analysis; FAS) (DCO: 27th August 2021)



Abbreviations: DCO: data cut-off; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

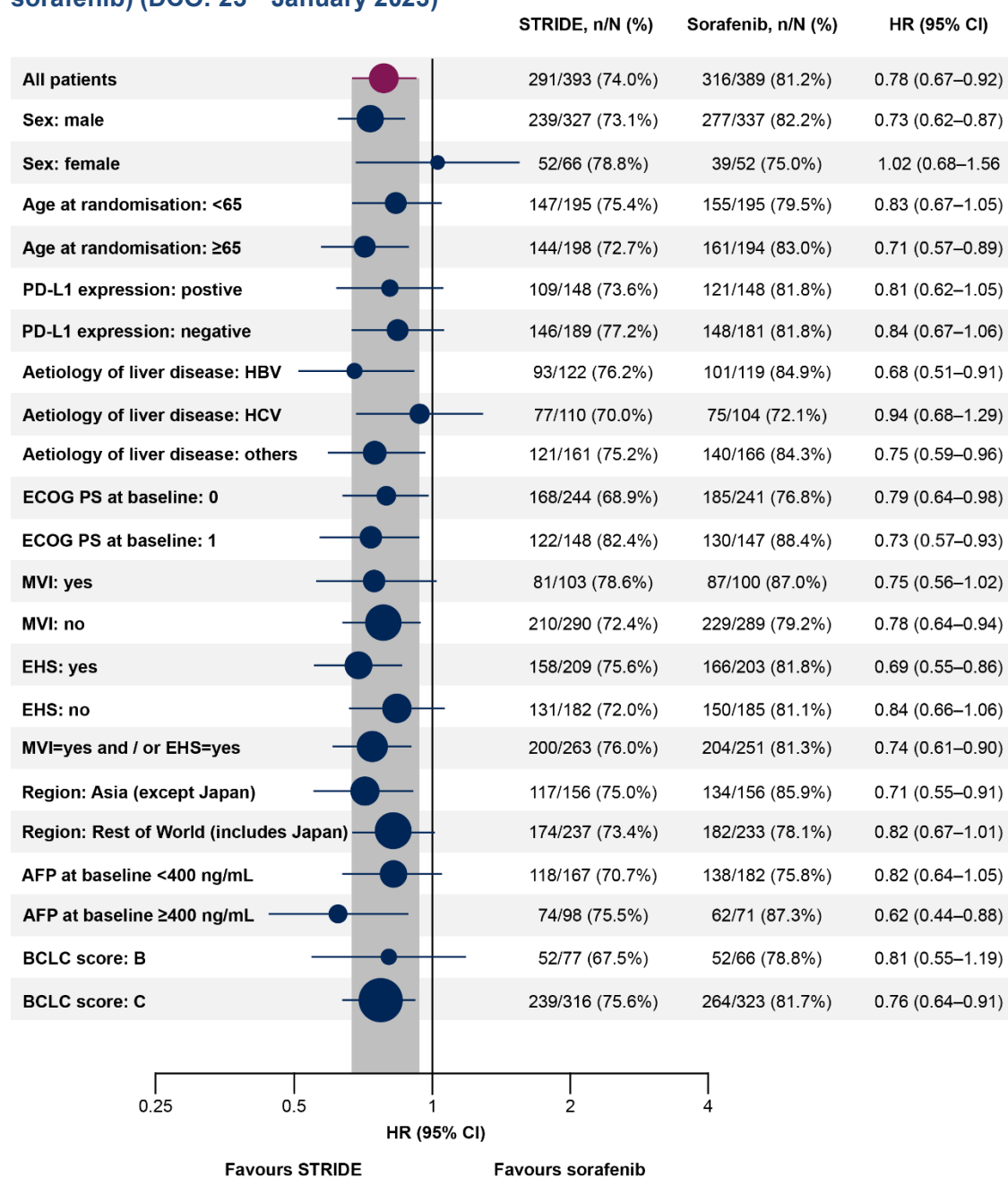
Source: AstraZeneca Data on File – Oral presentation on EQ-5D analysis from HIMALAYA at Eastern Association for the Study of the Liver (EASL) 2022.¹⁰⁸

B.2.7 Subgroup analysis

Subgroup analyses were undertaken to assess the consistency of treatment effect across a range of important clinical and demographic characteristics (Figure 13).

The OS benefit favouring STRIDE treatment vs. sorafenib treatment was consistent across most pre-specified subgroups, evidenced by the fact that the HR point estimate for each subgroup was contained within the 95% CI of the HR for the overall population. Some variability was observed, particularly in the female sex subgroup and the subgroup of patients with confirmed HCV disease. For analysis of the female sex subgroup, this variability is likely due to the small sample size (<100 patients were enrolled in each treatment arm). For HCV, a post-hoc analysis of baseline covariates within the HCV subgroup identified potential imbalances in prognostic factors between the groups. Despite this, the overall subgroup analyses demonstrate that the OS benefit observed in the intention-to-treat (ITT) population was consistent across stratification and pre-specified subgroups.⁴⁵ This benefit was also seen at the primary DCO (Appendix E).

Figure 13: Forest plot for updated OS subgroup analysis in HIMALAYA (STRIDE vs. sorafenib) (DCO: 23rd January 2023)



Footnotes: For all participants, OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. For the subgroup analysis, OS HRs and 95% CIs are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties.

Abbreviations: AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; CI: confidence interval; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EHS: extrahepatic spread; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; MVI: macrovascular invasion; OS: overall survival; PD-L1: programmed cell death ligand 1; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Sangro, B. et al. 2024a.⁹⁸ (Figure 2A, pg5).

Further exploratory analysis has been conducted on the presence and potential impact of cardiovascular and metabolic comorbidities on the efficacy and safety of STRIDE in patients with advanced or unresectable HCC.¹⁰⁹ This study found that OS rates at 3- and 4-years were higher with STRIDE compared to sorafenib, irrespective of cardiovascular or metabolic comorbidities,

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and were [REDACTED] with landmark OS rates previously reported in the FAS (Table 16; see section B.2.6.1). This reinforces that STRIDE is a safe and efficacious treatment regimen suitable for a diverse patient population. Additional information on long-term survival and safety in participants with comorbidities can be found in Appendix E.

Table 16: Landmark OS rates in participants with vs. without comorbidities (updated analysis I; SAS) (DCO: 23rd January 2023)

OS rate (%)	STRIDE (n=393)				Sorafenib (n=389)			
	Cardiovascular comorbidities		Metabolic comorbidities		Cardiovascular comorbidities		Metabolic comorbidities	
	Yes (n=[REDACTED])	No (n=[REDACTED])	Yes (n=[REDACTED])	No (n=[REDACTED])	Yes (n=[REDACTED])	No (n=[REDACTED])	Yes (n=[REDACTED])	No (n=[REDACTED])
3 years	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
4 years	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: DCO: data cut-off; OS: overall survival; SAS; safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Rimassa, L et al. (2024).¹⁰⁹

B.2.8 Meta-analysis

A meta-analysis is a common statistical method used to generate aggregate measures of effect from individual trials. As only one trial of STRIDE was performed (i.e. HIMALAYA), no meta-analysis was completed.

B.2.9 Indirect and mixed treatment comparisons

Summary of network meta-analysis

- The SLR identified 17 studies which were assessed for inclusion in the NMA, of which three studies were determined eligible for inclusion, including the HIMALAYA, IMbrave150 and REFLECT trials (Section B.2.9.2). These studies were used to form a network of evidence for STRIDE, atezolizumab + bevacizumab and lenvatinib, for both OS and PFS, connected via a common sorafenib treatment arm (Section B.2.9.3)
- The appropriateness of performing an NMA was assessed. Overall, the three trials were generally comparable in terms of study design and patient baseline characteristics (Section B.2.9.4)
- There was significant disparity in length of follow-up between the three trials. However, NMA models allowing for a time-varying treatment effect were not considered appropriate, as they would be limited in their ability to compare long-term efficacy due to the short follow-up for IMbrave150 in particular
- There was evidence of proportional hazard (PH) assumption violation for HIMALAYA and REFLECT for OS and PFS. Time-varying analyses conducted for REFLECT suggested a positive treatment effect for lenvatinib at the beginning of the study follow-up that diminishes over time, meaning that the results of the NMA may overpredict survival for lenvatinib
- There was no evidence of PH violation for IMBrave150, and therefore the estimate from the NMA of atezolizumab + bevacizumab vs sorafenib was unlikely to be biased
- A Bayesian NMA was conducted for both OS and PFS to provide estimates of the relative efficacy of STRIDE, atezolizumab + bevacizumab, lenvatinib and sorafenib. Both fixed and

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random effects models were fitted with the most appropriate model selected using the deviance information criterion (Section B.2.9.6)

- For both OS and PFS, the RE model with informative prior was selected (Section B.2.9.7)
- For OS, using the [REDACTED] OS data-cut from HIMALAYA, the NMA results found that STRIDE and atezolizumab + bevacizumab improved OS compared with sorafenib, with consistent point estimates to those seen in trial results ([REDACTED]); respectively). However, CrIs intervals all crossed 1, indicating no statistical differences between all comparators and sorafenib in the RE model with informative prior
- For OS, the NMA found that lenvatinib had a HR close to 1 in the comparison to sorafenib, with a similar point estimate to the non-inferiority REFLECT trial ([REDACTED])
- For investigator-assessed (INV) PFS, the NMA results found that atezolizumab + bevacizumab, lenvatinib and STRIDE all showed improved PFS compared with sorafenib (HR: [REDACTED]; respectively), again reflecting point estimates from trial results but with no statistical differences observed in the RE model with informative prior
- The key area of uncertainty in the NMA was related to the significant disparity in the length of follow-up reported across the included trials, with HIMALAYA having materially longer follow-up compared to IMbrave150 in particular
- The PH assumption for HIMALAYA and REFLECT was violated. The uncertainty associated with violations of the PH assumption was addressed in the economic model by independently fitting curves for HIMALAYA. For the comparative effectiveness input in the model for lenvatinib vs sorafenib, given the statistical non-inferiority observed in REFLECT between these two treatments, the HR is set to 1 for OS.⁷³ For PFS, time-varying analyses conducted for REFLECT suggested the positive treatment effect for lenvatinib diminishes over the course of the study, meaning that the application of a constant HR in the model could be considered conservative. The standard NMA results for atezolizumab + bevacizumab vs. sorafenib were not affected by PH assumption violations
- Overall, the NMA identified that STRIDE was associated with a comparable improvement in survival vs. sorafenib compared to atezolizumab + bevacizumab, the key comparator in this submission

B.2.9.1 Identification of comparator studies

As described in Section B.2.1, a clinical SLR was conducted which identified and synthesised relevant clinical evidence on the efficacy and safety of STRIDE and other first-line treatments in patients with advanced or unresectable HCC. The SLR identified 88 publications on 17 unique studies which were considered for inclusion in the NMA.

Full details of the SLR are provided in Appendix D.

B.2.9.2 Eligibility for the network meta-analysis

Studies identified in the SLR were assessed for their eligibility for inclusion in NMAs. To permit comparisons with STRIDE via the treatment arms in HIMALAYA, studies were eligible if they included as treatment arms only the comparators of interest, as shown in Table 17. Specifically, first-line treatments included were those considered comparators to STRIDE in current UK clinical practice for the treatment of advanced or unresectable HCC and align with the decision problem (Section B.1.1). Nivolumab was not included as a comparator given it has not been recommended in the UK for untreated, unresectable HCC. Otherwise, studies were not excluded on the basis of patient population, outcomes and study design, since the eligibility criteria applied

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in the SLR already restricted studies to Phase III RCTs reporting OS and PFS for the population investigated in STRIDE (Appendix D).

Table 17: Summary of eligibility criteria for the NMA

Domain	Eligibility Criteria
Population	Advanced or unresectable HCC
Intervention/Comparator	Reporting on at least two interventions/comparators of interest: ^a • STRIDE • Atezolizumab + bevacizumab • Lenvatinib • Sorafenib Not including any combinations with other therapies
Outcomes	OS and/or PFS INV
Study design	Phase III RCTs

Footnotes: ^aStudies identified by the SLR were investigated to determine if additional evidence could be included in a network via a comparator not of interest, this was not possible so the network only includes STRIDE, atezolizumab + bevacizumab and lenvatinib.

Abbreviations: HCC: hepatocellular carcinoma; INV: investigator-assessed; OS: overall survival; PFS: progression-free survival; RCTs: randomised control trials; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

These criteria were applied to the 17 studies identified by the SLR, with reasons for exclusion detailed in Appendix D. As a result, three studies (HIMALAYA, IMbrave150 and REFLECT) were included which connected via sorafenib to form networks for OS and PFS (INV).^{4, 73, 110}

Table 18: Summary of studies excluded for the NMA

Category of exclusion	Number excluded	Number remaining
Studies identified by the SLR	-	17
Interventions/Comparators ^a	14	3
Total	14	3

Footnotes: ^aAs the SLR only included studies reporting on an intervention/comparator of interest, in each instance the study was excluded on the basis of including only one intervention/comparator of interest and comparing this to a comparator not of interest.

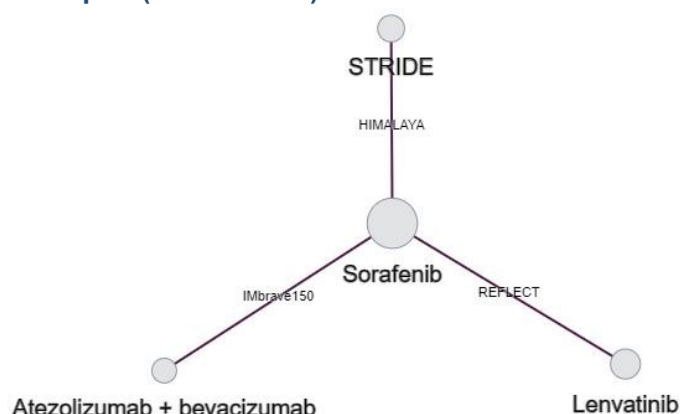
Abbreviations: NMA: network meta-analysis; SLR: systematic literature review.

B.2.9.3 Network of evidence

Based on data availability, requirements for economic modelling and alignment with the decision problem (Section B.1.1), the efficacy outcomes of interest investigated in the NMA were OS and PFS (assessed per investigator).

The network diagram for both outcomes is presented in Figure 14, where the three included studies are connected via a common sorafenib treatment arm.

Figure 14: Network plot (PFS and OS)



Footnotes: Node size indicates the number of patients receiving each intervention.

Abbreviations: OS: overall survival; PFS: progression-free survival.

B.2.9.4 Heterogeneity across included trials

B.2.9.4.1 Study design

The study designs of included studies were generally comparable (see Appendix D). All studies were large, international, Phase III RCTs. Eligibility criteria were similar across the studies, particularly in reference to HCC aetiology, ECOG PS, Child Pugh Score and presence of ascites. HIMALAYA and REFLECT both additionally specified BCLC criteria B or C. Notably, there were some differences in eligibility based on tumour location. IMbrave150 included 15% of patients with a tumour thrombus in the main trunk and/or contralateral portal vein (PVT stage VP4) whereas these patients were excluded from both HIMALAYA and REFLECT due to their poor prognosis.

B.2.9.4.2 Patient characteristics and treatment effect modifiers

The patient populations of the eligible studies were generally comparable, although there were some differences identified (see Appendix D). The difference in eligibility criteria relating to tumour location contributed to a difference in MVI prevalence in participants at baseline, with IMbrave150 having a higher prevalence than HIMALAYA and REFLECT.

A number of patient characteristics were identified as potential treatment effect modifiers (TEMs) in HCC, i.e., patient characteristics that impact the relative effect of a treatment. TEMs have the potential to bias analyses if there are notable imbalances across trials. There was some variation identified across three potential TEMs in the included studies (aetiology, MVI/EHS and region), and this was explored further. Other potential TEMs (AFP level, BCLC stage, ECOG score and gender) were found to have little differences in the distribution of characteristics across studies. Further details on all potential TEMs are provided in Appendix D.

Disease aetiology was investigated by assessing subgroup results across trials from patients with HBV, HCV and nonviral subgroups across HIMALAYA, REFLECT and IMbrave150 (Section B.2.7 for HIMALAYA). No clear conclusions could be drawn on HCV and nonviral subgroups, due to lack of clarity on the direction of bias for HCV subgroups and wide confidence intervals as a result of the relatively small sample sizes in the alcohol (nonviral) subgroup for REFLECT and both the HCV and nonviral subgroups for IMbrave150. However, patients with HBV across

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HIMALAYA, REFLECT and IMbrave150 trials demonstrated improved OS compared with the non-HBV populations in these trials. Based on these results, it was noted that the lower proportion of patients with HBV in HIMALAYA compared to IMbrave150 and REFLECT could lead to the treatment effect of STRIDE being underestimated relative to the two comparator studies. However, while there was some evidence of treatment effect modification in favour of lenvatinib and atezolizumab + bevacizumab based on disease aetiology, as disease aetiology was not a stratification factor during randomisation for either trial, the subgroups may not have been balanced for prognostic factors, and the studies were ultimately not designed to detect subgroup effects for these populations. Patients were stratified for disease aetiology in HIMALAYA. Clinicians interviewed by AstraZeneca further suggested that the role of aetiology as a TEM was not conclusive, and it was therefore decided not to explore more complex methods to adjust for disease aetiology in the NMA.

Differences in the location and degree of liver invasion across trials were expected due to differences in exclusion criteria for IMbrave150 compared with HIMALAYA and REFLECT highlighted above. As such, this was investigated further using data from Breder *et al.* which excluded patients with PVT stage VP4 from analyses.¹¹¹ This analysis found that the OS point estimate for this subgroup of patients in IMbrave150 (0.62 [0.34, 1.11])¹¹¹ was similar to that of the rest of the ITT population (0.67 [0.51, 0.88]). Furthermore, subgroup analyses of patients with (0.64 [0.49, 0.81]) and without (0.64 [0.38, 1.10]) MVI/EHS also had similar point estimates for OS, indicating a limited influence of differences in the location and degree of liver invasion in modifying treatment effect.

Geographical region was not included as a stratification factor for HIMALAYA but was included in REFLECT and IMbrave150. A greater proportion of study centres in REFLECT were in Asia compared with HIMALAYA and IMbrave150. However, OS results from REFLECT for subgroups of patients in both Western and Asia-Pacific regions both did not demonstrate a statistical difference between lenvatinib and sorafenib. OS results from IMbrave150 for a subgroup of patients in centres in Asia (excluding Japan), and centres in the rest of the world demonstrated a statistical difference between atezolizumab + bevacizumab and sorafenib.

In summary, differences identified in potential TEMs across the trials were not considered to bias the analyses. None of the trials investigated were sized for individual subgroup analyses, and many subgroup results were not based on stratified subgroups. Meta-regression techniques to adjust for these characteristics as sensitivity analyses using aggregate data were infeasible due to a small number of studies (<10) being included in NMAs. Therefore, methods for population adjustment were not considered further and unadjusted NMAs were conducted.

B.2.9.4.3 Progression-free survival assessor type

As only investigator-assessed PFS was collected in HIMALAYA, the NMA used investigator-assessed PFS across all studies to ensure alignment with HIMALAYA. Investigator-assessed PFS was available across all included studies, however exact definitions varied. Within HIMALAYA and IMbrave150, investigators assessed PFS according to RECIST 1.1 and in REFLECT, investigators assessed PFS according to the modified response evaluation criteria in solid tumours (mRECIST).¹¹² No adjustments can be made for the differences between mRECIST and RECIST 1.1, but a study comparing mRECIST to RECIST 1.1 found that the performance of both criteria in assessing disease progression is identical.

B.2.9.4.4 Follow-up time

Outcomes were measured from time of randomisation to either the event of interest or the clinical cut-off point. Median follow-up times varied across studies (Table 19).

Table 19: Summary of median follow-up times

Study	Treatment arm	OS	PFS (INV)
HIMALAYA	STRIDE	62.5	33.2
	Sorafenib	59.9	32.2
IMbrave150	Atezolizumab + bevacizumab	17.6	8.9
	Sorafenib	10.4	8.1
REFLECT	Lenvatinib	27.7	27.7
	Sorafenib	27.2	27.2

Abbreviations: INV: investigator-assessed; OS: overall survival; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

There were differences in follow-up across the studies, with HIMALAYA having the longest follow-up of the three studies in the network. Under proportional hazards, the effect of treatment is assumed to be constant over time, and differences in duration of follow-up are unlikely to bias results. Moreover, NMA models allowing for a time-varying treatment effect, such as piecewise parametric, spline or fractional polynomial NMAs were not considered appropriate, as they would nonetheless be limited in their ability to compare long term efficacy due to the short follow-up for IMbrave150 in particular.

B.2.9.5 Proportional hazards

The credibility of the PH assumption, which assumes that the relative hazard of the outcome of interest between treatment arms remains constant over time, was assessed for all studies included in the OS and PFS networks.

The assessment for HIMALAYA was based on the analysis of individual patient data (IPD). For REFLECT and IMbrave150, the published Kaplan-Meier curves were digitised and the IPD reconstructed based on the Guyot algorithm.¹¹³ Each digitised curve was compared to estimates reported in the original publication (including median time to event and HR) to ensure the validity of the digitisation step. The formal assessment of the PH assumption was then based on the visual inspection of the Kaplan-Meier curves, the log-log plot, the Schoenfeld residuals plot and the Grambsch and Therneau test.¹¹⁴⁻¹¹⁷

Table 20. Summary of proportional hazard assessment

Trial (Publication)	Interventions	Evidence of PH violation for OS	Evidence of PH violation for PFS
HIMALAYA	STRIDE vs. sorafenib	Yes: curves in log-log plot are not parallel despite Schoenfeld test not significant (p-value = 0.167)	Yes: curves in log-log plot are not parallel despite Schoenfeld test not significant (p-value = 0.099)
IMBRAVE150	Atezolizumab + bevacizumab vs. sorafenib	No: curves in log-log plot appear parallel after two months and Schoenfeld test not significant (p-value = 0.207)	No: ^a curves in log-log plot appear parallel after two months despite Schoenfeld test not significant (p-value = 0.356)

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Trial (Publication)	Interventions	Evidence of PH violation for OS	Evidence of PH violation for PFS
REFLECT	Lenvatinib vs. sorafenib	Yes: curves in log-log plot are not parallel despite Schoenfeld test not significant (p-value = 0.134)	Yes: curves in log-log plot are not parallel and Schoenfeld test significant (p-value < 0.001)

Footnotes: ^aAssessed based on PFS per BICR, as investigator-assessed PFS curves are not reported.

Abbreviations: OS: overall survival; PFS: progression-free survival; PH: proportional hazard; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Results from the assessment of PHs are summarised in Table 20, where evidence of violation is indicated by curves in the log-log plot not being approximately parallel, and/or the p-value of the Schoenfeld test being less than 0.05. Further details of the assessment are given in Appendix D. The assessment indicated that there was no evidence of proportional hazard (PH) violation for IMbrave150, and therefore the estimate from the NMA of atezolizumab + bevacizumab vs sorafenib was unlikely to be biased. However, there was evidence of PH assumption violation for HIMALAYA and REFLECT for OS and PFS. In particular, use of HRs estimated from an NMA for comparisons involving STRIDE and lenvatinib may be biased and are unlikely to be an accurate reflection of hazards over the full follow-up period for OS and PFS.

For treatment comparisons via sorafenib in the NMA, more advanced methods such as fractional polynomial or piecewise models were deemed unnecessary and overly complex. In particular, complex NMAs would either require strong assumptions or be limited to the follow-up period of the trial with the shortest follow-up, and therefore fail to capture the full treatment effect of STRIDE. While the limited reporting on longer follow-up for IMbrave150 and REFLECT constitutes a limitation for both the standard NMA and potential complex analyses, the comparison between atezolizumab + bevacizumab and sorafenib can be robustly estimated by a standard NMA given that there is no evidence of PH violation for IMbrave150 across PFS and OS endpoints.

As there was evidence of non-proportional hazards for REFLECT, the HR between lenvatinib and sorafenib may vary over the follow-up time. Therefore, time-varying HR was calculated from REFLECT for OS and PFS (detailed methodology and results in Appendix N). For this analysis, a series of parametric survival models were fit to a data set containing both arms (lenvatinib and sorafenib) of the REFLECT trial, with the inclusion of a treatment covariate (lenvatinib vs. sorafenib) on the shape and scale parameters.⁷³ The resulting models predict time-varying HRs. The time-varying HRs from the PFS and OS models suggest a positive treatment effect at the beginning of the study follow-up that diminishes over time, leading to convergence of the lenvatinib and sorafenib arms in both the PFS and OS curves; this is consistent with the Kaplan-Meier plots presented in Appendix N. Therefore, the results of the NMA may overpredict survival for lenvatinib.

For lenvatinib, given that it is hypothesised that the application of a constant HR for REFLECT may overpredict long-term survival for lenvatinib, results from the REFLECT trial were taken directly to inform the cost-effectiveness model for OS, specifically a HR of 1, capturing the statistical non-inferiority observed in REFLECT between the two treatments. This is viewed as conservative given that the time-varying analysis predicts HR above 1 over time for most models (see Appendix N). Non-inferiority for PFS was not observed in REFLECT, therefore the NMA

estimate for PFS is used in the model. This is considered a conservative approach, given the result of the time-varying analysis.

The uncertainty associated with violations of the PH assumption for HIMALAYA will be addressed in the economic model by independently fitting curves to the patient-level data from the HIMALAYA study, as recommend in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.¹¹⁸

B.2.9.6 Methods

Bayesian analyses were conducted for both OS and PFS, where input data preparation and models to be fitted were determined by OS and PFS being time-to-event outcomes. In a Bayesian NMA, a 'statistical difference' is ascertained by a result in which the 95% CrI does not include the null value (0) in the case of mean differences, and 1 in the case of odds/HRs.

For the NMAs of OS and PFS, a normal distribution with an identity link was specified, as recommended in the NICE DSU TSD 2 for an NMA of treatment differences, which was modelled using a log HR on the continuous scale.¹¹⁹

Both FE and RE models were fitted. The deviance information criterion (DIC), total residual deviance and effective number of parameters were generated and compared between models. If random effects models failed to converge, an informative prior on the between-study SD parameter τ was considered, using the methods of Turner *et al.*¹²⁰ For each analysis, the most appropriate model was selected by comparing the DIC between the RE and FE models; as the RE model allows for between-study heterogeneity, this was selected in preference to the FE model unless the DIC improved by at least five points in the FE model.

Each study had only two arms and therefore multi-arm adjustment was not required. No closed loops of evidence were present in the network (Figure 14), so an assessment of inconsistency was not required.

Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in OpenBUGS, version 3.2.3 (revision 1012).¹²¹⁻¹²³ The initial prior distributions used are listed in Table 21. Distribution parameters for each of the vague priors were modified as required if there were truncation or convergence issues. The informative priors used, as recommended by Turner *et al.* are detailed in Table 22.

Table 21: Initial prior distributions used for model parameters

Parameter	Chain 1
μ	Normal (0,100)
δ	Normal (0,100)
τ	Uniform (0,5)

Footnotes: The variance of the Normal distributions and upper limit of the Uniform distribution may be modified for each specific outcome.

Table 22: Informative prior distributions used

Outcome	Informative Prior	Justification
PFS	Log-normal (-2.93, 1.58 ²)	Recommended for subjective outcomes
OS	Log-normal (-4.18, 1.41 ²)	Recommended for all-cause mortality outcomes

Footnotes: Justifications are based on recommendations by Turner *et al.* for when comparing between pharmacological interventions.

Abbreviations: OS: overall survival; PFS: progression-free survival.

Convergence for each analysis was assessed using history trace plots, smoothed Kernel posterior density plots and Brook–Gelman–Rubin (BGR) diagnostic plots.

B.2.9.7 Results

All results in this section are presented as HR vs. sorafenib to align with the economic model where HRs are applied to sorafenib data for all comparators. Pairwise results between comparators are presented in Appendix D.

B.2.9.7.1 Overall survival

An NMA of overall survival was conducted for the network presented in Figure 14 (Section B.2.9.3).

Model fit statistics are presented in Table 23. For the RE models, convergence was only reached when an informative prior for the between-study standard deviation was used. The RE model with an informative prior was selected over the FE model, as the DIC was not improved by at least five points in the FE model and the RE model allowed between-study heterogeneity to be incorporated (Table 23). As the FE model was not selected, these results are presented in Appendix D.

Table 23: Model fit statistics OS

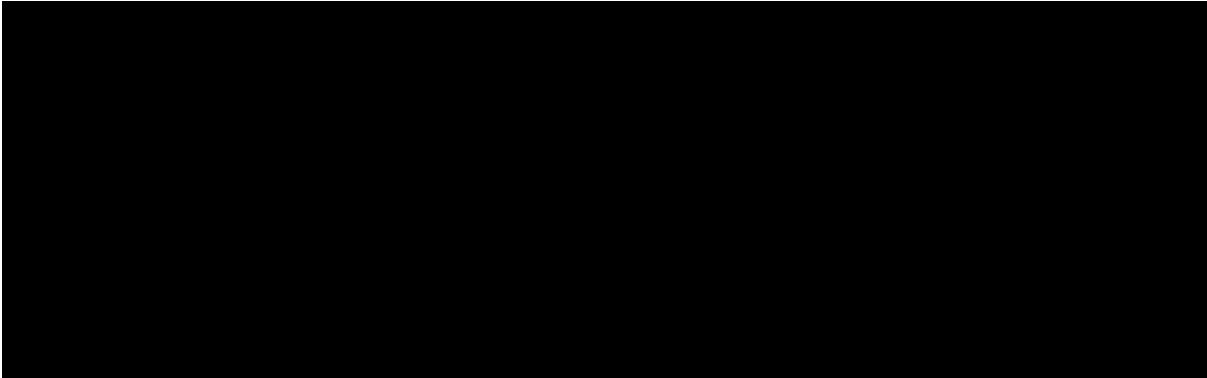
Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD
FE model	-2.86	-5.86	-8.87	3.01	3.01	NA
RE model with informative prior	-2.88	-5.87	-8.87	3.00	3.00	0.16

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 3 data points in this network.

Abbreviations: Dbar: posterior mean residual deviance; Dhat: point estimate of the deviance; DIC: deviance information criterion; FE: fixed effects; OS: overall survival; pD: effective number of parameters; RE: random effects; SD: standard deviation.

The RE model with informative prior results are presented in Figure 15. STRIDE, atezolizumab + bevacizumab and lenvatinib all improved OS compared with sorafenib, with similar point estimates to those seen in trial results ([REDACTED]); respectively). However, Crls all crossed 1, indicating no statistical differences between all comparators and sorafenib in the RE model with informative prior which allowed between-study heterogeneity to be incorporated. Similarly, pairwise results between comparators showed no statistical differences (Appendix D).

Figure 15: Forest plot for OS comparing with sorafenib, RE model with informative prior



Footnotes: Forest plot showing how each comparator treatment (right) performed vs. sorafenib; results are given as the OR and 95% CrIs.
Abbreviations: CrI: credible interval; HR: hazard ratio; OS: overall survival; RE: random effects; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.2.9.7.2 Progression-free survival

An NMA of investigator-assessed PFS was conducted for the network presented in Figure 14 (Section B.2.9.3).

Model fit statistics are presented in Table 24. For the RE models, convergence was only reached when an informative prior for the between-study standard deviation was used. The RE model with an informative prior was selected over the FE model, as the DIC was not improved by at least five points in the FE model and the moderate clinical variation identified across the trials was unlikely to satisfy the strong homogeneity assumption of an FE model (Table 24). As the FE model was not selected, these results are presented in Appendix D.

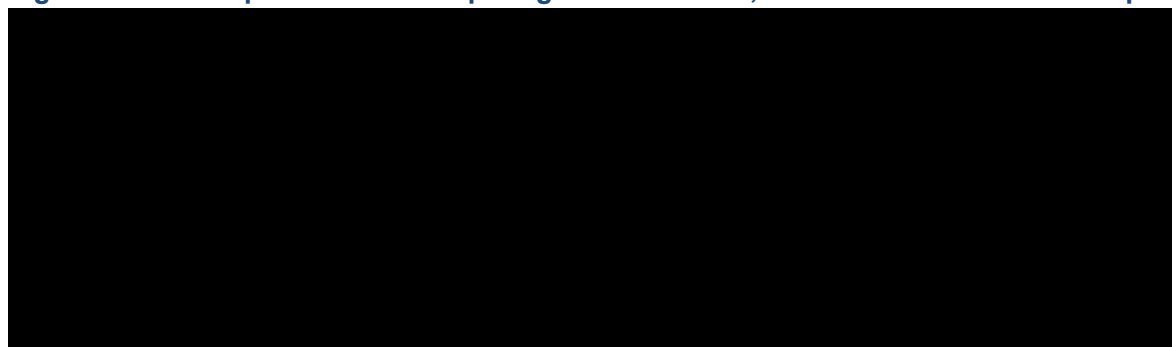
Table 24: Model fit statistics PFS

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD
FE model	-2.97	-5.98	-8.98	3.01	3.01	NA
RE model with informative prior	-2.97	-5.98	-8.98	3.00	3.00	0.31

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 3 data points in this network.
Abbreviations: Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; pD, effective number of parameters; PFS, progression-free survival; RE, random effects; SD, standard deviation.

The RE model with informative prior results are presented in Figure 16, with a full league table of pairwise comparisons provided in Appendix D. Atezolizumab + bevacizumab, lenvatinib and STRIDE all showed improved PFS compared with sorafenib ([REDACTED]; respectively), again reflecting point estimates from trial results but with no statistical differences observed in the RE model with informative prior. Similarly, pairwise results between comparators showed no statistical differences (see Appendix D).

Figure 16: Forest plot for PFS comparing with sorafenib, RE model with informative prior



Footnotes: Forest plot showing how each comparator treatment (right) performed vs. sorafenib; results are given as the OR and 95% CrIs.

Abbreviations: CrI: credible interval; HR: hazard ratio; PFS: progression-free survival; RE: random effects; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.2.9.8 Uncertainties in the indirect and mixed treatment comparisons

The eligibility criteria for inclusion of studies in the NMA required that all evidence considered was from Phase III RCTs, and as such ensured, as far as possible, that each included study provided high quality evidence.

While patient populations were largely similar across the three included studies, differences in aetiology may have underestimated NMA results for STRIDE due to the relatively low prevalence of HBV in the HIMALAYA population compared with IMbrave150 and REFLECT. However, as there is no conclusive evidence on the role of aetiology as a TEM, this is not considered a key uncertainty within the analyses and is not anticipated to have material impact on the results.

Follow-up times varied across studies, with a substantially longer follow-up time in HIMALAYA compared to REFLECT and IMbrave150. As a result, the standard NMA approach deployed will not have fully captured changes over time across the studies. However, more complex methods to address the difference in follow-up times were not expected to rectify this issue.

The violation of the PH assumption for HIMALAYA and REFLECT may have also introduced uncertainty to the results. However, models such as fractional polynomial or piecewise models were deemed unnecessary and overly complex, and would have strong limitations in their ability to compare long term efficacy due to the short follow-up for IMbrave150 in particular. Instead, the uncertainty associated with violations of the PH assumption for HIMALAYA was addressed in the economic model by independently fitting curves to the patient-level data from the HIMALAYA study, as recommend in NICE DSU TSD 14.¹¹⁸ For lenvatinib, given that it is hypothesised that the application of a constant HR to the sorafenib arm may overpredict long-term survival for lenvatinib, OS results from the REFLECT trial were taken directly to inform the cost-effectiveness model, specifically an HR of 1, capturing the statistical non-inferiority observed between the two treatments in the trial. Given non-inferiority between the two treatments was not observed for PFS in REFLECT, the NMA estimate is used for PFS in the model (Section B.3.3.2). The standard NMA results for atezolizumab + bevacizumab vs. sorafenib were unaffected by PH assumption violations and could therefore be used in the model.

B.2.9.9 Conclusions of the indirect and mixed treatment comparisons

The NMA showed that STRIDE is an effective treatment for advanced or unresectable HCC, with numerically improved OS and PFS compared with sorafenib. Overall, the NMA identified that

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STRIDE was associated with a comparable improvement in survival vs. sorafenib compared to atezolizumab + bevacizumab, the key comparator in this submission.

B.2.10 Adverse reactions

STRIDE demonstrated a favourable safety profile, with the overall evaluation of safety and tolerability of the STRIDE regimen was generally consistent with that observed in previous studies with durvalumab and tremelimumab.^{89, 124} No new adverse drug reactions were identified for the STRIDE regimen and no new safety findings were observed in patients with HCC.²² Furthermore, in both arms, AEs were manageable according to toxicity management guidelines.^{89, 124}

B.2.10.1 Treatment exposure

The duration of exposure for the STRIDE and sorafenib treatment arms in HIMALAYA at the updated analysis I (DCO: 23rd January 2023) is summarised in Table 25.¹²⁴ Treatment exposure was also assessed in the primary analysis (DCO: 27th August 2021; Appendix F). The median time on treatment for patients in the STRIDE treatment arm was [REDACTED].¹²⁴

Table 25: Duration of treatment exposure in HIMALAYA (updated analysis I; SAS) (DCO: 23rd January 2023)

10 January 2020

Treatment exposure	STRIDE (n=388)				Sorafenib (n=374)
	Tremelimumab		Durvalumab		Total study ^b
	Initial treatment ^a	Rechallenge	Initial treatment ^a	Rechallenge	
Total treatment duration (months) ^c					
N	■	■	■	■	■
Mean (SD)	■	■	■	■	■
Median (min–max)	■	■	■	■	■
Total treatment years	■	■	■	■	■
Actual treatment duration (months) ^d					
N	■	■	■	■	■
Mean (SD)	■	■	■	■	■
Median (min–max)	■	■	■	■	■
Total treatment years	■	■	■	■	■

Footnotes: ^aIncludes initial treatment phase. Includes start of study treatment to last treatment or last treatment prior to re-challenge (if re-challenge occurs); ^bTotal study exposure includes initial treatment and rechallenge phase, where rechallenge occurred; ^cTotal treatment duration for immunotherapies = (last dose date + 27 days or date of death or DCO, whichever occurred earlier – first dose date + 1)/(365.25/12). Total treatment duration for sorafenib = (last dose date or date of death or DCO, whichever occurred earlier – first dose date + 1)/(365.25/12); ^dActual treatment duration = (intended exposure – total duration of dose delays)/(365.25/12).

Abbreviations: DCO: data cut-off; NA: not applicable; SAS: safety analysis set; SD: standard deviation; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: AstraZeneca Data on File – HIMALAYA Study Protocol D419CC00002 (LTFU1).¹²⁴ (Table 14.3.1.1, pg 38–40)

B.2.10.2 Dose interruptions, reductions and discontinuations

B.2.10.2.1 Dose interruptions

In HIMALAYA, dose interruptions included dose delays as well as infusion interruptions. The majority of dose interruptions were due to dose delays.¹²⁴ At the updated analysis I (DCO: 23rd January 2023), durvalumab and tremelimumab dose delays were ■ with durvalumab-related dose or cycle delays in the STRIDE treatment arm occurring in ■ which were in part due to AEs (■).¹²⁴ The frequency of patients reporting three or more delays were ■, as shown in Table 26. ■ had a tremelimumab dose or cycle delay in the STRIDE treatment arm.¹²⁴ Comparable treatment delays were seen in the primary analysis (Appendix F).

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Table 26: Treatment delays in the STRIDE arm of HIMALAYA (updated analysis I; SAS) (DCO: 23rd January 2023)

	Days of treatment delay (N=388)										
	3	4	5	6	7	8	9	10	11	14	32
Number of individuals with a dose/cycle delay (%)	■	■	■	■	■	■	■	■	■	■	■

Abbreviations: DCO: data cut-off; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: AstraZeneca Data on File – HIMALAYA Study Protocol D419CC00002 (LTFU1).¹²⁴ (Table 14.3.1.3, pg 43)

Durvalumab infusion interruptions were ■ and there were ■ tremelimumab infusion interruptions at both the primary and updated I analysis.^{89, 124} As sorafenib is administered orally, infusion interruptions are not applicable.

B.2.10.2.2 Dose reductions

Dose reductions were only permitted for the STRIDE regimen (durvalumab and tremelimumab) if a patient's weight decreased to ≤30 kg. As ■ patients had a reduction in weight to ≤30 kg, there were ■ durvalumab or tremelimumab dose reductions.¹²⁴ At the updated analysis I (DCO: 23rd January 2023), approximately ■ of the patients in the sorafenib arm had dose reductions, which were mainly due to ■.¹²⁴

B.2.10.2.3 Discontinuations

At the updated analysis I (DCO: 23rd January 2023), discontinuations of study treatment due to AEs were low in both treatment arms (Table 27).¹²⁴ Similar rates of discontinuation were seen in the primary analysis (DCO: 27th August 2021; Appendix F).⁸⁹ Events occurring in two or more patients included diarrhoea, vomiting, upper gastrointestinal haemorrhage, oesophageal varices haemorrhage, colitis, ascites, hepatitis, hepatic failure, acute kidney injury, cholecystitis, immune-mediated hepatitis, rash, alanine aminotransferase increased, and aspartate aminotransferase increased, bone pain, polymyalgia rheumatica; these events were uncommon and incidence was similar across treatment arms.¹²⁴

Table 27: Adverse events leading to discontinuation in HIMALAYA (updated analysis I; SAS) (DCO: 23rd January 2023)

AE category ^a	Number of patients (%)	
	STRIDE (n=388)	Sorafenib (n=374)
Any AE leading to discontinuation of study treatment	■	■
Any AE leading to discontinuation of study treatment, possibly related to treatment ^b	■	■

Footnotes: ^aPatients with multiple events in the same category are counted only once in that category; ^bPatients with events in more than 1 category are counted once in each of those categories. Updates to AE categories post DCO 23rd Jan 2023 reflect changes due to serious adverse events. Non-serious adverse event reporting was not required post final analysis DCO. ^bAs assessed by the Investigator. Missing responses were counted as treatment-related.

Abbreviations: DCO: data cut-off; NA: not applicable; SAS: safety analysis set; SD: standard deviation; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

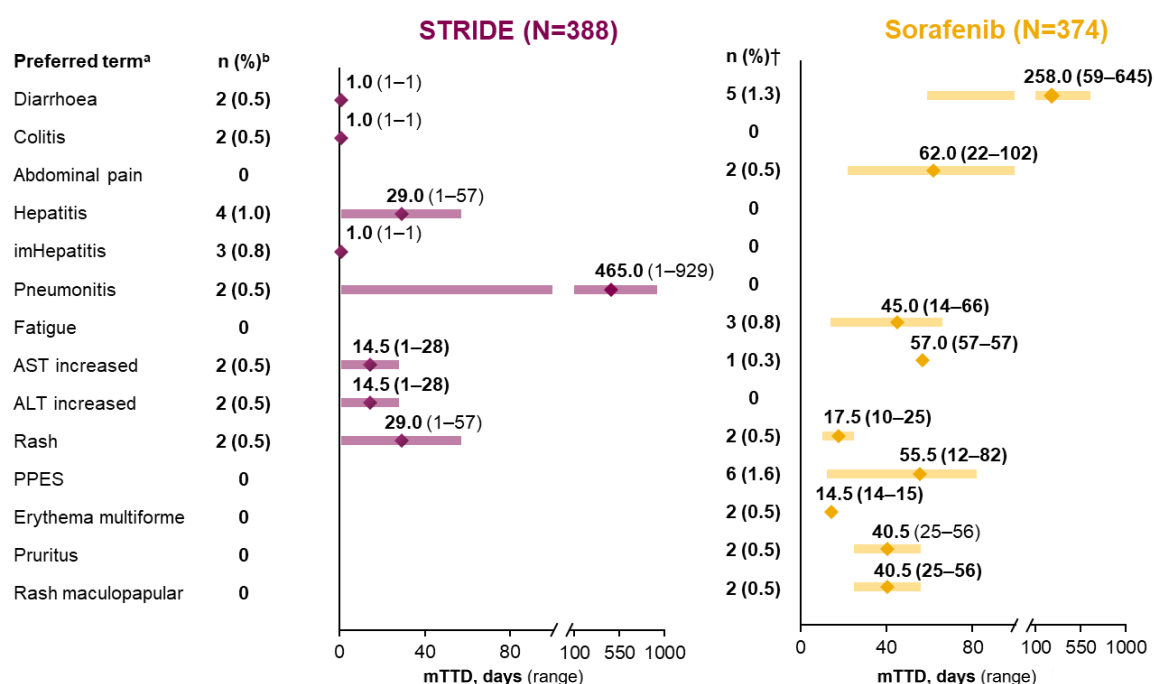
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Source: AstraZeneca Data on File – HIMALAYA Study Protocol D419CC00002 (LTFU1).¹²⁴ (Table 14.3.2.1, pg 48)

There were no observed trends in AEs or TRAEs leading to discontinuation, and the events aligned with the known safety profiles of each investigational product. The addition of tremelimumab to durvalumab therapy did not cause any meaningful increase in discontinuation due to toxicity.¹²⁴

Based on the primary analysis, most of the common TRAEs that led to discontinuation across arms occurred within 80 days, although the number of events was small. The time to treatment discontinuation (TTD) of STRIDE or sorafenib in at least two participants in either treatment arm is presented in Figure 17.⁹⁵

Figure 17: TTD of study treatment in ≥2 participants in either treatment arm in HIMALAYA (primary analysis; SAS) (DCO: 27th August 2021)



Footnotes: TRAEs that led to discontinuation in ≥2 patients in any treatment arm were included. ^aPreferred term was as reported by the investigator; ^bPercent calculated as the number of patients with event out of total number of patients in treatment arm.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; DCO: data cut-off; im: immune-mediated; mTTD: median time to treatment discontinuation; PPES: palmar-plantar erythrodysesthesia syndrome; Q4W: every 4 weeks; TRAE: treatment-related adverse event; mTTD: median time to treatment discontinuation; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Adapted from Sangro, B. et al. 2022.⁹⁵ (Slide 10).

B.2.10.3 Treatment-related adverse events

Most patients in the treatment arms experienced one or more AE, regardless of causality. However, the nature and frequency of these events was consistent with that expected for the selected study population, with the toxicity profile of STRIDE considered comparable to sorafenib.⁹³ A summary of TRAEs experienced by patients in the STRIDE and sorafenib treatment arms of HIMALAYA at the primary analysis are presented in Table 28.⁴

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Table 28: Summary of TRAEs experienced by patients in HIMALAYA (primary analysis; SAS) (DCO: 27th August 2021)

AEs	STRIDE (n=388)	Sorafenib (n=374)
TRAEs of any cause, n (%)		
Any	378 (97.4)	357 (95.5)
Any serious	157 (40.5)	111 (29.7)
Any grade 3 or 4	196 (50.5)	196 (52.4)
Leading to discontinuation	53 (13.7)	63 (16.8)
Leading to dose delay	134 (34.5)	178 (47.6)
Immune-mediated requiring high-dose steroids	78 (20.1)	7 (1.9)
Any grade 3 or 4 immune-mediated	49 (12.6)	9 (2.4)
Immune-mediated leading to death	6 (1.5)	0
Any grade 3 or 4 hepatic SMQ	54 (13.9)	39 (10.4)
TRAEs, n (%)		
Any	294 (75.8)	317 (84.8)
Any serious	68 (17.5)	35 (9.4)
Grade 3 or 4	100 (25.8)	138 (36.9)
Leading to discontinuation	32 (8.2)	41 (11.0)
Leading to dose delay	83 (21.4)	144 (38.5)
Leading to death	9 (2.3) ^a	3 (0.8) ^b
Grade 3 or 4 immune-mediated	49 (12.6)	9 (2.4)
Any immune-mediated leading to death	6 (1.5) ^c	0
Grade 3 or 4 hepatic SMQ	23 (5.9)	17 (4.5)

Footnotes: ^aTRAEs leading to death in the STRIDE arm included myasthenia gravis, nervous system disorder, myocarditis, acute respiratory distress syndrome, pneumonitis, hepatic failure, hepatitis (all n=1 each), and immune-mediated hepatitis (n=2); ^bTRAEs leading to death in the sorafenib arm included cerebral hematoma, hepatic failure, and haematuria (all n=1 each); ^cTRAEs leading to death in the STRIDE arm included pneumonitis, hepatitis, myocarditis, myasthenia gravis (all n=1 each), and immune-mediated hepatitis (n=2).

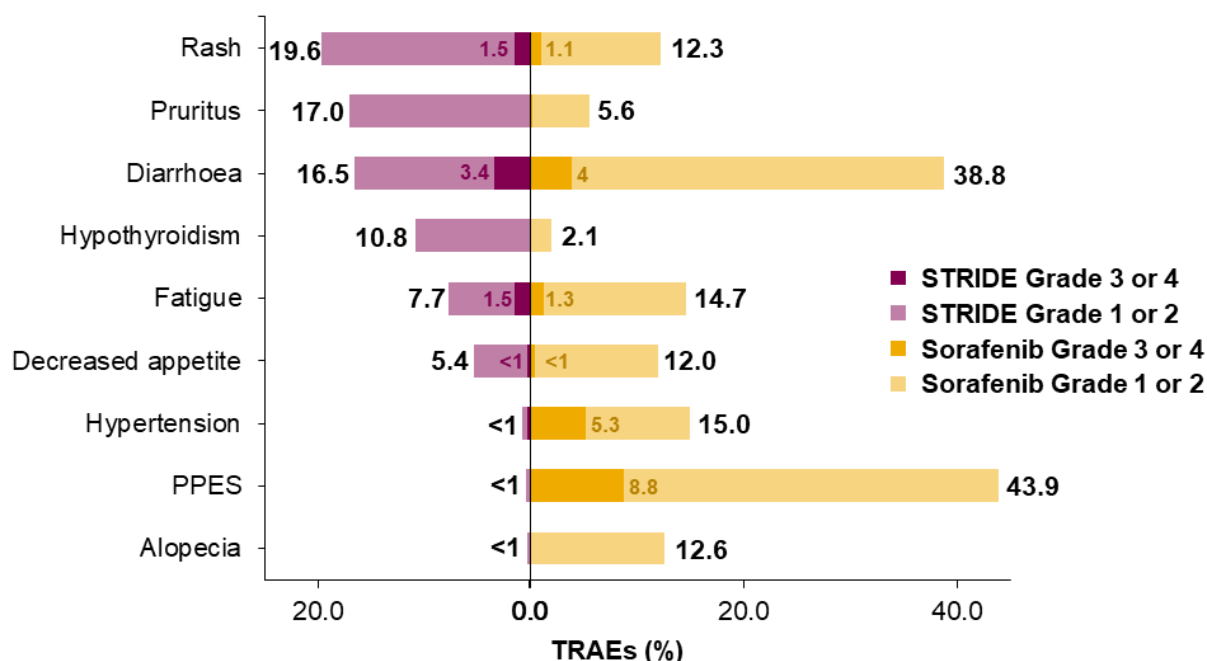
Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set; SMQ: standardised MedDRA queries; TRAE: treatment-related adverse event; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Abou-Alfa, G. et al. 2022b.⁴ (Table 3, pg 9).

B.2.10.3.1 Common treatment related adverse events

At the primary analysis (DCO: 27th August 2021), most patients in HIMALAYA experienced at least one TRAE. A summary of the most common TRAEs (experienced by ≥10% of patients in either the STRIDE or sorafenib treatment arms) in HIMALAYA is presented in Figure 18.⁹⁵ Sorafenib treatment resulted in the greatest number of any grade TRAEs and grade 3 or 4 TRAEs, driven by palmar-plantar erythrodysaesthesia syndrome, diarrhoea, and hypertension. In the STRIDE arm, grade 3 or 4 TRAEs were predominantly driven by transient elevations in liver transaminases and asymptomatic increases in amylase/lipase.⁴

Figure 18: Common TRAEs experienced by patients in HIMALAYA (occurring in ≥10% of patients in the STRIDE or sorafenib treatment arms; primary analysis; SAS) (DCO: 27th August 2021)



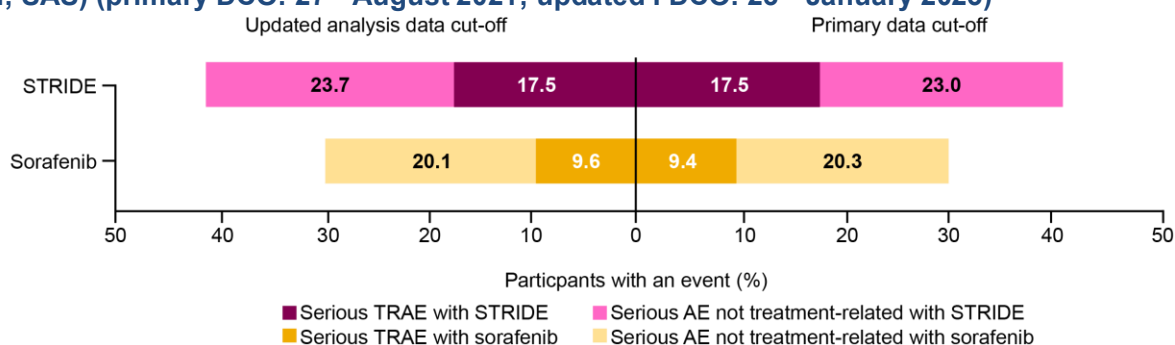
Footnotes: Treatment-related was as assessed by the investigator.

Abbreviations: DCO: data cut-off; PPES: palmar-plantar erythrodysesthesia syndrome; SAS: safety analysis set; TRAE: treatment-related adverse event; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Adapted from Sangro, B. et al. 2022.⁹⁵ (Slide 7)

At the updated analysis I (DCO: 23rd January 2023), the frequency of serious adverse events (SAEs) was generally consistent with the primary analysis (DCO: 27th August 2021), with no new serious TRAEs occurring after the primary analysis for STRIDE (Figure 19).⁹⁷

Figure 19: Serious TRAEs and AEs that were not treatment-related experienced by patients in HIMALAYA with STRIDE vs. sorafenib (primary analysis and updated analysis I; SAS) (primary DCO: 27th August 2021; updated I DCO: 23rd January 2023)



Footnotes: Treatment-related was as assessed by the investigator. AEs include AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy.

Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TRAE: treatment-related adverse event.

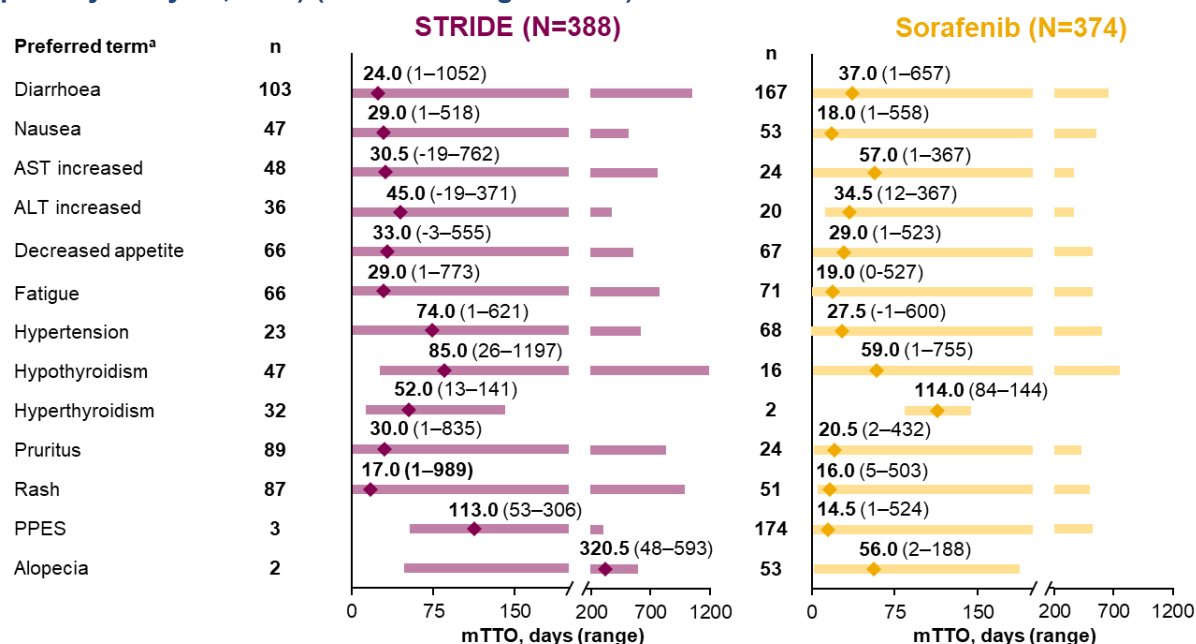
Source: Sangro, B. et al. 2023.⁹⁷ (Slide 12). Abou-Alfa, G. et al. 2022a.⁴⁵ (Slide 15).

At the primary analysis (DCO: 27th August 2021), the median time to onset for the majority of the most common (≥10%) TRAEs was <90 days from the first dose of study treatment across

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treatment arms (Figure 20).⁹⁵ The median time to resolution was <60 days for the majority of the most common TRAEs that were resolved across treatment arms (Figure 21).⁹⁵

Figure 20: Time to onset of the most common TRAEs experienced by patients in HIMALAYA (occurring in ≥10% of patients in the STRIDE or sorafenib treatment arms; primary analysis; SAS) (DCO: 27th August 2021)

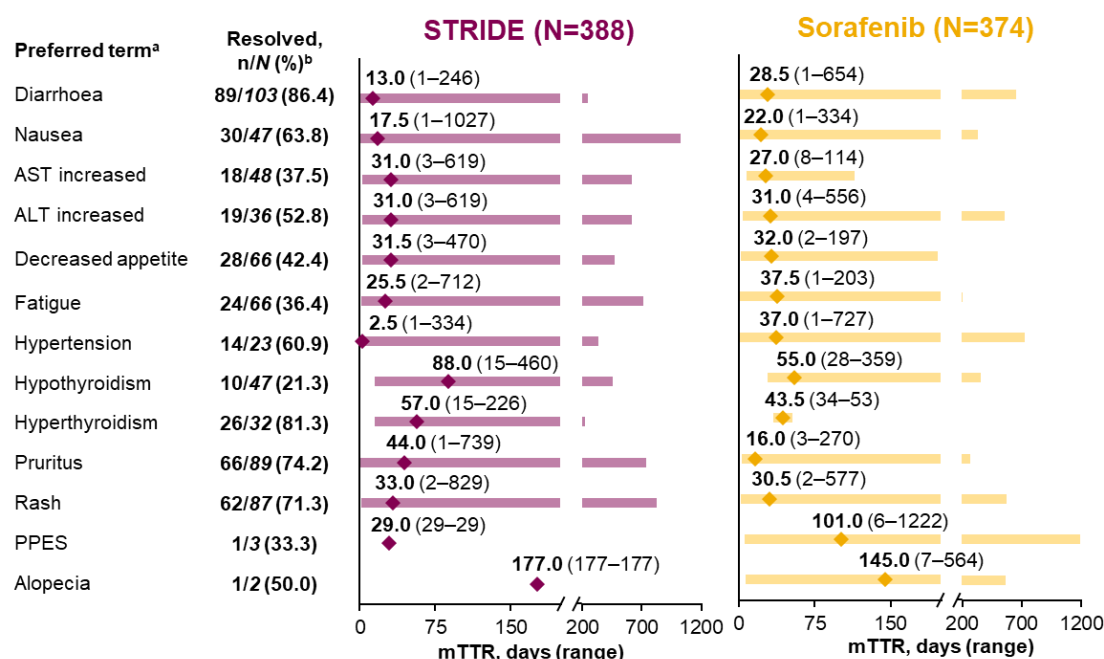


Footnotes: Time to onset of TRAE from the first dose of treatment. All AEs of all grades were recorded (one patient could have more than one grade of one type of AE). ^aPreferred term was as reported by the investigator.

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DCO: data cut-off; mTTO: median time to onset; PPES: palmar-plantar erythrodysesthesia syndrome; TRAE: treatment-related adverse event; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Adapted from Sangro, B. et al. 2022.⁹⁵ (Slide 8).

Figure 21: Time to resolution of the most common TRAEs experienced by patients in HIMALAYA (occurring in ≥10% of patients in the STRIDE or sorafenib treatment arms; primary analysis; SAS) (DCO: 27th August 2021)



Footnotes: Time to resolution of TRAE from the first dose of treatment. All AEs of all grades were recorded (one patient could have more than one grade of one type of AE). ^aPreferred term was as reported by the investigator; ^bPercent calculated as the number of TRAEs resolved out of total TRAEs experienced.

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DCO: data cut-off; mTTR: median time to resolution; PPES, palmar-plantar erythrodysesthesia syndrome; TRAE: treatment-related adverse event; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Adapted from Sangro B. et al. 2022.⁹⁵ (Slide 9).

B.2.10.3.2 Haemorrhagic events

Due to their underlying liver disease and high incidence of portal hypertension, patients with advanced or unresectable HCC are at a particularly high risk of GI bleeding. This risk may be exacerbated by antiangiogenic agents such as bevacizumab, for which bleeding is a known safety concern.^{57, 68} As such, it is recommended that all individuals undergo an endoscopy to assess the presence of gastroesophageal varices before starting treatment with atezolizumab + bevacizumab. However, access to an endoscopy in the NHS can be challenging, potentially delaying or precluding treatment.^{3, 57}

The overall frequency of haemorrhagic-related TRAEs was very low for both total and grade ≥3 events, with the frequency of patients reporting any haemorrhagic TRAE [REDACTED] in the sorafenib arm ([REDACTED]) compared with the STRIDE arm ([REDACTED] Table 29).⁸⁹ No gastrointestinal or intra-abdominal events were observed with STRIDE, whereas gastrointestinal haemorrhages (n=3, 0.8%) and intra-abdominal haemorrhages (n=1, 0.3%) were observed with sorafenib. No oesophageal varices haemorrhages were seen with either STRIDE or sorafenib (Table 29). Furthermore, no treatment-related deaths due to AEs in the haemorrhage standardised MedDRA queries (SMQs) were reported in the STRIDE arm. In contrast, the sorafenib arm reported [REDACTED] treatment-related deaths: [REDACTED] from a cerebral haematoma and [REDACTED] from haematuria.⁸⁹ These findings indicate that STRIDE is not associated with an increased bleeding risk.

Table 29: Summary of haemorrhage-related TRAEs experienced by patients in HIMALAYA, by maximum reported CTCAE grade (primary analysis; SAS) (DCO: 27th August 2021)

Maximum reported CTCAE grade ^a	STRIDE ██████████ n (%)	Sorafenib ██████████ n (%)
Patients with any haemorrhage SMQ AE		
Total	██████████	██████████
Grade ≥3	██████████	██████████
Gastrointestinal haemorrhage		
Total	█	██████████
Grade ≥3	█	██████████
Intra-abdominal haemorrhage		
Total	█	██████████
Grade ≥3	█	██████████
Oesophageal varices haemorrhage		
Total	█	█
Grade ≥3	█	█

Footnotes: ^aEach patient has only been represented with the maximum reported CTCAE grade for each SMQ/PT.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; SAS: safety analysis set; SMQ: Standardized MedDRA Queries; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: AstraZeneca Data on File - HIMALAYA CSR, Jan 2022.⁸⁹ (Table 72, pg 257).

B.2.10.3.3 Hepatic events

At the primary analysis (DCO; 27th August 2021), hepatic AEs and hepatic treatment-related AEs, as captured by hepatic Standardised MedDRA Queries (SMQs), were comparable across both treatment arms (Table 30 and Table 31).⁸⁹ These findings indicate that STRIDE has a tolerable liver toxicity profile.^{4, 89} The full list of hepatic AEs can be found in Appendix F.

Table 30. Hepatic AEs by Hepatic Disorder SMQs and Preferred Term (occurring in ≥2% of patients in either arm) (primary analysis; SAS) (DCO: 27th August 2021)

Hepatic SMQ MedDRA Preferred Term	Number (%) of patients ^a	
	STRIDE (N=388)	Sorafenib (N=374)
Patients with any hepatic SMQ AE	██████████	██████████
Liver-related investigations, signs and symptoms	██████████	██████████
Aspartate aminotransferase increase	██████████	██████████
Alanine aminotransferase increased	██████████	██████████
Ascites	██████████	██████████
Blood bilirubin increased	██████████	██████████
Gamma-glutamyl transferase increased	██████████	██████████
Hypoalbuminaemia	██████████	██████████

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Hepatic SMQ MedDRA Preferred Term	Number (%) of patients ^a	
	STRIDE (N=388)	Sorafenib (N=374)
Blood alkaline phosphatase increased	██████	██████
Hyperbilirubinaemia	██████	██████
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	██████	██████
Hepatitis non-infectious	██████	█
Hepatitis	██████	█
Liver-related coagulation and bleeding disturbances	██████	██████
Liver infections	██████	██████

Footnote: This includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

^aEach patient has only been represented with the maximum reported CTCAE grade for each SMQ/PT.

Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; DNA: deoxyribonucleic acid; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SMQ: Standardised MedDRA Query; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 69, pg 251)

Table 31. Treatment-related AEs Under Hepatic SMQs (occurring in ≥2% of patients in either STRIDE or sorafenib) (primary analysis; SAS) (DCO: 27th August 2021)

Hepatic SMQ MedDRA Preferred Term	Maximum reported CTCAE grade	Number (%) of patients ^a	
		STRIDE (N=388)	(Sorafenib (N=374))
Patients with any hepatic SMQ AE	Total	██████	██████
	Grade ≥ 3	██████	██████
Liver-related investigations, signs and symptoms	Total	██████	██████
	Grade ≥ 3	██████	██████
Aspartate aminotransferase increased	Total	██████	██████
	Grade ≥ 3	██████	██████
Alanine aminotransferase increased	Total	██████	██████
	Grade ≥ 3	██████	██████
Blood bilirubin increased	Total	██████	██████
	Grade ≥ 3	██████	██████
Hepatitis, non-infectious	Total	██████	█
	Grade ≥ 3	██████	█
Hepatitis	Total	██████	█
	Grade ≥ 3	██████	█

Footnote: This includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). Possibly related to treatment is based on Investigator assessment, and any missing responses are counted as related. ^aEach patient has only been represented with the maximum reported CTCAE grade for each SMQ/PT. ^bPT in 2 SMQs.

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Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; DNA: deoxyribonucleic acid; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SMQ: Standardised MedDRA Query; SAS: safety analysis set; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 70, pg 252)

B.2.11. Ongoing studies

There are currently no ongoing studies of relevance to this evaluation.

B.2.12. Interpretation of clinical effectiveness and safety evidence

The clinical effectiveness and safety of durvalumab in combination with tremelimumab for patients with advanced or unresectable HCC was assessed in HIMALAYA, a randomised, multicentre, open-label, Phase III trial. This study considered patients with advanced or unresectable HCC who were ineligible for locoregional therapy and had not received prior systemic therapy for HCC (first-line setting).⁴

HIMALAYA met its primary endpoint (DCO: 27th August 2021), with STRIDE demonstrating a statistically significant and clinically meaningful improvement in OS vs. sorafenib, with a median survival of 16.43 months (95% CI: 14.16–19.58) vs. 13.77 months (95% CI: 12.25–16.13).⁴ At all recorded landmarks, a greater number of patients were alive in the STRIDE treatment arm compared with the sorafenib treatment arm; in the primary DCO (three years) OS rates were 30.7% and 20.2% in the STRIDE treatment arm and sorafenib treatment arm, respectively (95% CI: 25.8–35.7);⁴ in updated analysis I (four years), 25.2% survival was observed in the STRIDE treatment arm vs. 15.1% for sorafenib;⁹⁸ most recently, in updated analysis II (five years), the survival probability in the STRIDE arm was 19.6% compared to 9.4% in the sorafenib arm.⁹⁰ The maturity of the OS dataset in HIMALAYA is unprecedented, capturing the longest OS follow-up period in any study in advanced or unresectable HCC to date. These sustained, improved OS results can be easily understood by patients and their caregivers, highlighting the crucial role of improved long-term survival in alleviating clinical burden and enhancing health-related quality of life for patients and their carers.⁷

STRIDE also demonstrated positive results for the secondary outcomes in HIMALAYA. A greater proportion of patients in the STRIDE treatment arm achieved a confirmed ORR compared with patients in the sorafenib treatment arm (20.1% vs. 5.1%, respectively). Additionally, 3.1% of patients in the STRIDE arm achieved a CR, a key surrogate outcome for OS, whereas no patients achieved this in the sorafenib arm.⁴⁵ The median DoR based on Investigator assessment was numerically longer in the STRIDE treatment arm than in the sorafenib treatment arm (22.3 months vs. 18.4 months, respectively), with a numerically higher for the STRIDE treatment arm compared with the sorafenib treatment arm (■■■■ vs. ■■■■ respectively).⁴⁵

At the primary DCO (27th August 2021), a greater proportion of patients were progression-free in the STRIDE treatment arm compared with the sorafenib arm (12.5% vs. 4.9%, respectively). The median PFS for STRIDE and sorafenib were comparable (HR: 0.90; 95% CI: 0.77–1.05).⁴⁵ As discussed in Section B.2.6.2, this aligns with the typical efficacy pattern of IO-IO therapies, where observed PFS benefits are minor, but OS improvement is clinically and statistically significant. UK HCC experts confirmed that PFS is not a reliable surrogate for OS in advanced or unresectable HCC. This is due to the subjective nature of radiologic progression and the continuation of treatment beyond progression. This finding is further supported by a recent publication by Huang et al., which demonstrated a weak correlation between PFS and OS in

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patients with unresectable HCC.⁹⁴ Collectively, these findings indicate weak surrogacy between PFS and OS in HCC, particularly with IO-IO therapies. Therefore, OS is considered the most valuable metric when assessing the efficacy of different treatment options in this disease area.⁷

STRIDE further resulted in improvements in PROs, including longer median time to deterioration of all EORTC QLQ-C30 and EORTC QLQ-HCC18 scores, including GHS/QoL, physical functioning and disease-related symptoms, except for jaundice, where sorafenib was nominally higher. Furthermore, it well-tolerated from the patient perspective with no meaningful impact on HRQoL compared with treatment with sorafenib.⁹⁵

Importantly, STRIDE demonstrated a favourable safety profile; all AEs were manageable according to toxicity management guidelines and the overall evaluation of safety and tolerability in HIMALAYA was generally consistent with that observed in previous studies with durvalumab and tremelimumab.^{89, 124} STRIDE demonstrated overall lower rates of grade 3/4 treatment-related adverse events (TRAEs) and TRAEs leading to discontinuation than sorafenib.²² Furthermore, haemorrhagic-related TRAEs were lower in STRIDE than sorafenib and hepatotoxicity rates were similar, indicating that STRIDE does not increase the bleeding risk or liver toxicity.^{4, 89} This favourable safety profile provides a notable advantage over the current SoC, and is reflected in its recent first-line recommendation in the BSG guidelines.³

Three of the 17 unique studies identified by the SLR were determined eligible for inclusion in the NMA, including the HIMALAYA trial. The appropriateness of performing an NMA was assessed following the methodology outlined in NICE DSU Document 2.¹²⁵ Overall, the three trials were generally comparable in terms of study design and patient baseline characteristics. There was evidence of PH assumption violation for HIMALAYA and REFLECT for OS and PFS. However, there was no evidence of PH violation for IMbrave150. These studies were used to form a network of evidence for both OS and PFS, connected via a common sorafenib treatment arm. The analysis found that STRIDE and atezolizumab + bevacizumab improved OS compared to sorafenib, although no statistical differences were observed ([REDACTED] [REDACTED]). The NMA found that lenvatinib had a HR close to 1 in the comparison to sorafenib, with a similar point estimate to the non-inferiority REFLECT trial ([REDACTED]). Similarly, for PFS, STRIDE, atezolizumab + bevacizumab and lenvatinib showed improvements over sorafenib, yet these results lacked statistical significance ([REDACTED] [REDACTED]), respectively). Overall, the NMA identified that STRIDE was associated with a comparable improvement in survival vs. sorafenib compared to atezolizumab + bevacizumab, the key comparator in this submission

HIMALAYA was deemed to be of high quality following critical appraisal (Section B.2.5). This RCT recruited a large sample size and randomised stratification by key prognostic factors which led to balanced treatment arms. Patient characteristics were further representative of the advanced or unresectable HCC patient population in the UK, as supported by clinician validation (Section B.2.4). As referred to above, the five-year OS data is a key strength of the evidence base supporting the STRIDE regimen, providing substantial certainty of the long-term clinical benefits associated with this regimen.

Limitations of HIMALAYA included the open-label design. This was necessary due to the differing drug administration methods of the treatments; STRIDE is administered intravenously while sorafenib is taken orally. Furthermore, despite not having UK centres in this trial, the trial participant characteristics closely align with an advanced HCC patient audit in the UK, ensuring

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the trial is generalisable to patients in the UK.¹⁰³ The alignment between the HIMALAYA trial and the UK population was validated through clinician interviews.⁷ While slight deviations in baseline populations (such as non-viral HCC, HCV, and HBV) were noted, attributed to higher rates of MASLD and alcohol consumption in UK cities, clinicians anticipated these variations and still deemed the dataset generalisable to UK clinical practice.⁷

An additional limitation of HIMALAYA was the absence of a direct comparisons to two of the current first-line treatment options: lenvatinib and atezolizumab + bevacizumab, noting that the latter was not reimbursed SoC at the time the trial was designed. However, an NMA was conducted to provide comparative treatment effectiveness estimates.⁷ During the NMA feasibility assessment, violation of the PH assumption for HIMALAYA and REFLECT was identified, which may have introduced uncertainty to results. However, models such as fractional polynomial or piecewise models were deemed unnecessary and overly complex, and ultimately did not address the key limitation which is the lack of long-term efficacy published for REFLECT and IMbrave150. Instead, the uncertainty associated with violations of the PH assumption was addressed in the economic model by independently fitting curves for HIMALAYA. For lenvatinib vs sorafenib, as per the results of the REFLECT trial, where statistical non-inferiority between lenvatinib and sorafenib was observed for OS, the HR was set to 1, to indicate equivalence in efficacy. This is viewed as conservative given that the time-varying analysis exploring non-proportionality in REFLECT predicts HRs above 1 over time for most models (see Appendix N). For PFS, the time-varying analysis also concluded that using a constant HR in the economic model was a conservative choice (Section B.3.3.2). The standard NMA results for atezolizumab + bevacizumab vs. sorafenib were not affected by PH assumption violations.

In summary, the STRIDE regimen demonstrated a significant improvement in OS vs. sorafenib, leading to approximately 20% of patients surviving at least five years.⁹⁰ Furthermore, STRIDE demonstrated a favourable safety profile, including a low risk of haemorrhagic and hepatic events,⁸⁹ providing confidence in the safety of the regimen and re-enforcing its value as an important treatment alternative for all patients with advanced or unresectable HCC. STRIDE is supported by unprecedented and highly mature evidence demonstrating significant prolongation of survival within this patient population. The unprecedented OS results underscore the critical importance of STRIDE for patients, affirming STRIDE as a well-tolerated and effective treatment alternative for patients with advanced or unresectable HCC ineligible for locoregional therapy in the UK.^{57, 68, 126}

B.3 Cost effectiveness

Summary of the cost effectiveness analysis

- A *de novo* cost-effectiveness model was developed to assess the cost-effectiveness of STRIDE in adult patients with advanced or unresectable HCC, in line with the HIMALAYA patient population, licence and decision problem for this submission (Section B.3.2.1)
- The comparators to STRIDE considered within the analysis were atezolizumab + bevacizumab, sorafenib and lenvatinib (Section B.3.2.3)
- The model adopted a partitioned survival approach with three health states: progression free (PF), progressed disease (PD) and dead, over a lifetime time horizon (40 years) (Section B.3.2.2)
- Parametric survival extrapolations were fit to OS and PFS data for STRIDE and sorafenib from the HIMALAYA trial in order to extrapolate outcomes over the full modelled time horizon (Section B.3.3.2, B.3.3.4 and B.1.1.1)
- Within HIMALAYA, STRIDE is compared to sorafenib only. Therefore, comparative

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effectiveness evidence vs. atezolizumab + bevacizumab for OS and PFS was sourced from the NMA (Section B.2.9). In line with the REFLECT trial, which showed statistical non-inferiority between lenvatinib and sorafenib, a HR of 1 between lenvatinib and sorafenib was applied in the model for OS. The NMA estimate was used for PFS. HRs for atezolizumab + bevacizumab and lenvatinib vs. sorafenib were applied to the parametric survival extrapolations for OS and PFS for sorafenib in order to generate long-term survival estimates for these two comparators.

- Costs included in the model were drug acquisition, drug administration, subsequent treatment, health state resource use, AE and end-of-life costs, adopting an NHS and PSS perspective^{127, 128} (Section B.3.5)
- Utility values for the PF and PD states were derived from values obtained from the HIMALAYA trial via the EQ-5D-5L questionnaires. These values were cross-walked to the EQ-5D-3L, in line with the methods described in Hernández-Alava et al.,⁹⁹ as recommended by NICE (Section B.3.4.5)

Base case cost-effectiveness results

- In the base case, STRIDE was associated with a dominant deterministic incremental cost-effectiveness ratio (ICER) relative to atezolizumab + bevacizumab, the principle comparator and current SoC in NHS clinical practice for patients with advanced or unresectable HCC. At a willingness-to-pay (WTP) threshold of £30,000/QALY gained, STRIDE therefore represents a cost-effective use of NHS resources (Section B.3.10)
- STRIDE was associated with deterministic, pairwise ICERs of [REDACTED] and [REDACTED] per QALY, relative to alternative therapies sorafenib and lenvatinib, respectively, which are alternative first-line treatments when IOs cannot be used (Section B.3.10)

Sensitivity and scenario analysis

- The deterministic and probabilistic base case results show that incremental QALYs for the comparison between STRIDE and atezolizumab + bevacizumab fall either side of zero, indicating, at a minimum, likely clinical equivalence between the two interventions, which is further supported by the results of the NMA. To investigate this equivalence, a cost comparison was conducted, the results of which showed that STRIDE is associated with cost-savings when compared to atezolizumab + bevacizumab
- Pairwise probabilistic ICERs for the comparison between STRIDE and sorafenib and STRIDE and lenvatinib were consistent with the deterministic ICERs
- A deterministic sensitivity analysis (DSA) was conducted. The model was robust to the variation in the majority of model inputs, however in the comparison of STRIDE to lenvatinib, results were influenced by the PFS HR for lenvatinib vs. sorafenib (Section B.3.11.2)
- Scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness analysis. In the majority of scenarios, STRIDE remains dominant vs. atezolizumab + bevacizumab. The ICERs vs. sorafenib and lenvatinib remain relatively stable between scenarios, illustrating the robustness of the model to uncertainty. (Section B.3.11.4)

Conclusions

- There is a significant unmet need in UK clinical practice for an efficacious treatment that leads to improved survival for patients with advanced or unresectable HCC, without an associated increase in bleeding risk (Section B.1.3.3)
- STRIDE represents an alternative therapeutic option that is supported by mature, five-year OS data that is associated with minimal added bleeding risk compared to current SoC in the UK, atezolizumab + bevacizumab
- These analyses demonstrate that STRIDE represents a cost-effective use of NHS resources with the potential to reduce the clinical and humanistic burden for adults with advanced or unresectable HCC, as well as the economic burden on the NHS

B.3.1 *Published cost-effectiveness studies*

A SLR was conducted to identify and synthesise relevant economic models, cost and healthcare resource use, and humanistic burden (utilities and HRQoL) of STRIDE and other first-line treatments in adults with advanced or unresectable HCC. The original SLR was conducted in May 2020, and subsequently underwent updates in October 2021 and June 2024.

In the recent SLR update, following de-duplication of results, a total of 400 publications were screened at the title and abstract stage, of which 29 were reviewed at the full-text stage. After excluding publications that did not meet the eligibility criteria, five (three economic model publications, two HRQoL publications) publications were included in the SLR from database searches. Supplementary searches retrieved an additional two articles (one economic model publication, one HRQoL publication), resulting in a total of seven articles included from both the electronic database and supplementary searches.

Additionally, 160 articles (104 publications on economic models or cost and resource use, 56 humanistic publications) were included from the original SLR and first update. Therefore, a total of 107 publications comprising economic models and cost and resource use studies and 58 humanistic publications were ultimately included in the SLRs.

A description of the SLR methodology and results can be found in Appendix G. No prior economic evaluations were identified for STRIDE in the population of relevance to this submission, however, the most applicable economic models to this submission were reported in the previous NICE appraisals for atezolizumab + bevacizumab, lenvatinib and sorafenib, the details of which can be found in Table 32.⁸⁻¹⁰

B.3.2 *Economic analysis*

As described in Section B.3.1, no economic evaluations of STRIDE in advanced or unresectable HCC were identified in the economic SLR. As such, a *de novo* cost-effectiveness analysis was conducted to inform this evaluation through a model built in Microsoft Excel®.

The objective of this economic evaluation was to assess the cost effectiveness of STRIDE in adult patients with advanced or unresectable HCC relative to atezolizumab + bevacizumab, sorafenib and lenvatinib.

B.3.2.1 Patient population

The economic analysis considered patients with advanced or unresectable HCC in line with the HIMALAYA patient population, the licensed indication for STRIDE and the decision problem defined in Section B.1.1.

B.3.2.2 Model structure

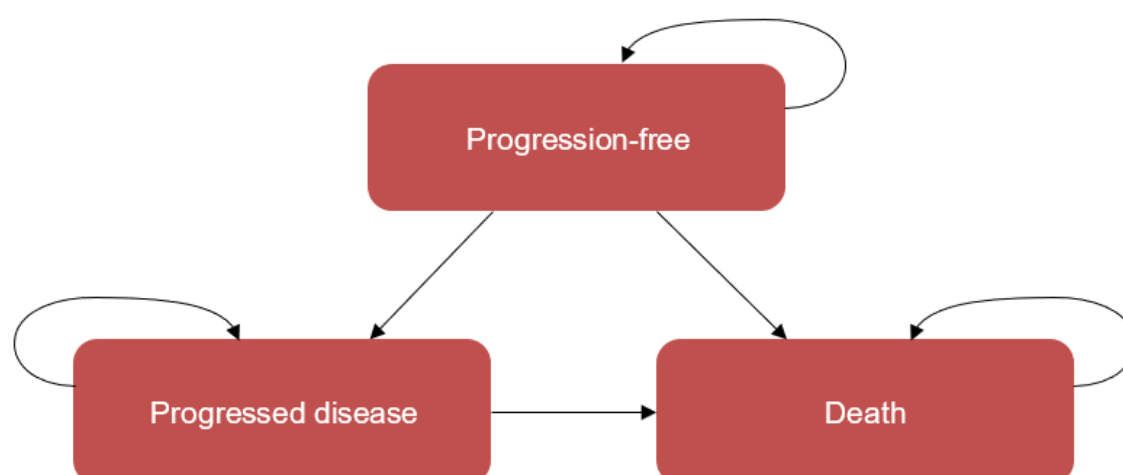
The cost-effectiveness analysis was conducted using a partitioned survival model (PSM). This model structure was deemed the most appropriate based on the clinical data available. It also aligns with the structure adopted in previous NICE evaluations in advanced or unresectable HCC.^{8-10, 129} The model structure directly leverages key time-to-event endpoints in the HIMALAYA study, namely OS and PFS. It reflects the natural disease course and the primary objectives of treatment for patients with advanced or unresectable HCC in the form of delaying progression and in extending survival.

The three health states included in the PSM are:

- **PF:** patients who are alive and whose disease has not progressed
- **PD:** patients who are alive but whose disease has progressed
- **Death:** patients who have died

A simplified model schematic is presented in Figure 22, showing the potential transitions between the three health-states.

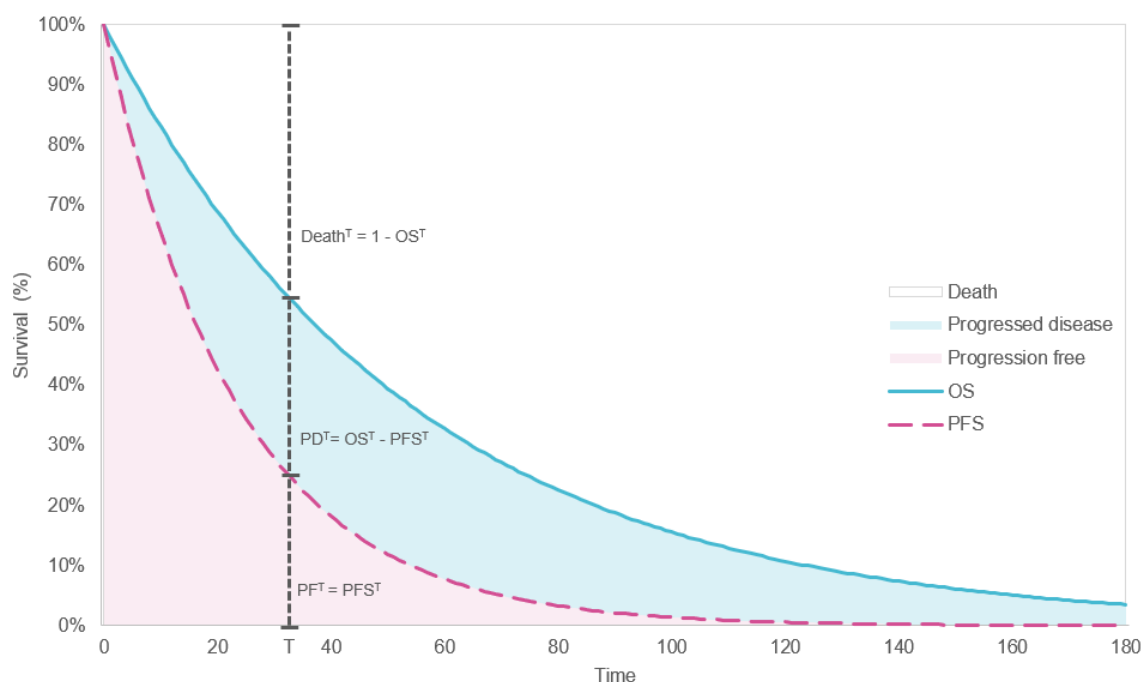
Figure 22: Simplified model schematic



All patients enter the model in the 'progression-free' state, receiving STRIDE or a comparator treatment (atezolizumab + bevacizumab, sorafenib, lenvatinib). Patients may remain progression-free, progress, or die. Patients in the 'Progressed disease' health state can either remain alive with progressed disease or die, but the model does not allow for patients to improve their health state. The separation of pre- and post-progression states helps capture differences in both costs and patient HRQoL before and after progression. In line with clinical practice, within the progression-free and progressed health states, patients may either be on or off treatment. The 'Death' health state is an absorbing state.

The proportion of patients within each health state was determined by OS and PFS curves via an area-under-the-curve approach (Figure 23). This ensures that the model closely reflects disease progression and the observed survival profile of patients treatment with STRIDE and comparator therapies.

Figure 23: Health state occupancy at time T



Abbreviations: OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression free survival.

Features of the cost-effectiveness analysis

Costs and health state utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle, which were totalled at the end of the time horizon. The output of the model was the ICER of STRIDE vs. the relevant comparators.

In line with the NICE reference case,¹³⁰ the perspective on costs and outcomes was that of the NHS and Personal Social Services (PSS). A lifetime time horizon of 40 years was chosen to capture patient outcomes up to a potential age of 100 years. This was considered appropriate as 4% of patients remain alive in the intervention arm after a 20-year period (the time horizon used in previous models)^{9, 10} and thus enables the model to capture the full set of accumulated costs and QALYs in all treatment arms. A 1-week cycle length was considered in the base case as this was deemed appropriate given the rate at which clinical events may occur, and the frequency with which treatment regimens are administered. This aligns with the most recent NICE evaluation in advanced HCC (TA666, see below).¹⁰ A half-cycle correction was applied. Costs and effects were discounted at 3.5% annually, in line with the NICE reference case.¹³⁰

Features of the analysis were based on previous NICE evaluations of HCC including:

- TA666: atezolizumab + bevacizumab for treating advanced or unresectable HCC¹⁰
- TA474: sorafenib for treating advanced HCC⁹
- TA551: lenvatinib for treating advanced HCC⁸

A summary of the key features of the evaluations of the three relevant comparators, as well as the economic analysis and justifications for the current evaluation, are provided in Table 32.

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Table 32: Features of the economic analysis

Factor	Previous evaluations			Current evaluation	
	TA666 ¹⁰	TA474 ⁹	TA551 ⁸	ID2757	Justification
Intervention	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib	STRIDE	In line with the decision problem (Section B.1.1)
Population	Patients with untreated locally advanced or metastatic and/or unresectable HCC who have Child-Pugh Class A, liver impairment, a ECOG PS 0–1 and have not had previous systemic treatment	Patient with advanced stage HCC disease who have Child-Pugh grade A liver impairment	Adults with untreated advanced or unresectable HCC and Child-Pugh Class A liver impairment and an ECOG of 0 or 1	Patients with advanced or unresectable HCC and no previous systemic therapy	The approach is in line with the licensed indication, the decision problem in the final NICE scope and supported by evidence from the HIMALAYA RCT
Comparator	• Sorafenib • Lenvatinib	• BSC	• Sorafenib	• Atezolizumab + bevacizumab • Sorafenib • Lenvatinib	All relevant comparators with regards to current UK clinical practice for advanced or unresectable HCC are considered, as described in detail in Section B.1.1
Outcomes	• OS • PFS • AEs • HRQoL	• OS • PFS • AEs • HRQoL • TTP	• OS • PFS • AEs • HRQoL	• OS • PFS • AEs • HRQoL	In line with the NICE decision problem (Section B.1.1)
Model structure	PSM with three health states (PFS, PD and death)	PSM with three health states (PFS, PD and death)	Markov model with four health states (non-progressive advanced disease, PD, BSC and death)	PSM with three health states (PFS, PD and death)	A PSM closely reflects disease progression and the observed survival profile of patients treated with STRIDE and comparator therapies, and the UK treatment pathway for advanced or unresectable HCC. A PSM is in line with the

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Factor	Previous evaluations			Current evaluation	
	TA666 ¹⁰	TA474 ⁹	TA551 ⁸	ID2757	Justification
					recent prior NICE evaluations in advanced or unresectable HCC
Time horizon	Lifetime horizon (20 years)	Lifetime horizon (20 years)	Lifetime horizon (14 years)	Lifetime horizon (40 years)	This extended lifetime horizon captures all costs and QALYs associated with STRIDE and its comparators
Cycle length	1 week	28 day	1 month	1 week	A 1-week cycle was deemed appropriate given the rate at which relevant clinical events may occur, and the frequency with which treatment regimens are administered. This aligns with the most recent NICE evaluation, TA666 ¹⁰
Half-cycle correction	Yes	Yes	Yes	Yes	A half-cycle correction was applied in line with previous appraisals
Treatment waning effect?	No	No	No	No	No treatment waning effect was included in the model in line with the past three evaluations in this indication
Source of utilities	Utility values were sourced from the IMbrave150 trial	Utilities sourced from the REFLECT trial ⁷³	Mapping from FACT-G to a set of time trade-off utility values using an algorithm developed by Dobrez <i>et al.</i> 2007 ¹³¹	EQ-5D-5L was collected in the HIMALAYA trial and values were cross-walked to the EQ-5D-3L using the algorithm developed by Hernández <i>et al.</i> ^{4, 99, 132}	Approach to health state utility values is in line with the NICE manual ¹³²
Source of costs	- NHS Reference Costs - PSSRU	- NHS Reference Costs - PSSRU	- NHS Reference Costs - PSSRU	- NHS Reference Costs 2021/22 - PSSRU	Established sources of costs within the NHS, in alignment with the NICE reference case

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Factor	Previous evaluations			Current evaluation	
	TA666 ¹⁰	TA474 ⁹	TA551 ⁸	ID2757	Justification
	- BNF - TA474 (sorafenib) - Nuffield Trust	- BNF - TA474 (sorafenib) - Nuffield Trust - Marie Curie Cancer Care	- NHS Health and Social Care Information Centre - Newcastle Upon Tyne 2006/07 tariffs^a - Plymouth Hospital NHS Trust 2008^a - UCL lab tariff 2007^a - Mullhaven Medical Laboratory 2008^a - BNF	- BNF - eMIT¹³³ - TA666 (atezolizumab + bevacizumab) - TA551 (lenvatinib)	Where necessary, costs were inflated using the NHS Cost Inflation Index in the PSSRU Unit Costs of Health and Social Care 2023 Manual to ensure values used in the model were current. ^{127, 134, 135}

Footnote: ^aThe references provided in the TA474 submission are no longer available.

Abbreviations: AE: adverse event; BNF: British National Formulary; BSC: best supportive case; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D-3L; EuroQol-5 Dimensions-3 Levels; EQ-5D-5L; EuroQol-5 Dimensions-5 Levels; eMIT: electronic market information tool; FACT-G: Functional Assessment of Cancer Therapy – General; HCC: hepatocellular carcinoma; HRQoL: health-related quality of life; ID: identification; ITC: indirect treatment comparison; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ORR: objective response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PSM: partitioned survival model; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; RCT: randomised controlled trial; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TA: technology appraisal; TTP: time to progression; UCL: University College London; UK: United Kingdom.

Source: Abou-Alfa et al. (2022b);⁴ BNF (2024);¹³⁶ Finn et al. (2020);⁴⁴ NHS Reference Costs (2023);¹²⁸ NICE TA666 (2020);¹⁰ NICE TA551 (2018);⁸ NICE TA474 (2017);⁹ PSSRU 2023;.¹²⁷ Kudo et al. (2018).⁷³

B.3.2.3 Intervention technology and comparators

Intervention

As discussed in Section B.1.2, the intervention of interest to the cost-effectiveness analysis is STRIDE. As per the SmPC, it is advised that STRIDE is administered until disease progression or unacceptable toxicity occurs.^{1, 6}

Comparators

As discussed in Section B.1.3, atezolizumab + bevacizumab is the current first-line SoC for patients with advanced or unresectable HCC who are ineligible for locoregional therapy in the UK, however, there is an elevated risk of bleeding associated with this regimen (Section B.1.3.4.1).^{44, 126} For those contraindicated to atezolizumab + bevacizumab or those who decline IV therapy in favour of oral therapy, sorafenib and lenvatinib are alternative first-line therapies for advanced or unresectable HCC (Section B.1.3.4.2). Accordingly, three comparators have been included in the model: atezolizumab + bevacizumab, sorafenib and lenvatinib.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

The baseline characteristics of the modelled patient population were informed by the HIMALAYA trial (Table 33). As noted in Section B.2.4, and confirmed by clinical expert feedback, the baseline characteristics of the HIMALAYA trial were considered to be generally representative of patients in UK clinical practice.⁷

Table 33: Baseline characteristics for the model population

Model parameter	Value	Source
Mean age, years	■	HIMALAYA (FAS)
Percentage male, %	■	HIMALAYA (FAS)
Mean weight, kg	■	HIMALAYA (FAS)
Mean height, cm	■	HIMALAYA (FAS)
Patient BSA, m ²	■	HIMALAYA (FAS)

Abbreviations: BSA: body surface area; FAS: full analysis set.

Source: AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 14.1.5, Slide 37)

B.3.3.2 Survival analyses methodology

As discussed in Section B.2.3.3, there are three key DCOs from the HIMALAYA trial:

- **Primary analysis:** The primary analysis was performed once 555 OS events had occurred in the STRIDE and sorafenib arms combined (representing 71% maturity), 46 months after the first patient was randomised (DCO: 27th August 2021)^{4, 89}
- **Updated analysis I:** The updated analysis evaluated the OS and safety of STRIDE vs. sorafenib with 4 years of follow-up (DCO: 23rd January 2023)⁹⁸

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- **Updated analysis II:** An additional five-year OS analysis has been conducted for STRIDE vs. sorafenib, representing the longest follow up period to date in Phase III studies in advanced or unresectable HCC (DCO: 1st March 2024).

Within the model, efficacy data for STRIDE and sorafenib were informed by the most mature DCO available for the outcome in question: OS was informed by the updated analysis II DCO, while PFS and TTD were informed by the primary analysis.

Survival analyses methodology: STRIDE and sorafenib

For STRIDE and sorafenib, as presented in Section B.2.6.2.1, individual patient data (IPD) were directly available from the HIMALAYA trial over a median follow-up duration of 5 years for OS, and a median follow-up duration of approximately 2.5 years for PFS and TTD.^{90, 137}

Parametric survival functions were fitted to the Kaplan-Meier data for each arm in HIMALAYA. As recommend in NICE DSU TSD 14 and 21,^{89, 118} the following steps were undertaken to select best-fitting and clinically valid parametric survival extrapolations for the STRIDE and sorafenib arms:

- **Assessment of proportional hazards (PH) assumption**
 - The PH assumption between treatment arms in HIMALAYA was assessed through visual assessment of Kaplan-Meier curves, log-log plots, plots of the Schoenfeld residual and consideration of time-varying HR, if reported. If the PH assumption holds, as indicated by approximately parallel log-log plots, a Schoenfeld's residual p-value >0.05 (indicating no autocorrelation among residuals at a 95% confidence interval), or a relatively stable HR over time, joint parametric models accounting for both treatment arms can be considered. Otherwise, independent models may be fit to each treatment arm. Further details on the PH assessments conducted for HIMALAYA are presented in Section B.2.9.5 and Appendix D.
- **Assessment of observed trial hazards**
 - The hazards (rates of events) for each treatment arm within the HIMALAYA trial period were assessed through visual inspection of the observed raw and smoothed hazard plots. Assessment of the hazard plots can indicate whether standard parametric survival models such as proportional hazards and accelerated failure time (AFT) models are suitable, or whether models with greater flexibility, such as spline-based models, should be explored.
 - Within the hazard plots, the within-trial period hazard was also visually compared to the hazards predicted by each parametric model on a long-term basis. Hazards over a 20-year timeframe were considered to confirm that the extrapolated hazards for the chosen base case extrapolations were clinically plausible.
- **Statistical goodness of fit**
 - The statistical goodness of fit of each extrapolation was assessed by considering the ranking of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
- **Visual fit to Kaplan-Meier plots**

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- The goodness of fit of the parametric extrapolation to the Kaplan-Meier data was visually assessed, with consideration given to the entire trial period for which data were available.
- **External validation is desirable in understanding the suitability of the extrapolations**
 - Although HIMALAYA trial data are highly mature, clinical plausibility in the long-term remains an important consideration. UK clinical expert opinion was therefore sought to understand outcomes that could be expected for both the sorafenib and STRIDE arms in NHS clinical practice. External evidence was also considered and used where appropriate to validate the model extrapolations.

Approach to comparator efficacy: atezolizumab + bevacizumab and lenvatinib

In the absence of a direct comparison between STRIDE and each of atezolizumab + bevacizumab and lenvatinib, comparative effectiveness from the NMA described in Section B.2.9 were explored to inform the model. Long-term survival estimates for atezolizumab + bevacizumab and lenvatinib could be generated through the application of the relevant HR from the NMA to the selected parametric survival function for the sorafenib treatment arm, the common comparator arm from the NMA. In order to explore this approach, the assessments of PH between atezolizumab + bevacizumab and sorafenib, and lenvatinib and sorafenib, for both OS and PFS, were reviewed. These assessments are presented in Table 20, Section B.2.9.5 and detailed further in Appendix D.

With regards to the comparison with lenvatinib, the PH assessment indicated that there was evidence of PH violation within REFLECT for OS and PFS. As such, NMA-derived HRs for comparisons of lenvatinib to sorafenib may be biased; following an assessment of the time-varying HR from REFLECT and the trend towards a HR of 1 for lenvatinib vs. sorafenib, the direction of this bias appears to favour lenvatinib (Section B.2.9.5). Therefore, the application of a constant HR from the NMA for lenvatinib in the economic model may overestimate the long-term effect of lenvatinib treatment (see Section B.2.9.5 and Appendix N). Further to this, the REFLECT study was a non-inferiority study, which concluded that lenvatinib was statistically non-inferior compared with sorafenib in terms of OS. Accordingly, a HR for lenvatinib vs. sorafenib of 1 was used in the base case for OS. For PFS, statistical non-inferiority was not observed in REFLECT, and thus the HR from the NMA was used, which may be considered a conservative approach.

There was no evidence of PH violation for IMBrave150, and therefore the survival estimate for this comparator informed by the NMA-derived HR for atezolizumab + bevacizumab vs sorafenib was unlikely to be biased.

It is noted that choice of parametric extrapolation for the sorafenib treatment arm (to which relevant HRs would be applied) was not limited to proportional hazards models, but also considered functions such as accelerated failure time (AFT) models and spline-based models. The purpose of this was to maximise choice from a range of potentially clinically valid extrapolations. Whilst the combining of HRs with survival probabilities estimated from an AFT model is technically mixing assumptions on how treatment effects would (theoretically) be applied in the survival model (acting on the time scale for an AFT model) and how they are modelled in the comparative analysis (acting on the hazard scale). However, there is no reason to artificially constrain the comparator curves to the same form. If the estimated curves for the comparators are clinically valid, the conflating of technical assumptions is immaterial.

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B.3.3.3 Overall survival

B.3.3.3.1 Assessment of PH assumption – STRIDE vs sorafenib

As discussed in Section B.2.9, the PH assessment for the STRIDE and sorafenib OS outcomes was based on IPD from HIMALAYA. The formal assessment of the PH assumption, based on the visual inspection of the Kaplan-Meier curves, the log-log plot, the Schoenfeld residuals plot and the Grambsch and Therneau test, found that the PH assumption was violated.¹¹⁴⁻¹¹⁷ Further details of this assessment can be found in Section B.2.9.5.

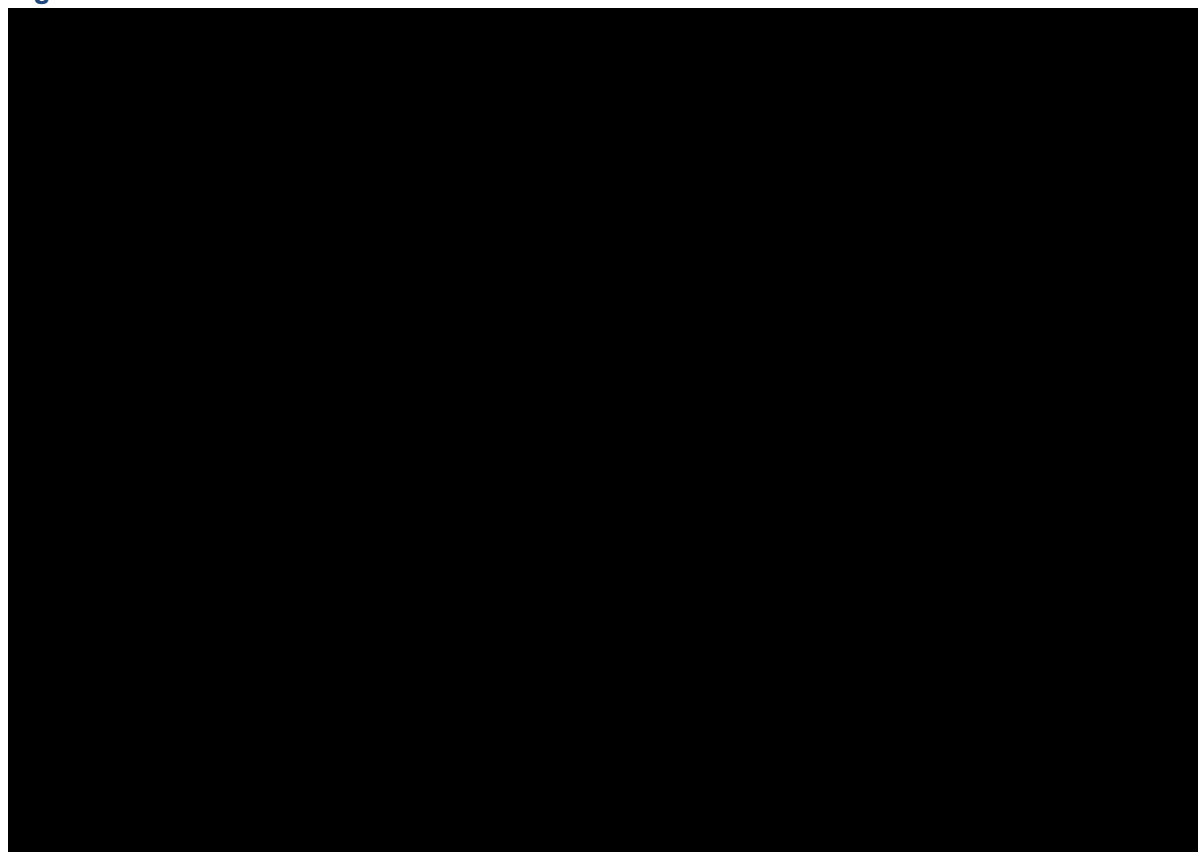
Given the PH assumption was violated, it was considered necessary to explore independently fitted models rather joint-fitting models. Additionally, as patient-level data are available for HIMALAYA, it is considered unnecessary to consider a joint approach as fitting separate parametric models to each treatment arm involves fewer assumptions.¹¹⁸

B.3.3.3.2 Assessment of observed trial hazards – STRIDE vs sorafenib

Plots of the observed raw and smoothed hazards were assessed to judge the complexity of observed trial hazards and determine whether parametric models with greater flexibility should be considered alongside standard parametric models. [REDACTED]

[REDACTED] To capture the changes observed in these hazards, independent spline models were considered the most appropriate parametric extrapolations for both arms, as they offer flexibility to capture changing hazards.¹³⁸

Figure 24: Observed raw and smoothed hazards from the HIMALAYA trial



Abbreviations: ITT: intention-to-treat; OS: overall survival; sora: sorafenib; TREME 300 + DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE).

B.3.3.3.3 STRIDE

As described above, independent fitting of spline-based models was considered the most appropriate approach to capturing the varying hazards observed in the STRIDE arm of HIMALAYA. As such, the goodness of fit assessment of spline-based models is discussed in the sections that follow, with all information related to fitting of standard models for the STRIDE arm presented in Appendix N for completeness. Scenario analyses are conducted with the most appropriate standard model.

Statistical fit of parametric survival functions

The model fit statistics (AIC and BIC) for the spline-based models explored for OS for STRIDE are presented in Table 34. Visual assessment of the fit of spline models to the Kaplan-Meier data for STRIDE was assessed in Figure 25 (extrapolation over the model time horizon provided in Figure 26). Proportions alive at various landmarks are provided in Table 35.

All models provided a similar fit to the trial data, with all AIC statistics within 5 points of each other. The range of BIC statistics among the different models was slightly wider, but remained comparable. Visual assessment of the extrapolations to the Kaplan-Meier curves further

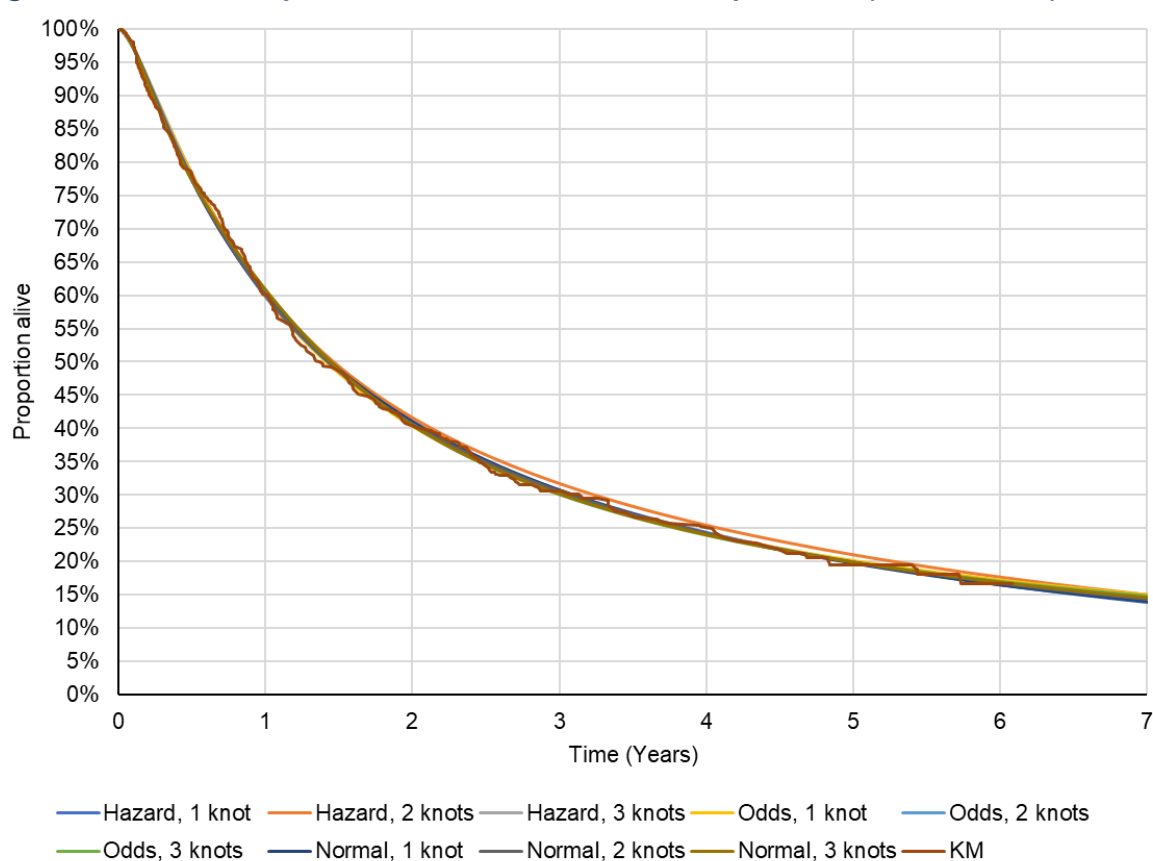
confirmed that all models fit the trial data well. The best-fitting models by AIC/BIC statistics were the Normal 1 knot, Hazard 1 knot, Normal 2 knots and Odds 1 knot.

Table 34: Model fit statistics for OS parametric survival functions for STRIDE

Function		AIC	Rank (AIC)	BIC	Rank (BIC)
Hazard	1 knot	2719.30	3	2731.20	2
	2 knots	2721.20	6	2737.10	5
	3 knots	2722.20	9	2742.10	9
Odds	1 knot	2719.90	4	2731.80	3
	2 knots	2721.60	7	2737.50	6
	3 knots	2722.10	8	2742.00	8
Normal	1 knot	2717.10	1	2729.00	1
	2 knots	2718.90	2	2734.80	4
	3 knots	2720.10	5	2740.00	7

Footnotes: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Figure 25: STRIDE OS parametric survival function extrapolations (within-trial fit)



Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Table 35: Landmark proportions alive (STRIDE OS)

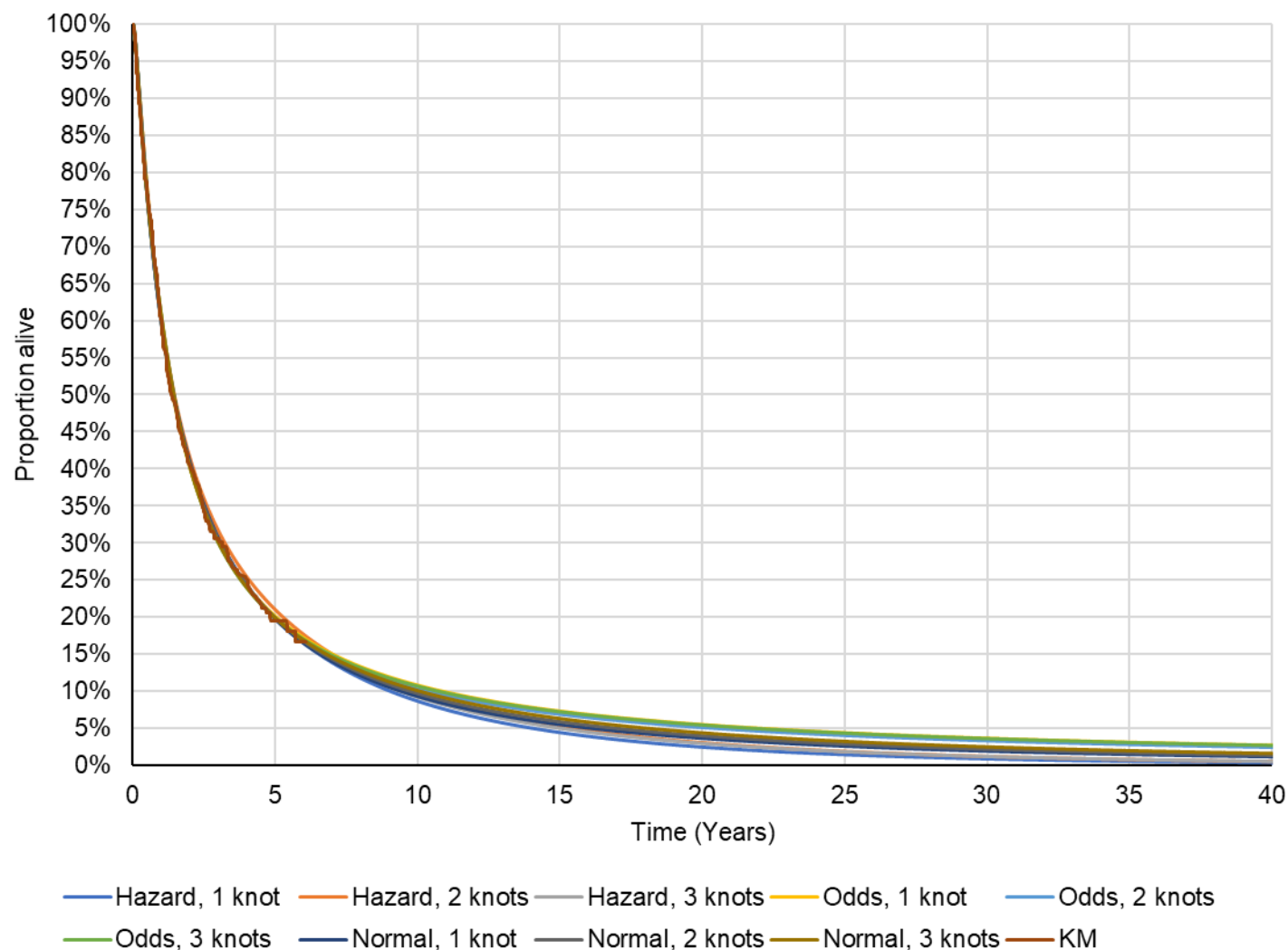
Function					
Kaplan-Meier Curve			NA	NA	NA

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Function						
Hazard	1 knot					
	2 knots					
	3 knots					
Odds	1 knot					
	2 knots					
	3 knots					
Normal	1 knot					
	2 knots					
	3 knots					

Footnotes: NA: not applicable; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Figure 26: STRIDE OS parametric survival function extrapolations (over the model time horizon)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

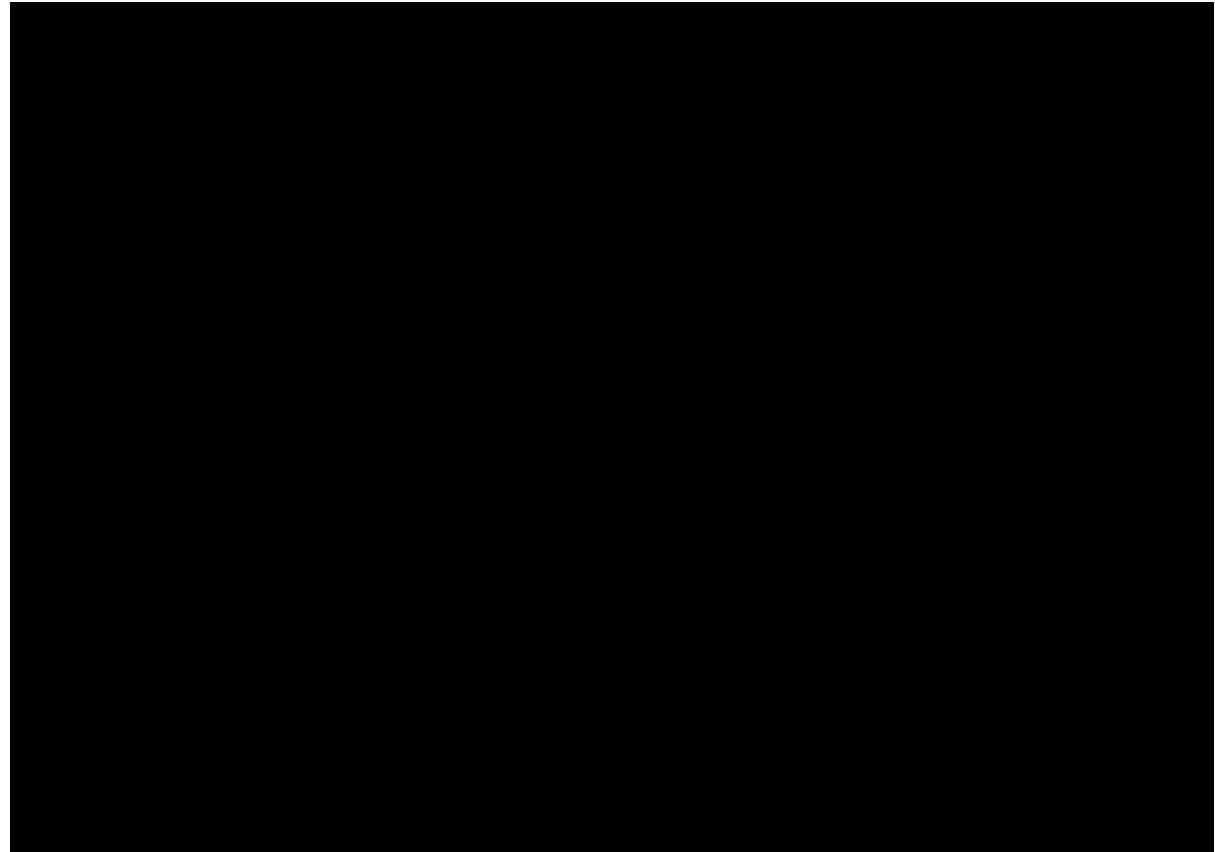
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Observed vs modelled hazard rate

The observed hazard of the STRIDE arm from HIMALAYA was compared with the hazards of spline-based survival models in Figure 27, Figure 28 and Figure 29 below. [REDACTED]

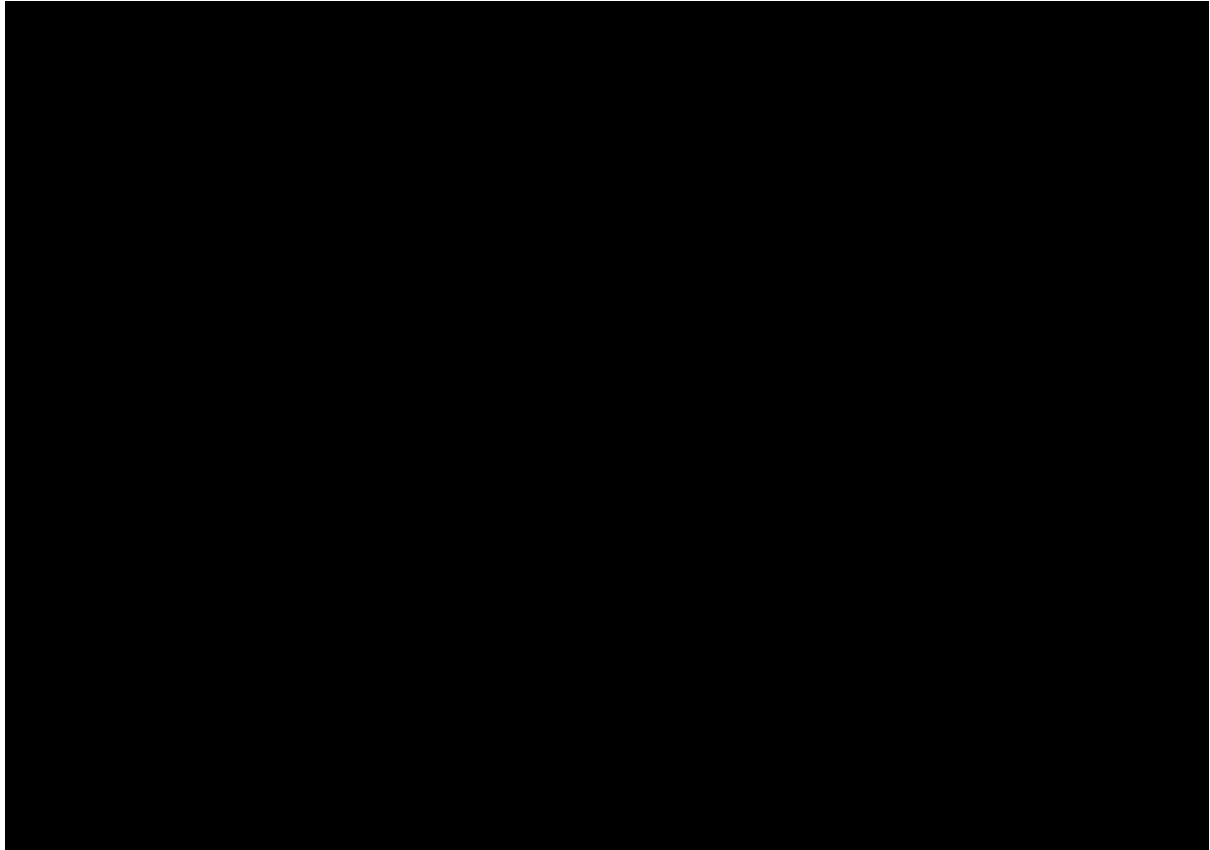
[REDACTED]

Figure 27: Smoothed hazard plots for OS for STRIDE (Hazard models)



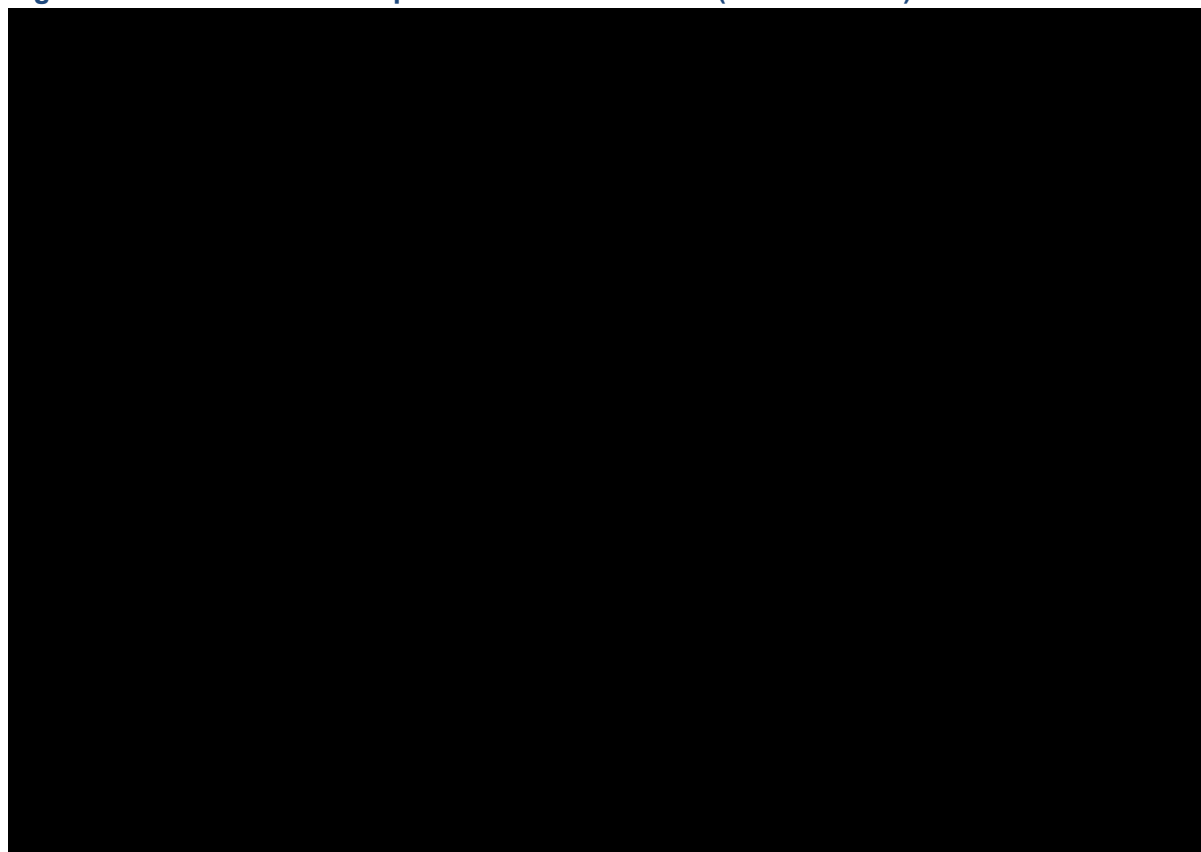
Abbreviations: OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Figure 28: Smoothed hazard plots for OS for STRIDE (Normal models)



Abbreviations: ITT: intention-to-treat; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TREME 300 + DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE).

Figure 29: Smoothed hazard plots for OS for STRIDE (Odds models)



Abbreviations: ITT: intention-to-treat; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TREME 300 + DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE).

External validation

The HIMALAYA trial provides highly mature OS data from a median follow-up of five years. This represents a significant strength of the evidence base supporting STRIDE, as it substantially reduces uncertainty in the resulting long-term survival extrapolations in the model. In particular, the goodness of fit statistics can be considered particularly informative in the consideration of extrapolation selection, given the long-term Kaplan-Meier data available with which to statistically compare each extrapolation.

To supplement the mature data from HIMALAYA further, and in line with recommendations from NICE TSD 14, clinical feedback was also sought from UK-based oncologists on survival expectations should patients receive STRIDE in NHS clinical practice, and the long-term clinical validity of the modelled survival extrapolations.¹¹⁸

The consulted oncologists consistently confirmed that a long-term benefit of STRIDE on patient survival was in line with their expectations. In particular, the observation of a “tail” or “plateau” in the long-term survival estimates for STRIDE aligned with their expectations. The clinicians confirmed that this pattern of survival was expected given the dual IO mechanism of action of the STRIDE regimen, and the resulting strong stimulation of the immune system to attack cancer cells. As can be observed in Figure 26, all extrapolations assessed demonstrate a long-term survival benefit of STRIDE, with a “tail” observed in their shape, in line with clinician expectations. Upon presentation of a selection of the better fitting extrapolations (Odds 1 knot, Normal 1 knot and Hazard 1 knot) under assessment to the clinicians, preference was expressed

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at least once for each of the three extrapolations, and so all extrapolations were considered plausible.

Considering the combination of factors above, specifically, observed trial hazards, goodness of fit statistics and clinical opinion, the Normal 1 knot model was selected as the base case. When comparing the 1-knot models, which were considered clinically plausible (see Table 34), the Normal 1 knot model provided the middle estimate between the proportion alive at later timepoints: ■■■ estimated by the Hazard model, ■■■ estimated by the Odds model, ■■■ estimated by the Normal model at 20 years). It represents a robust fit to the Kaplan-Meier data from HIMALAYA and captures expected OS in the long-term for patients treated with STRIDE in NHS clinical practice. For completeness, the generalised gamma extrapolation was assessed in a scenario analysis as it was considered a clinically plausible alternative that was one of the best-fitting statistically among the set of standard models assessed (Appendix N).

B.3.3.3.4 Sorafenib

As described above, independent fitting of spline-based models was considered the most appropriate approach to capturing the varying hazards observed in the sorafenib arm of HIMALAYA. As such, the goodness of fit assessment of spline-based models are discussed in the sections that follow, with all information related to fitting of standard models fitted to the sorafenib arm presented in Appendix N for completeness. Scenario analyses are conducted with the most appropriate standard model.

Statistical fit of parametric survival functions

The model fit statistics (AIC and BIC) for the spline-based parametric survival functions explored for OS for sorafenib are presented in Table 36. Visual assessment of the fit of spline models to the Kaplan-Meier data for sorafenib was assessed in Figure 30 (extrapolation over the model time horizon provided in Figure 31). Proportions alive at various landmarks are provided in Table 37.

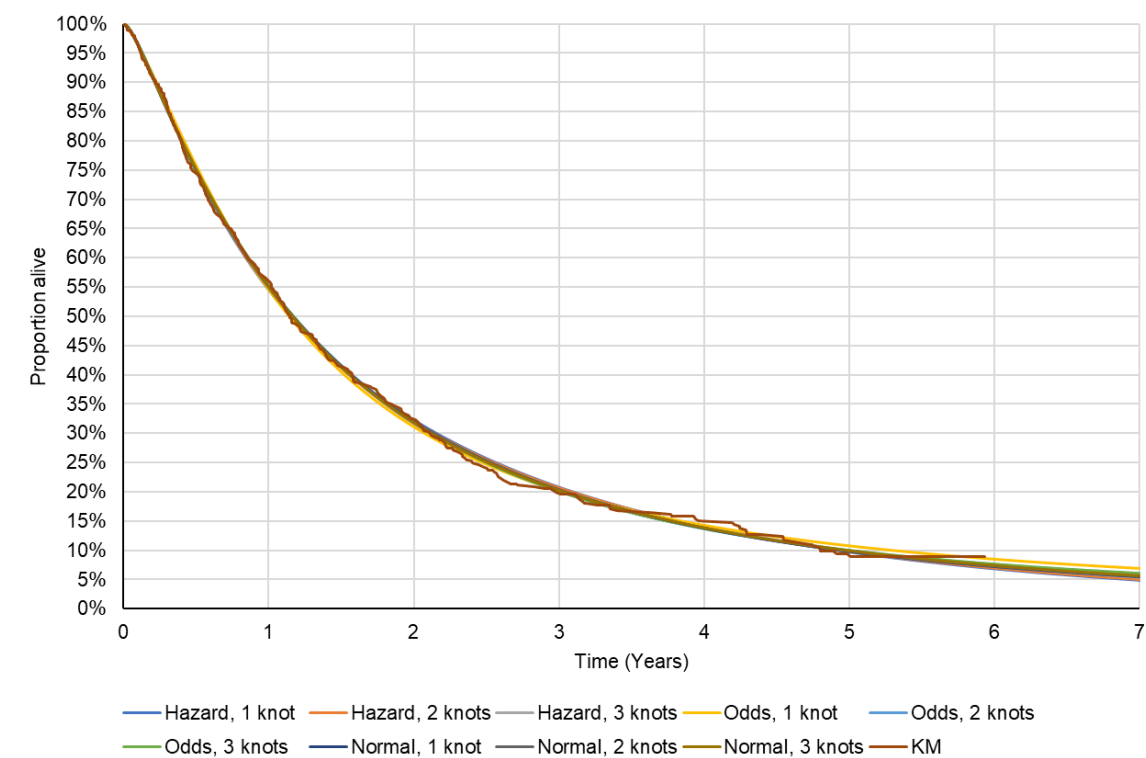
All models provided a similar fit to the trial data, with all AIC statistics within 4 points of each other. The range of the BIC statistics was slightly wider, but remain comparable. Visual assessment of the extrapolations to the Kaplan-Meier curves further confirmed that all models fit the trial data well. The best-fitting models by AIC/BIC statistics were the Odds 1 knot, Hazard 1 knot, followed by the Normal 1 knot.

Table 36: Model fit statistics for OS parametric survival functions for sorafenib

Function		AIC	Rank (AIC)	BIC	Rank (BIC)
Hazard	1 knot	2729.9	2	2741.8	2
	2 knots	2731.7	6	2747.6	6
	3 knots	2733.2	7	2753.0	7
Odds	1 knot	2729.3	1	2741.2	1
	2 knots	2731.3	4	2747.2	5
	3 knots	2733.3	8	2753.1	8
Normal	1 knot	2731.2	3	2743.1	3
	2 knots	2731.3	4	2747.1	4
	3 knots	2733.3	8	2753.2	9

Footnotes: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 30: Sorafenib OS parametric survival function extrapolations (within-trial fit)



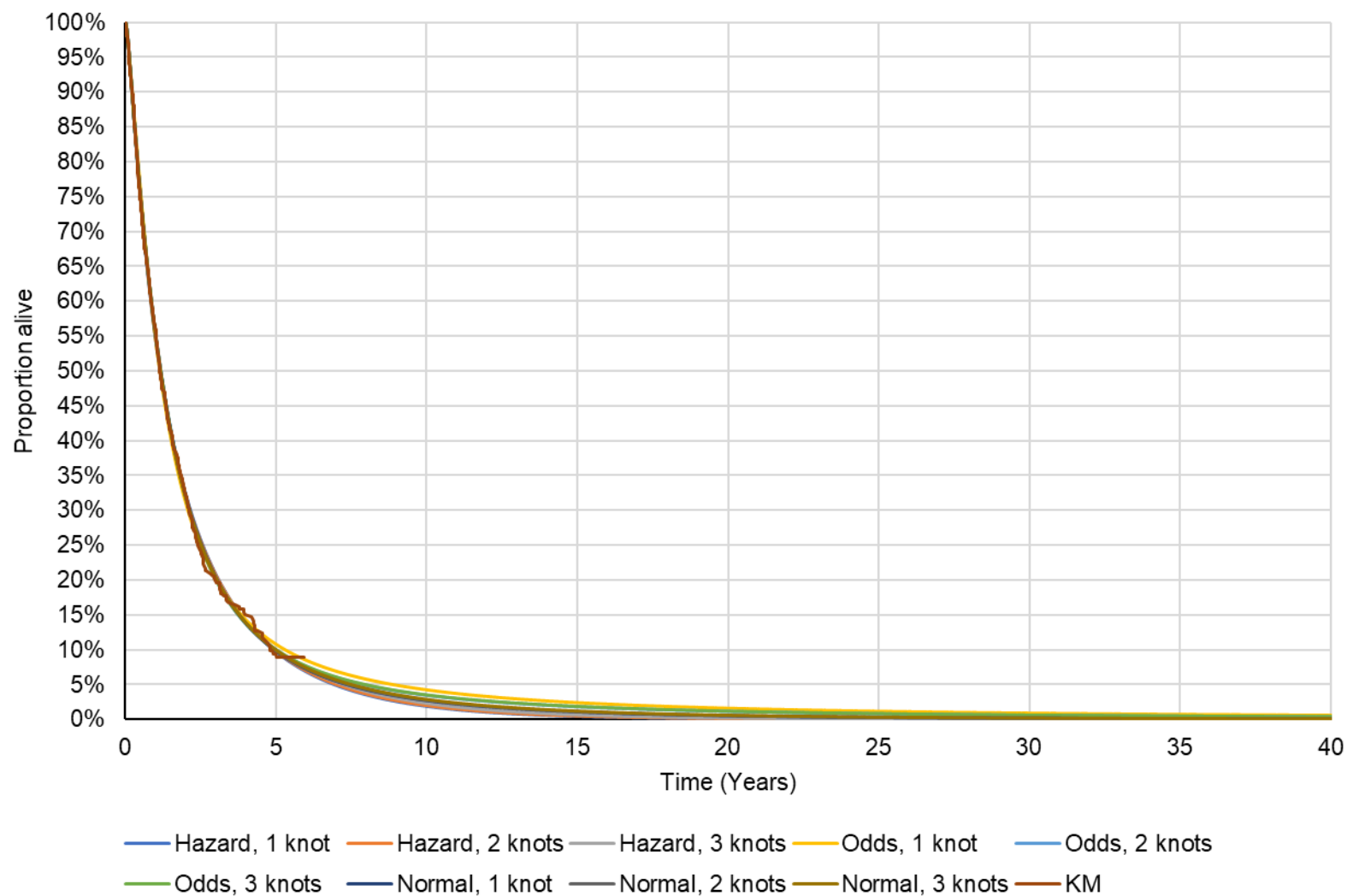
Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Table 37: Landmark proportions alive (sorafenib OS)

Function						
Kaplan-Meier Curve				NA	NA	NA
Hazard	1 knot					
	2 knots					
	3 knots					
Odds	1 knot					
	2 knots					
	3 knots					
Normal	1 knot					
	2 knots					
	3 knots					

Footnotes: NA: not applicable; OS: overall survival.

Figure 31: Sorafenib OS parametric survival function extrapolations (extrapolated fit)



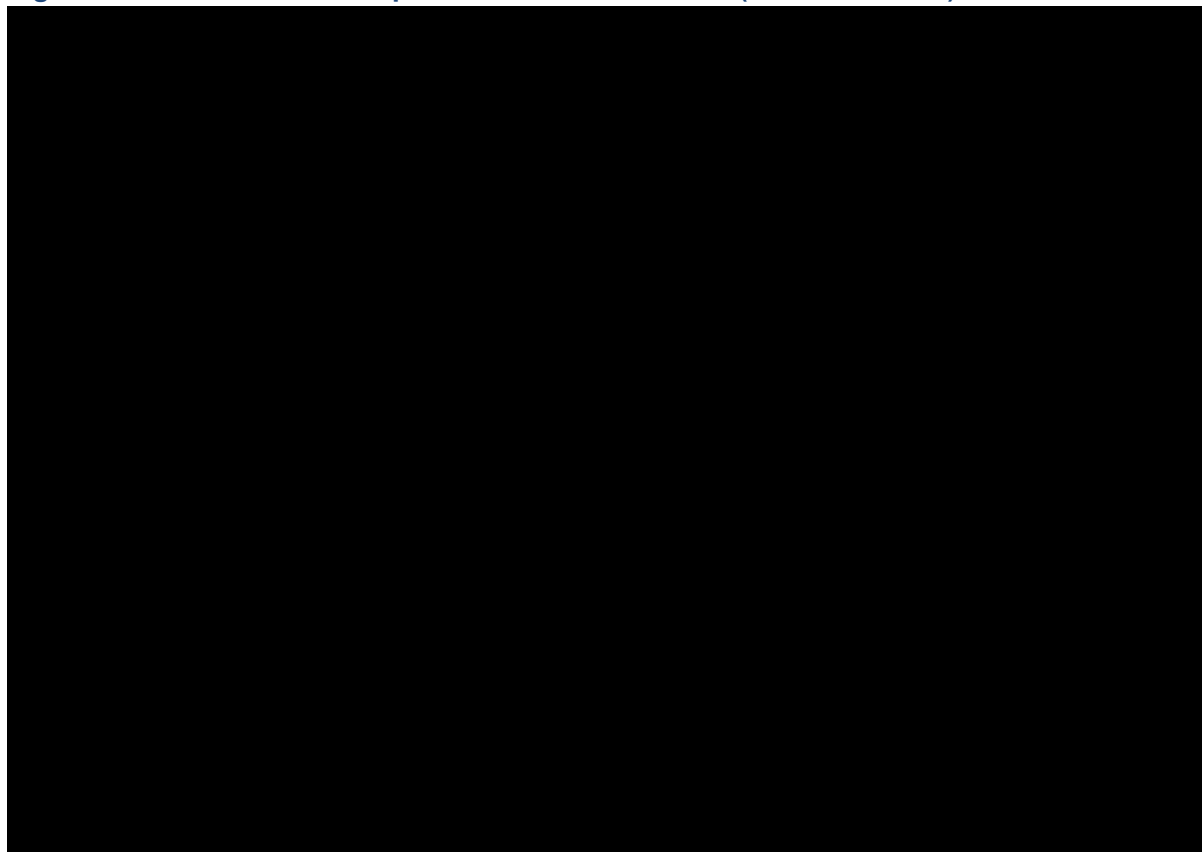
Abbreviations: KM: Kaplan-Meier; OS: overall survival.

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Observed vs modelled hazard rate

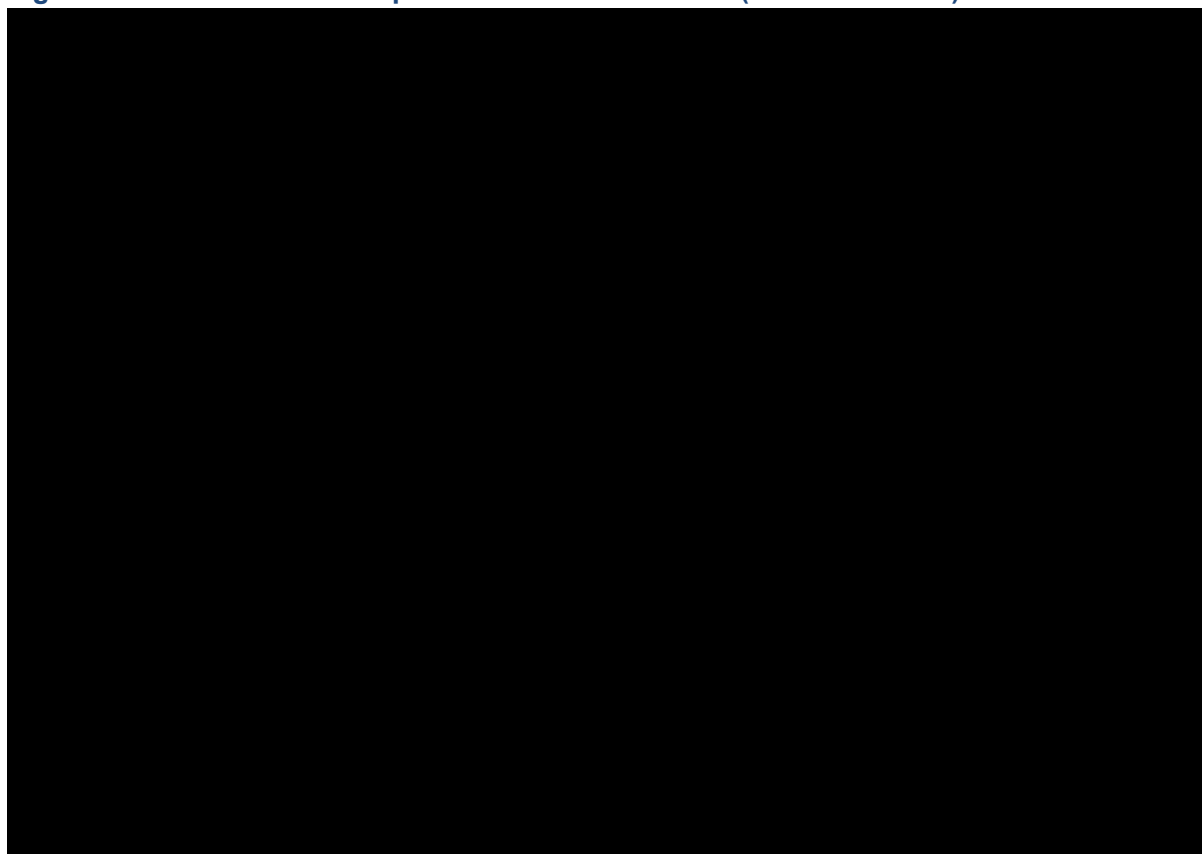
The observed hazard of the sorafenib arm from HIMALAYA was compared with the hazards of spline-based survival models in Figure 32, Figure 33 and Figure 34 below. All models appear to capture the initial increase followed by decrease of the trial hazards sufficiently. Over the long term, the smoothed hazards show that the hazards decrease over time for all models.

Figure 32: Smoothed hazard plots for OS for sorafenib (Hazard models)



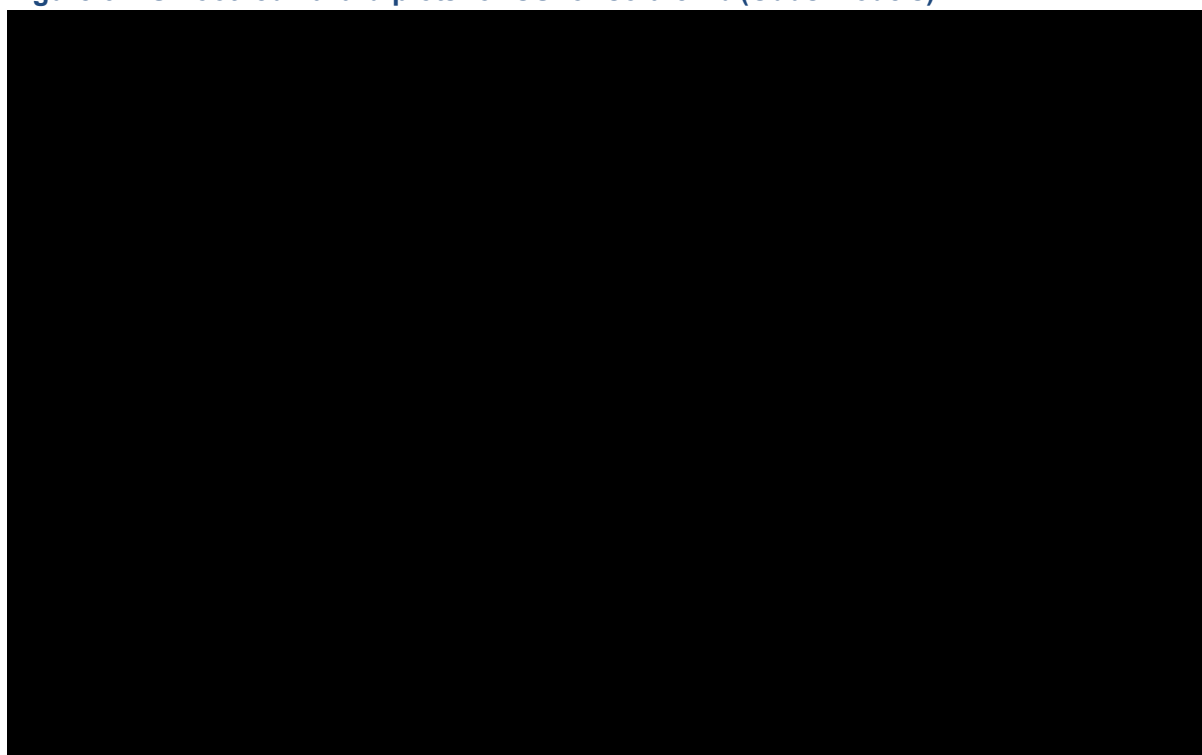
Abbreviations: ITT: intention-to-treat; OS: overall survival; sora: sorafenib.

Figure 33: Smoothed hazard plots for OS for sorafenib (Normal models)



Abbreviations: OS: overall survival.

Figure 34: Smoothed hazard plots for OS for sorafenib (Odds models)



Abbreviations: ITT: intention-to-treat; OS: overall survival; sora: sorafenib.

External validation

As previously described, the HIMALAYA trial provides highly mature OS data from a median follow-up of five years, thereby minimising uncertainty in the resulting long-term survival extrapolations in the cost-effectiveness model. In particular, the goodness of fit statistics can be considered particularly informative in the consideration of extrapolation selection, given the long-term Kaplan-Meier data available with which to statistically compare each extrapolation.

To supplement the mature data from HIMALAYA further, and in line with recommendations from NICE TSD 14, clinical feedback was sought from UK-based oncologists on the long-term clinical validity of the modelled parametric survival curves.¹¹⁸

Clinicians noted that survival of patients receiving sorafenib in NHS clinical practice is poor; in contrast to their expectations of STRIDE where a “tail” in the curve is expected (as described in Section B.3.3.4.3). The clinicians’ expectation of the pattern of long-term survival with sorafenib was such that the proportions of patients alive would progressively and successively drop to zero.⁷ This pattern of survival is aligned with the shape of all extrapolations presented in Figure 31. Clinicians commented that survival for sorafenib may be overestimated by these extrapolations. One possible reason for this overestimation is the use of subsequent IO in the sorafenib arm in the trial: █ of patients in the sorafenib arm in the trial received a subsequent IO, compared to just █ in the STRIDE arm. This was made up predominately of nivolumab (█ followed by pembrolizumab (█) and atezolizumab (█). No adjustment was made to the survival data for these subsequent IOs. Given the poor survival expectations associated with sorafenib in NHS clinical practice, among the best fitting extrapolations presented, the oncologists considered the extrapolations predicting the lowest survival expectations to be the most clinically plausible (see Table 35).¹¹⁸ The three best fitting curves (Odds 1 knot, Hazard 1 knot, Normal 1 knot) identified above through the AIC/BIC statistics all demonstrated comparable long-term survival over the full model time horizon, and given the clinicians’ feedback, Hazard 1 knot was selected in the base case .

To further support the clinical validity of the chosen base case extrapolation, given that sorafenib has been licensed for the treatment of advanced HCC for a number of years, a targeted literature search for external evidence on survival data with sorafenib was conducted. This search identified two papers - a meta-analysis of randomised trials evaluating sorafenib in advanced HCC by Tan et al (2023) and a retrospective review of electronic prescribing records in advanced HCC patients in Scotland by Peters (2018).^{139, 140} The retrospective review found a median survival of 10.4 months, and the meta-analysis estimated a median OS of 10.43 months. The Hazard 1 knot model for sorafenib estimates a median of ~13.8 months, indicating that the curve selection may represent a conservative model choice for the base case.

B.3.3.3.5 Base case parametric extrapolation selections

The base case parametric extrapolation selection was informed by the collective assessment reported above, with the extrapolation choices included in the base case presented in Table 38. As with the STRIDE arm, for completeness, a scenario analysis has been performed with one of the clinically plausible and statistically best-fitting standard models, the generalised gamma. As a scenario, the best fitting standard models, as described in Appendix N, were tested.

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Table 38: Base case and scenario extrapolation choices

Technologies	OS	
	Base Case	Scenario
STRIDE	Normal 1 knot	Generalised gamma
Sorafenib	Hazard 1 knot	Generalised gamma

Abbreviations: OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

OS for atezolizumab + bevacizumab and lenvatinib

As noted above, in order to inform long-term estimates of OS for atezolizumab + bevacizumab and lenvatinib within the model, HRs were applied to the sorafenib arm extrapolation.

The HRs applied to the sorafenib extrapolation are presented in Table 39. For atezolizumab + bevacizumab, the HR generated by the NMA described in Section B.2.9 was applied. As explained above, lenvatinib and sorafenib were considered to have equivalent OS efficacy given the result of the REFLECT study, which showed that lenvatinib was non-inferior to sorafenib but that superiority could not be established. This equivalence was achieved through setting the HR equivalent to 1.

Table 39: OS HRs applied to sorafenib arm extrapolation

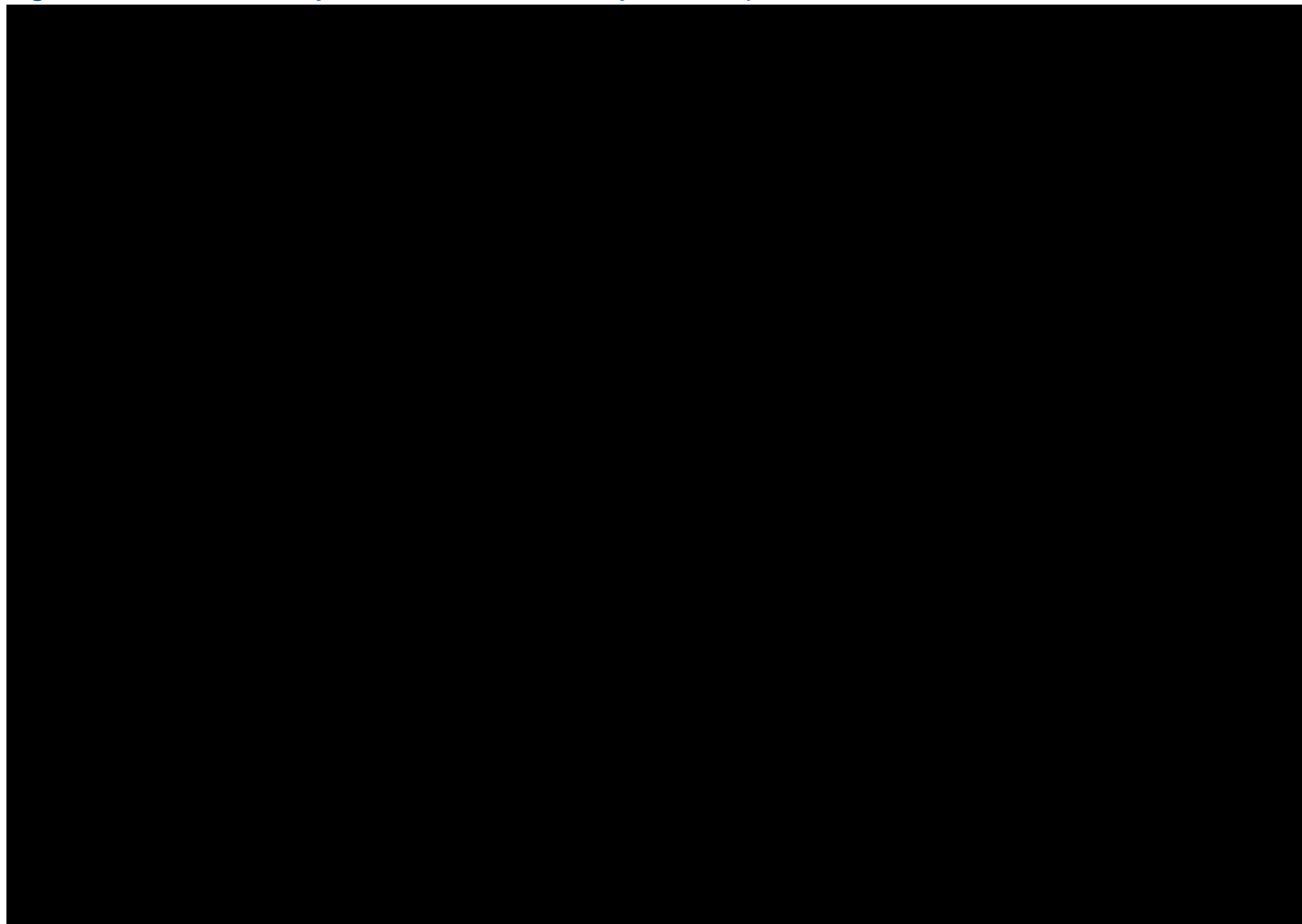
Intervention	HR vs sorafenib (95% CrI)
Atezolizumab + bevacizumab	
Lenvatinib	1

Abbreviations: CrI: credible interval; HR: hazard ratio; OS: overall survival.

OS parametric survival extrapolations used within the model

The parametric survival extrapolations for OS selected for the base case are presented in Figure 35, for STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib.

Figure 35: Base case OS parametric survival extrapolations (STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

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B.3.3.4 Progression-free survival

Within each treatment arm, the PFS extrapolations were constrained by the OS extrapolations in the model. This ensured that the PFS extrapolation for each intervention did not exceed the OS extrapolation, maintaining clinically meaningful model outputs.

The extrapolation selection process for PFS aligned with that taken for OS.

B.3.3.4.1 Assessment of PH assumption – STRIDE vs sorafenib

As discussed in Section B.2.9, the PH assessment for the STRIDE and sorafenib PFS outcomes from HIMALAYA was based on IPD from the trial. The formal assessment of the PH assumption, based on the visual inspection of the Kaplan-Meier curves, the log-log plot, the Schoenfeld residuals plot and the Grambsch and Therneau test, found that there was violation of the PH assumption.¹¹⁴⁻¹¹⁷ Further details of this assessment can be found in Section B.2.9.5.

As the PH assumption had been violated, it was considered necessary to explore independently fitted models rather joint-fitting models.

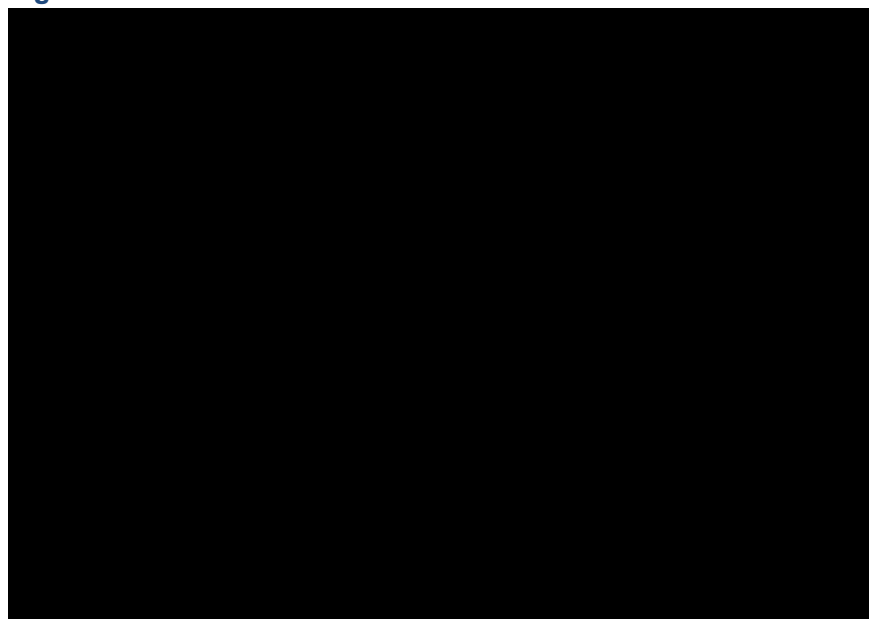
B.3.3.4.2 Assessment of observed trial hazards – STRIDE vs sorafenib

Plots of the observed raw and smoothed hazards were assessed to judge the complexity of observed trial hazards and decide whether more flexible parametric models should be considered alongside the standard parametric models. [REDACTED]

[REDACTED]

[REDACTED] To capture the changes observed in these hazards, spline-based models were considered the most appropriate for both arms as they offer flexibility to capture changing hazards.¹¹⁹

Figure 36: Observed raw and smoothed hazards from the HIMALAYA trial



Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; sora: sorafenib; TREME 300 + DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE).

B.3.3.4.3 STRIDE

As described above, independent fitting of spline-based models was considered the most appropriate approach to capturing the varying hazards observed in the STRIDE arm of HIMALAYA. As such, the goodness of fit assessment of spline-based models are discussed in the sections that follow, with all information related to fitting of standard models fitted to the STRIDE arm presented in Appendix O for completeness.

Statistical fit of parametric survival functions

The model fit statistics (AIC and BIC) for the parametric survival functions explored for PFS for STRIDE are presented in Table 40. Visual assessment of the parametric survival functions to the Kaplan-Meier data for STRIDE was assessed in Figure 37. Proportions progression-free at various landmarks are provided in Table 41. Extrapolated models are provided in Figure 38.

According to AIC/BIC statistics, the 3 knot models provided the best fit to the observed Kaplan-Meier data for the STRIDE treatment arm, with the Hazard 3 knot survival function providing the best fit. Visual assessment of the extrapolations to the Kaplan-Meier curves in Figure 37 confirmed that all models fitted the trial data well.

Table 40: Model fit statistics for PFS parametric survival functions for STRIDE

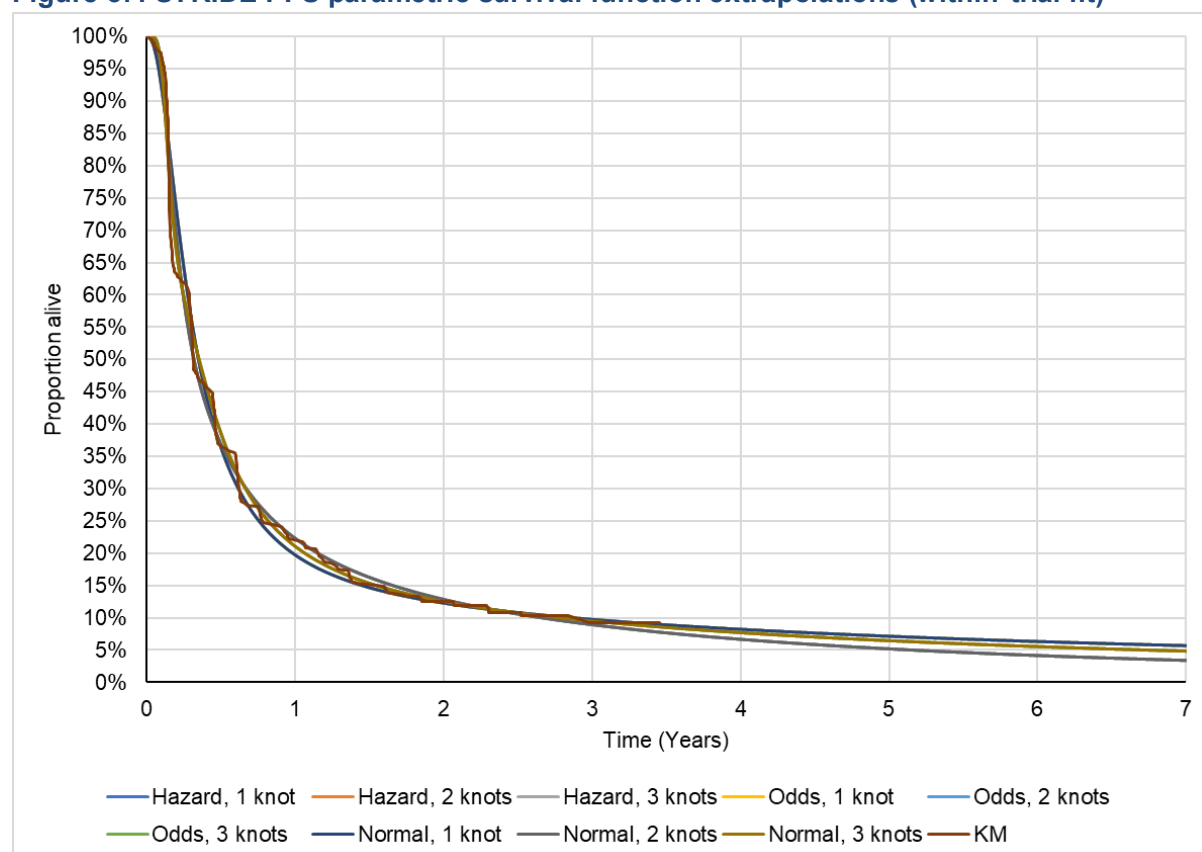
Function		AIC	Rank (AIC)	BIC	Rank (BIC)
Hazard	1 knot	1996.5	9	2008.5	9
	2 knots	1970.1	6	1986.0	6
	3 knots	1959.3	1	1979.1	1
Odds	1 knot	1986.6	7=	1998.5	7=
	2 knots	1967.2	4=	1983.1	4=
	3 knots	1961.4	2=	1981.3	2=
Normal	1 knot	1986.6	7=	1998.5	7=
	2 knots	1967.2	4=	1983.1	4=
	3 knots	1961.4	2=	1981.3	2=

Footnote: The bolded function represents the best-fitting parametric survival function.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

S

Figure 37: STRIDE PFS parametric survival function extrapolations (within-trial fit)



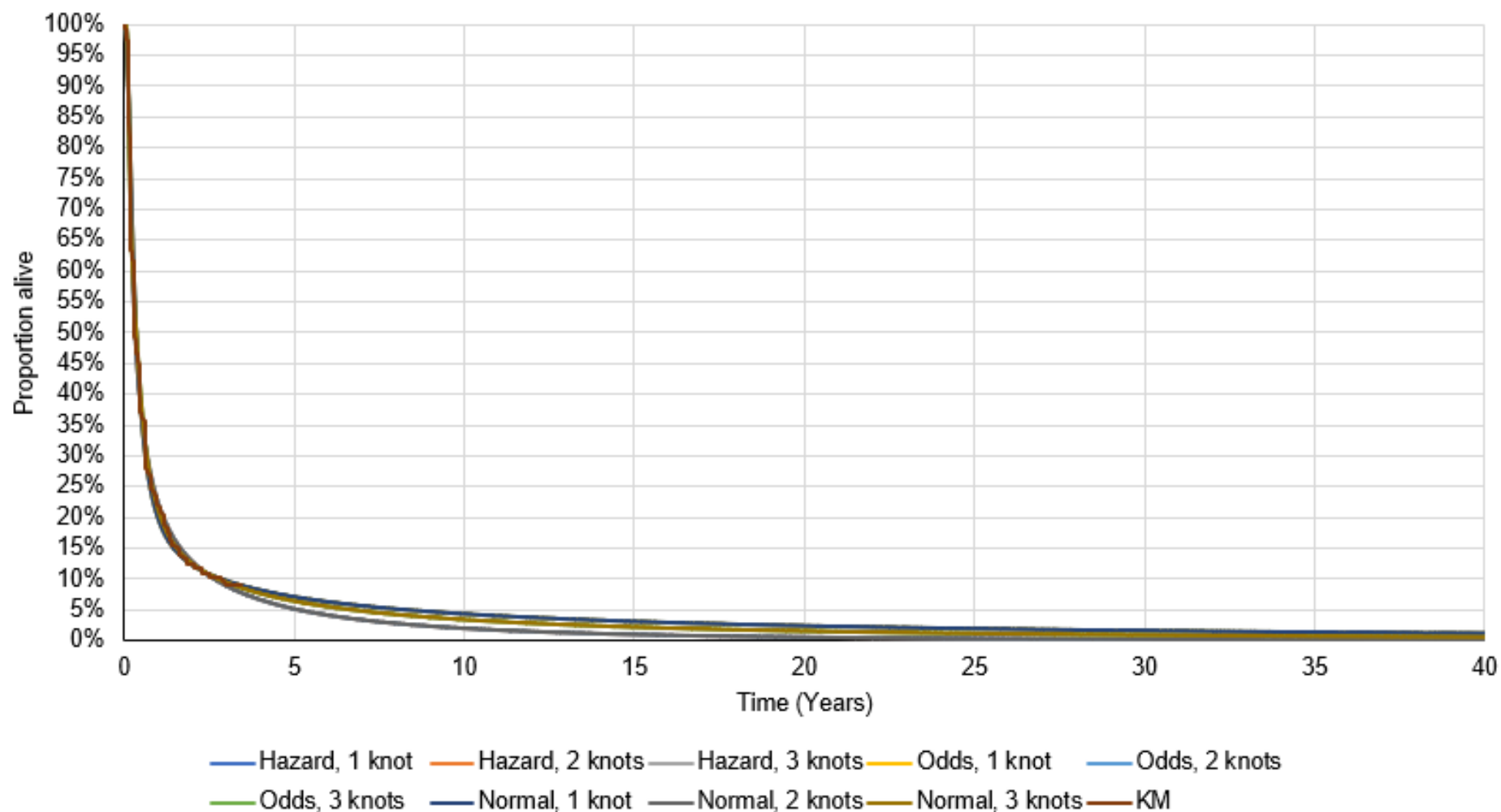
Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Table 41: Landmark proportions progression-free (STRIDE PFS)

Function		1 year	5 years	7 years	10 years	20 years
Kaplan-Meier Curve		21.9%	NA	NA	NA	NA
Hazard	1 knot	19.5%	7.1%	5.7%	4.4%	2.4%
	2 knots	22.1%	5.2%	3.4%	2.0%	0.6%
	3 knots	20.8%	6.5%	4.8%	3.4%	1.6%
Odds	1 knot	19.8%	7.2%	5.9%	4.7%	3.0%
	2 knots	22.2%	5.4%	3.9%	2.8%	1.4%
	3 knots	21.1%	6.6%	5.1%	3.9%	2.3%
Normal	1 knot	20.9%	6.4%	4.8%	3.5%	1.8%
	2 knots	21.5%	5.9%	4.3%	3.0%	1.4%
	3 knots	21.6%	5.8%	4.2%	2.9%	1.3%

Footnotes: PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Figure 38: STRIDE PFS parametric survival function extrapolations



Footnotes: KM: Kaplan-Meier; PFS: progression-free survival; STRIDE: singular tremelimumab regular interval durvalumab.

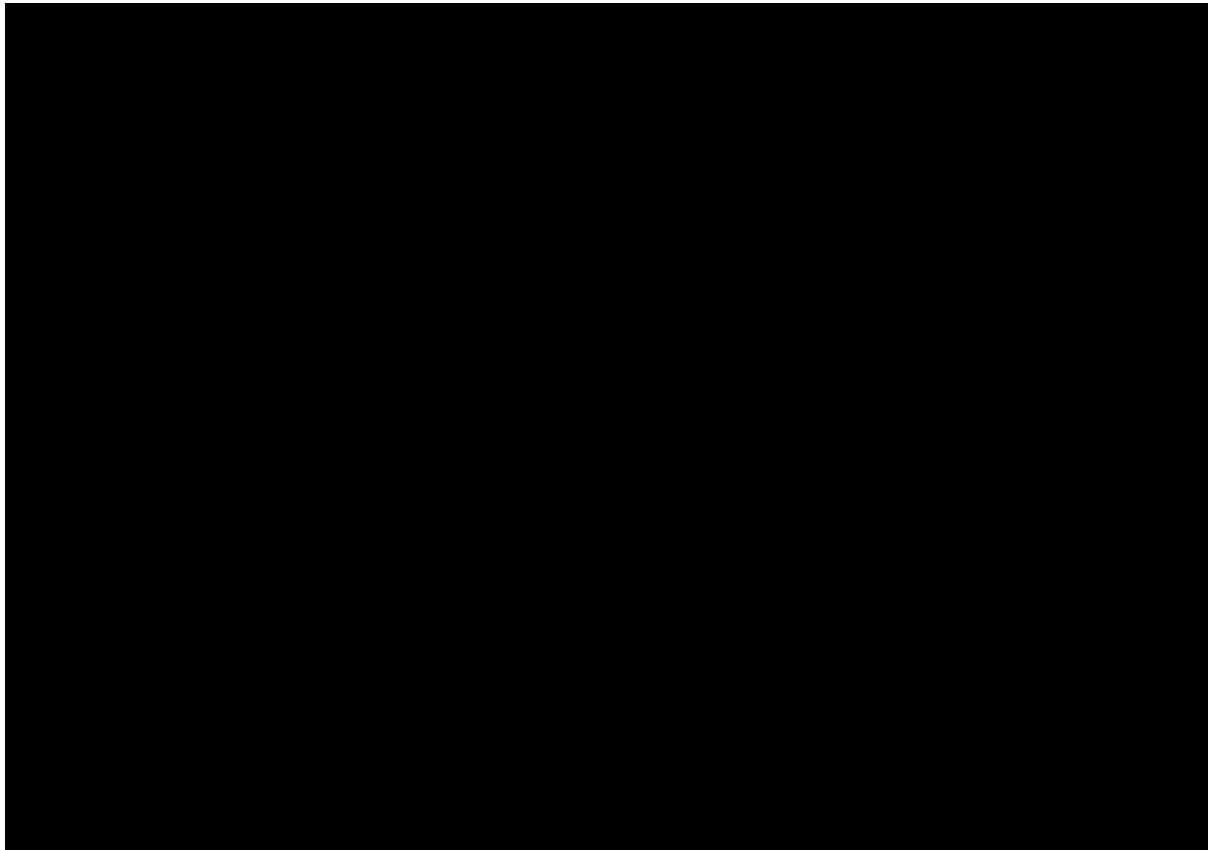
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Observed vs modelled hazard rate

The observed hazard of the STRIDE arm from HIMALAYA was compared with the hazards of spline-based survival models in Error! Reference source not found., Figure 40 and Figure 41 below. [REDACTED]

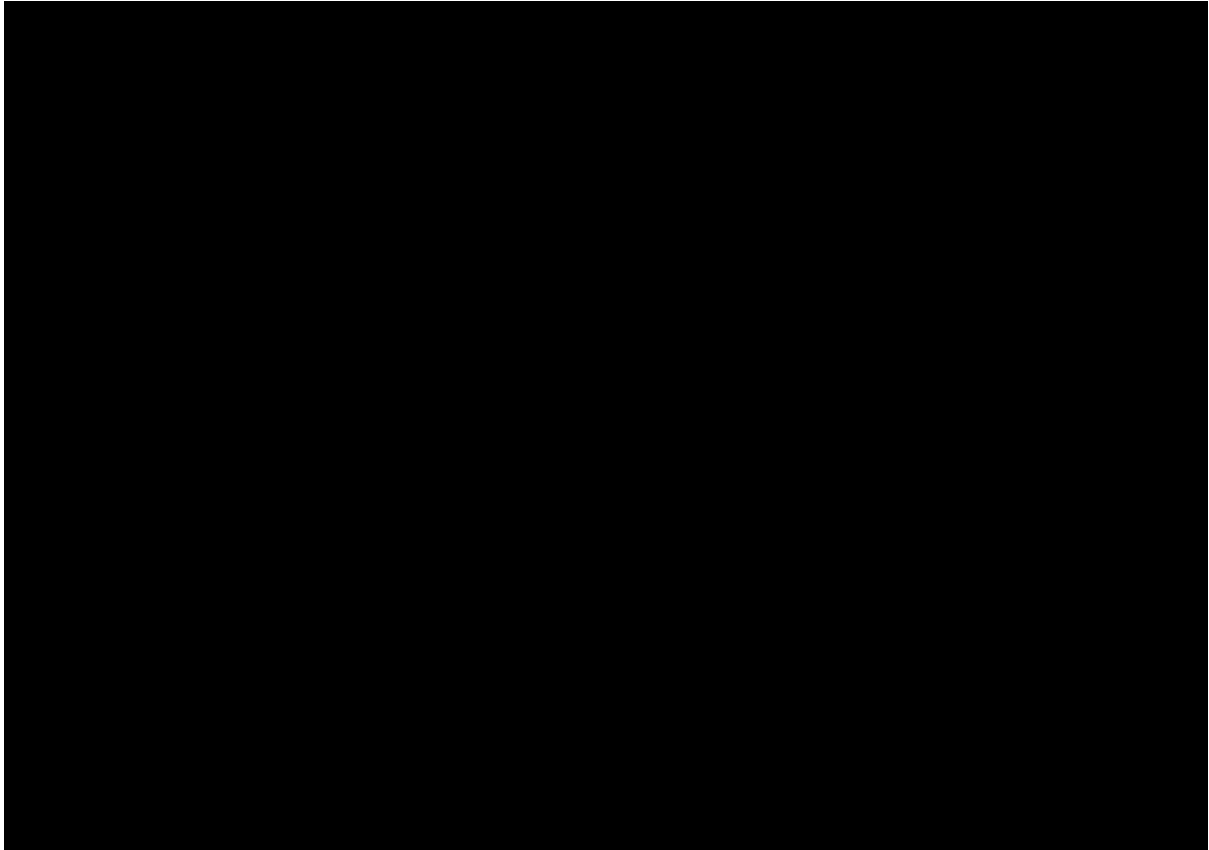
Over the long term, the smoothed hazards show that the hazards decreases over time for all models.

Figure 39 Smoothed hazard plots for PFS for STRIDE (Hazard models)



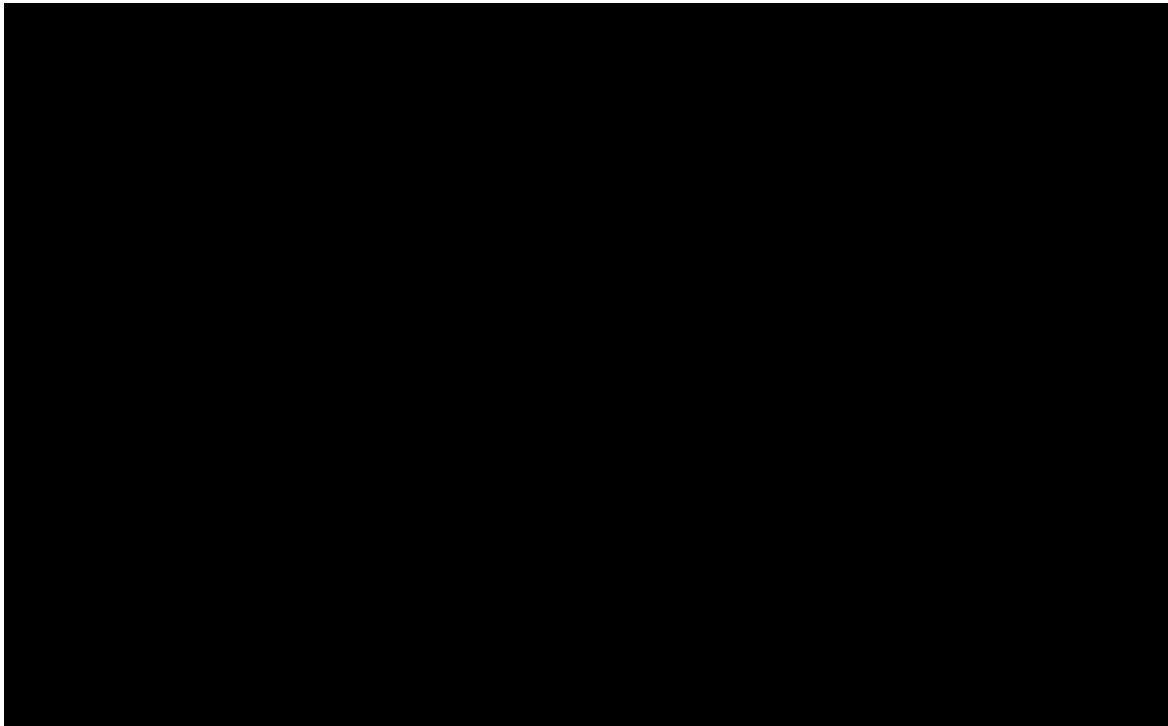
Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TREME 300 + DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE).

Figure 40: Smoothed hazard plots for PFS for STRIDE (Normal models)



Abbreviations: PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Figure 41: Smoothed hazard plots for PFS for STRIDE (Odds models)



Abbreviations: PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

External validation

As described for OS, data were extrapolated to provide long-term estimates for PFS for STRIDE and its comparators. In line with recommendations from NICE TSD 14, clinical feedback was sought from UK-based oncologists on the long-term clinical validity of the modelled parametric survival extrapolations.¹¹⁸

The majority of the clinical experts agreed that the Hazard 3 knot extrapolation was the most appropriate choice for the STRIDE arm, justifying this extrapolation as the most clinically plausible. As the Hazard 3 knot extrapolation was also the best fitting extrapolation according to the model fit statistics and showed a good visual fit to the Kaplan-Meier data from HIMALAYA, it was considered the most robust choice of extrapolation. For completeness, the second best fitting standard model, the generalised gamma, was explored in a scenario analysis.

B.3.3.4.4 Sorafenib

As described above, independent fitting of spline-based models was considered the most appropriate approach to capturing the varying hazards observed in the sorafenib arm of HIMALAYA. As such, the goodness of fit assessment of spline-based models are discussed in the sections that follow, with all information related to fitting of standard models fitted to the sorafenib arm presented in Appendix O for completeness.

Statistical fit of parametric survival functions

The model fit statistics (AIC and BIC) for the parametric survival functions explored for PFS for sorafenib are presented in Table 42. Visual assessment of the parametric survival functions to the Kaplan-Meier data for sorafenib was assessed in Figure 42. Proportions progression-free at various landmarks are provided in Table 43. Extrapolated models are provided in Figure 43.

According to AIC/BIC statistics, the Hazard 1 and 2 knots extrapolations had the best statistical fit to the observed Kaplan-Meier data for the sorafenib treatment arm. This is also reflected in the visual assessment of the fit of function to the observed Kaplan-Meier data.

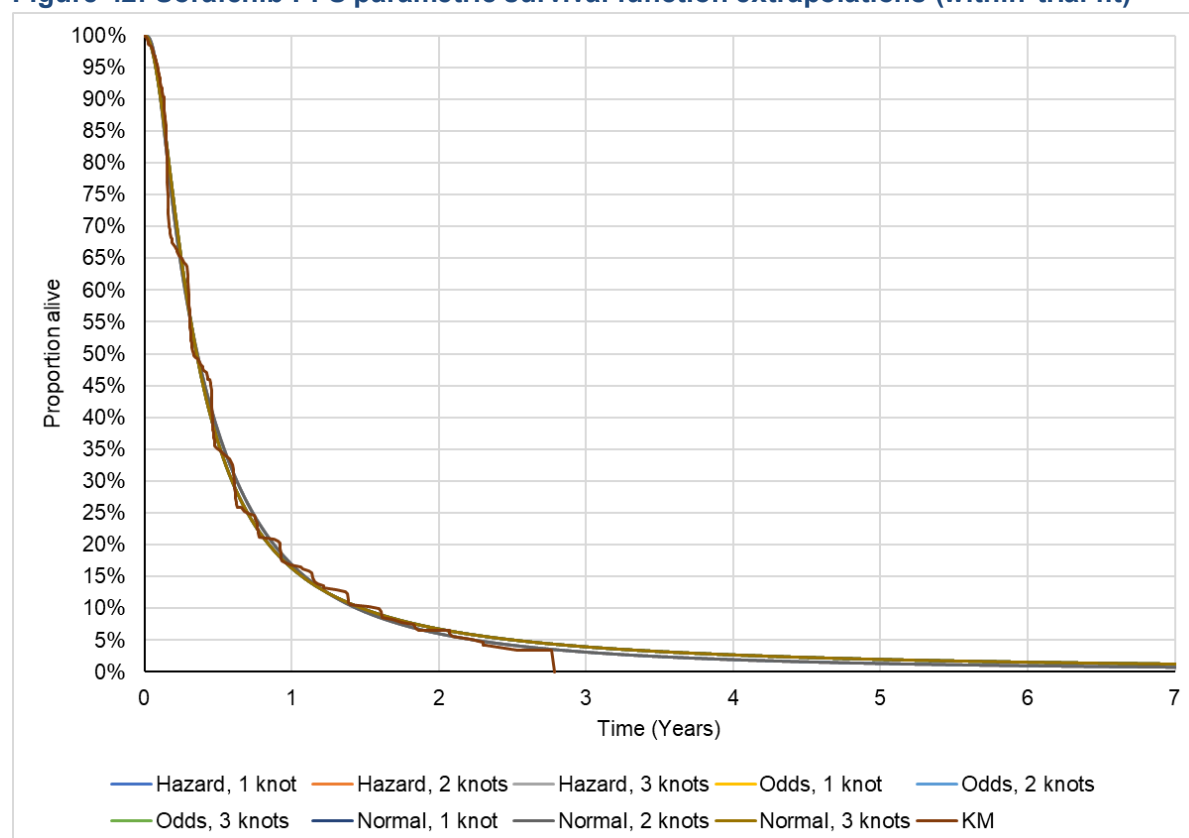
Table 42: Model fit statistics for PFS parametric survival functions for sorafenib

Function		AIC	Rank (AIC)	BIC	Rank (BIC)
Hazard	1 knot	1896.7	4	1908.6	1
	2 knots	1894.7	1	1910.6	4
	3 knots	1896.3	3	1916.1	7
Odds	1 knot	1898.1	6	1910.0	2
	2 knots	1895.0	2	1910.8	5
	3 knots	1897.8	5	1917.6	8
Normal	1 knot	1898.4	7	1910.3	3
	2 knots	1900.0	8	1915.8	6
	3 knots	1901.0	9	1920.8	9

Footnote: The bolded function represents the best-fitting parametric survival function.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 42: Sorafenib PFS parametric survival function extrapolations (within-trial fit)



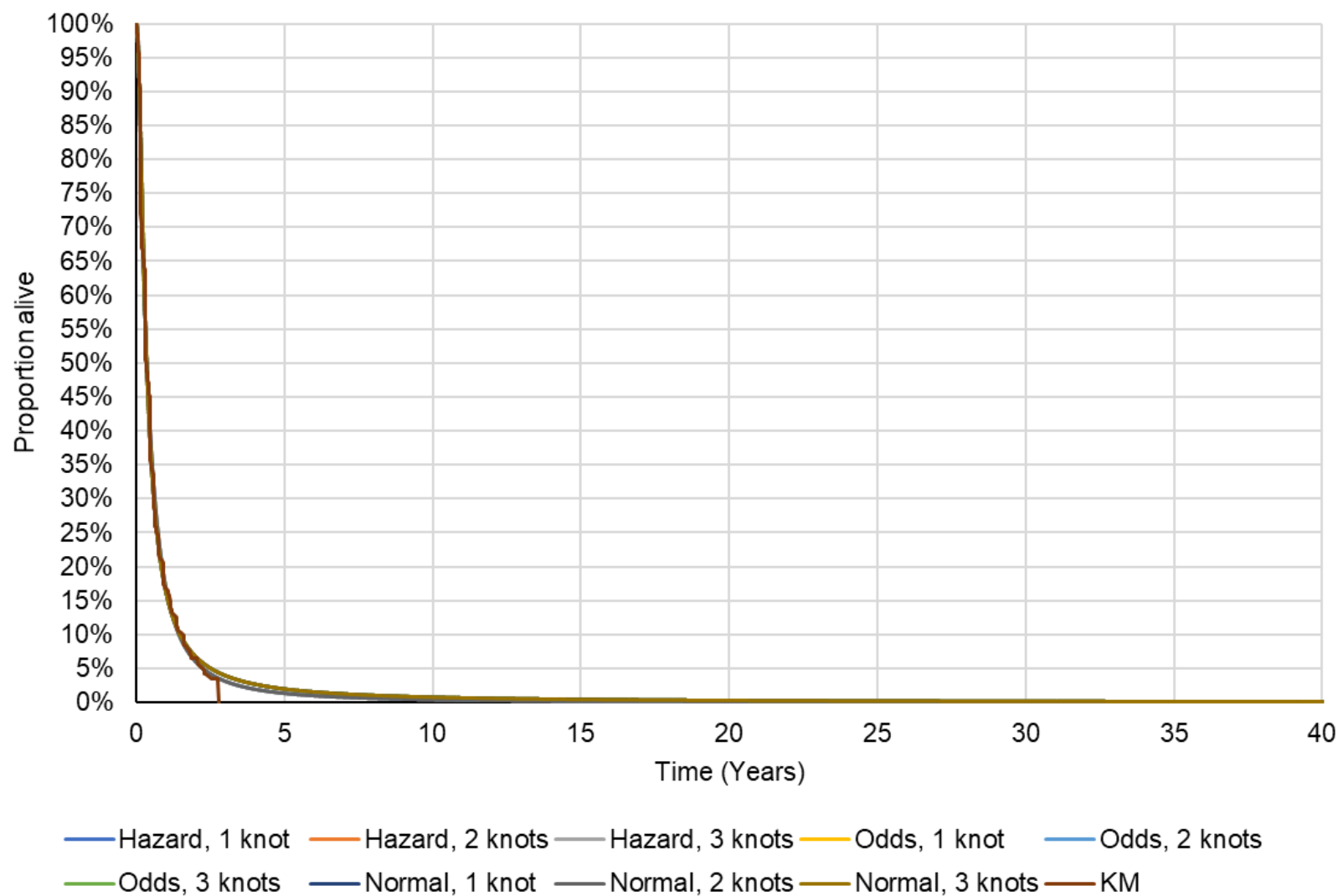
Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Table 43: Landmark proportions progression-free (Sorafenib PFS)

Function		1 year	5 years	7 years	10 years	20 years
Kaplan-Meier Curve		16.5%	NA	NA	NA	NA
Hazard	1 knot	16.2%	1.0%	0.4%	0.1%	0.0%
	2 knots	17.1%	0.6%	0.2%	0.0%	0.0%
	3 knots	16.7%	0.8%	0.3%	0.1%	0.0%
Odds	1 knot	16.0%	2.0%	1.3%	0.8%	0.3%
	2 knots	16.6%	1.3%	0.8%	0.4%	0.1%
	3 knots	16.4%	1.5%	0.8%	0.5%	0.2%
Normal	1 knot	16.8%	0.9%	0.4%	0.1%	0.0%
	2 knots	16.5%	1.1%	0.5%	0.2%	0.0%
	3 knots	16.7%	1.0%	0.4%	0.2%	0.0%

Footnotes: PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Figure 43: Sorafenib PFS parametric survival function extrapolations



Footnotes: KM: Kaplan-Meier; PFS: progression-free survival.

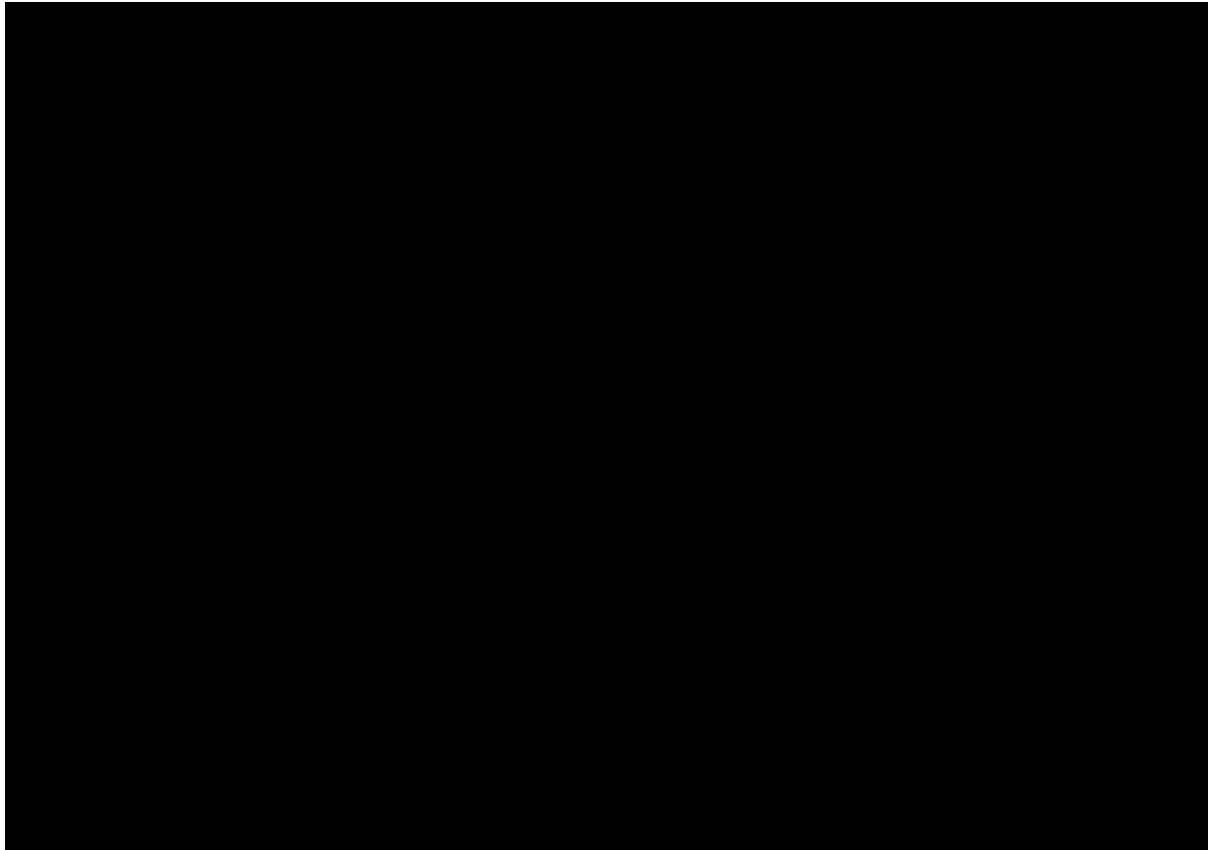
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Observed hazard rate of the treatment arms

The observed hazard of the sorafenib arm from HIMALAYA is displayed in **Error! Reference source not found.**, Figure 45 and Figure 46 below. [REDACTED]

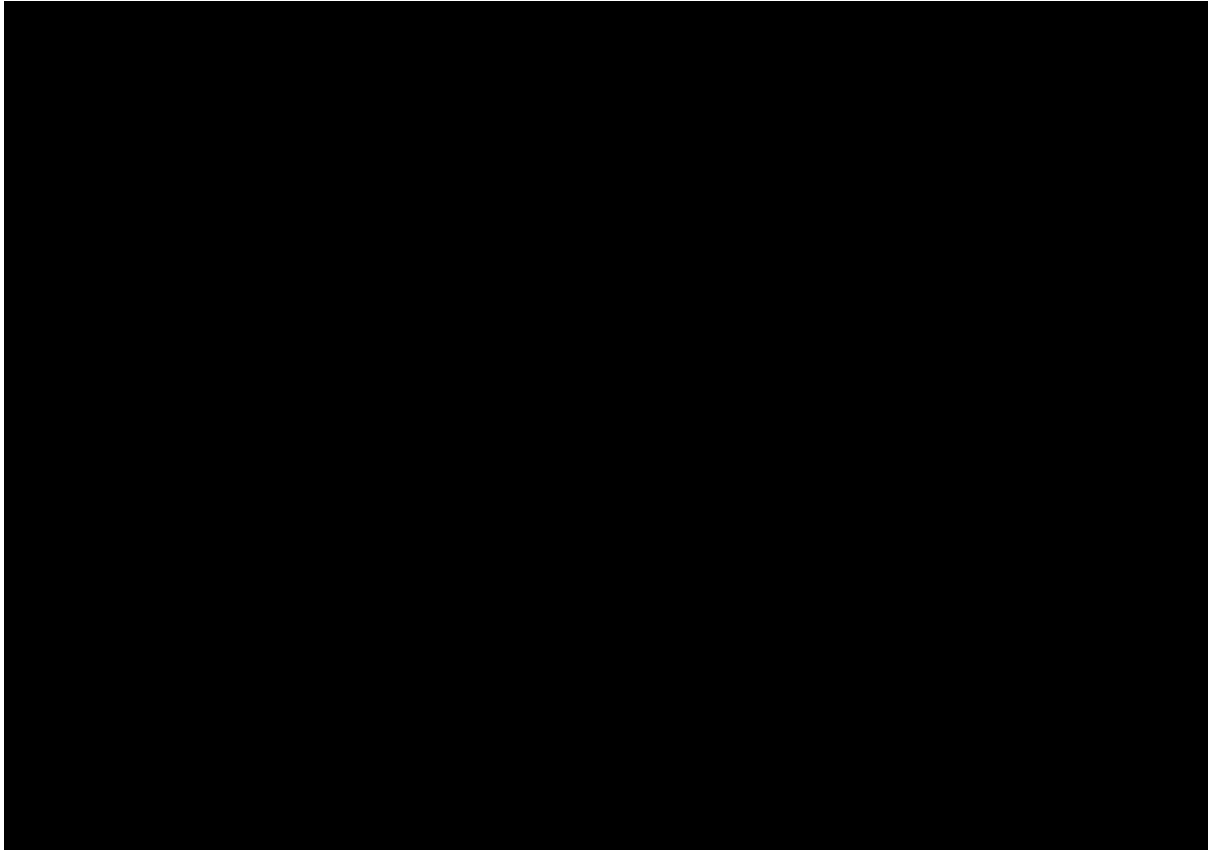
[REDACTED]. Over the long term, the smoothed hazards show that the hazards decreases over time for all models.

Figure 44 Smoothed hazard plots for PFS for sorafenib (Hazard models)



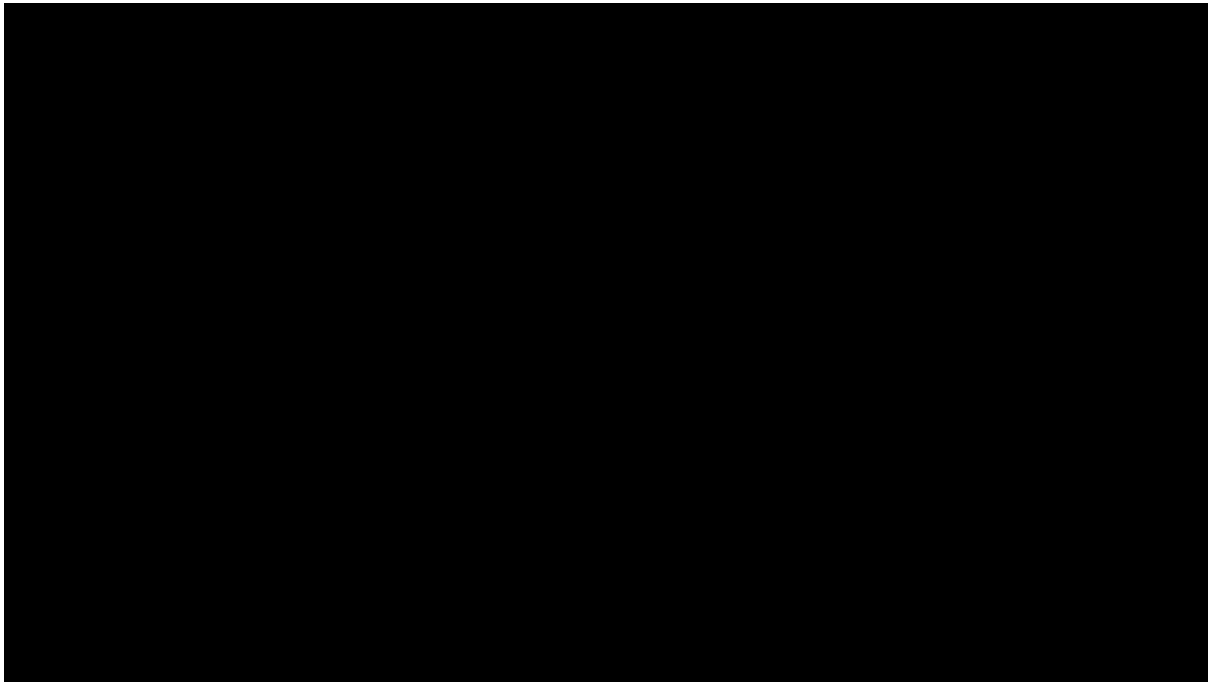
Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; sora: sorafenib.

Figure 45: Smoothed hazard plots for PFS for sorafenib (Normal models)



Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; sora: sorafenib.

Figure 46: Smoothed hazard plots for PFS for sorafenib (Odds models)



Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; sora: sorafenib.

External validation

As described for OS, data were extrapolated to provide long-term estimates for PFS for STRIDE and its comparators. In line with recommendations from NICE TSD 14, clinical feedback was sought from UK-based oncologists on the long-term clinical validity of the modelled parametric survival extrapolations for sorafenib and STRIDE.¹¹⁸ Whilst the hazard 2 knot model (the best fitting spline model by AIC/BIC) specifically was not validated with clinical experts (standard models were presented only), of the extrapolations presented, the clinicians deemed the log-normal to be the most clinically plausible model relative to NHS clinical practice. A comparison of the log-normal and hazard 2 knot model illustrates that the PFS predictions are lower with the log-normal model vs. the hazard 2 knot (5-year landmark: 1.49% vs. 5.2%; 10-year landmark: 0.3% vs. 2.0%).

In order to account for the varying observed hazard in the sorafenib Kaplan-Meier data (Figure 36), the hazard 2 knot model was selected for the base case. This model represented the best fitting model among the spline models assessed. Furthermore, based on the clinical feedback described above, this extrapolation represents a conservative choice as it likely overestimates PFS on sorafenib relative to NHS clinical practice, and as a result likely underestimates the treatment benefit of STRIDE with regards to PFS. For completeness, a scenario analysis using the log-normal curve was conducted.

B.3.3.4.5 Base case parametric extrapolation selections

The base case parametric extrapolation selection was informed by the collective assessment above with the extrapolation choices included in the base case as well as a scenario presented in Table 38.

Table 44: Base case and scenario extrapolation choices

Technologies	PFS extrapolation	
	Base Case	Scenario
STRIDE	Hazard 3 knots	Generalised gamma
Sorafenib	Hazard 2 knots	Log-normal

Abbreviations: PFS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

PFS for atezolizumab + bevacizumab and lenvatinib

In order to inform long-term estimates of PFS for atezolizumab + bevacizumab and lenvatinib within the model, HRs generated by the NMA described in Section B.2.9 were applied to the sorafenib arm extrapolation. The HRs applied are presented in Table 45.

Table 45: PFS HRs applied to sorafenib arm extrapolation

Intervention	HR (95% CrI)
Atezolizumab + bevacizumab	██████████
Lenvatinib	██████████

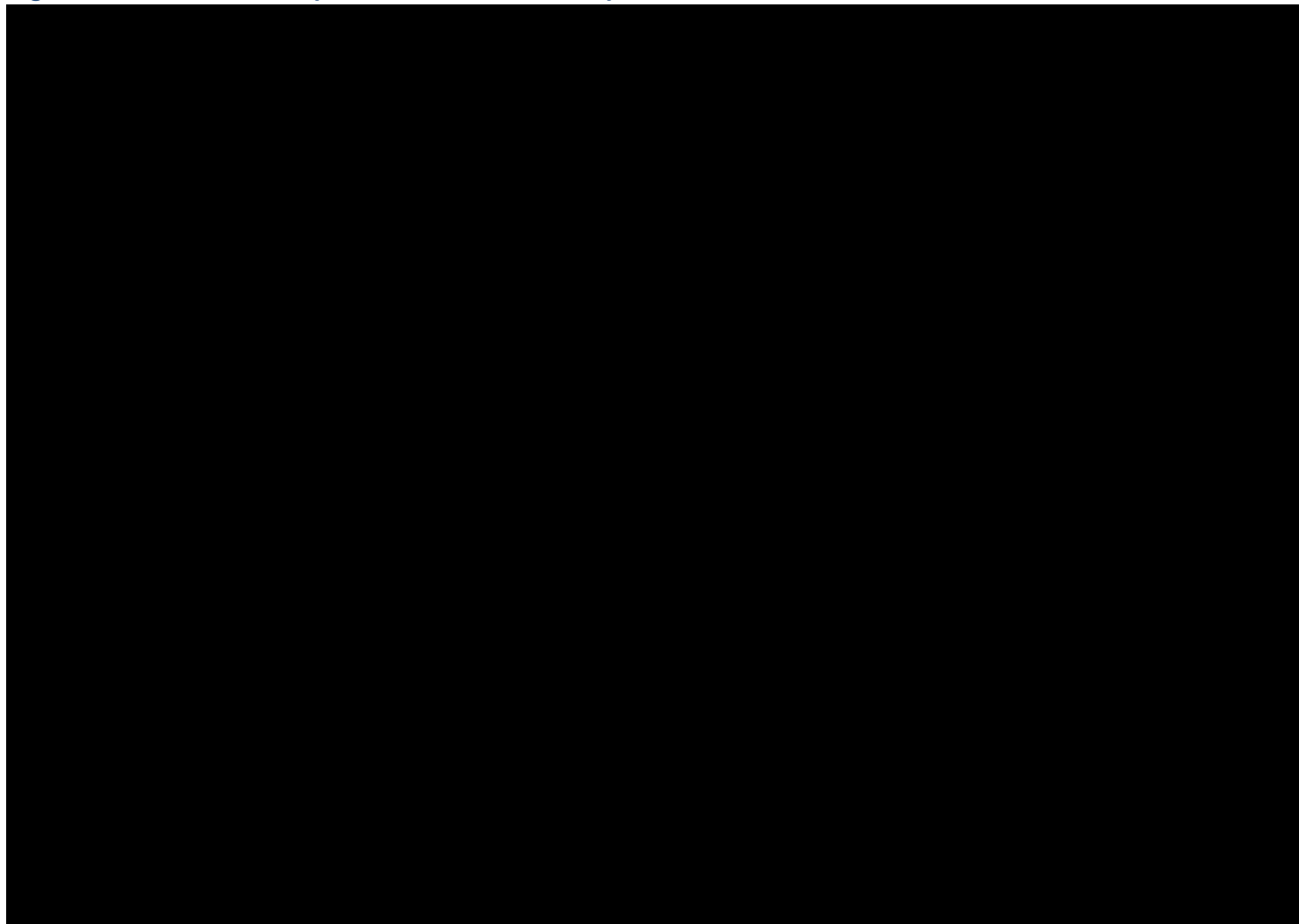
Abbreviations: CrI: credible interval; HR: hazard ratio; PFS: progression free survival.

PFS extrapolations used within the model

The parametric survival extrapolations for PFS selected for the base case are presented in Figure 47 for STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib.

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Figure 47: Base case PFS parametric survival extrapolations for STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib



Footnotes: KM: Kaplan-Meier; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

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B.3.3.5 Time to treatment discontinuation

TTD for STRIDE and sorafenib was modelled consistently with the approach taken for PFS and OS, with parametric survival functions applied to TTD data from the HIMALAYA trial. For STRIDE, only TTD for durvalumab was extrapolated; tremelimumab is administered as a one-off administration and applied as a singular cost at treatment initiation at the start of the model.

In the absence of TTD data from HIMALAYA for atezolizumab + bevacizumab and lenvatinib, TTD for these interventions was assumed to align with their corresponding extrapolations for PFS (as described in Section B.3.3.4). Since atezolizumab + bevacizumab is recommended for use until loss of clinical benefit or unacceptable toxicity, and lenvatinib is recommended for as long as clinical benefit is observed or until unacceptable toxicity, this can be considered a conservative assumption, as patients may receive treatment beyond progression in clinical practice.^{141, 142}

B.3.3.5.1 Assessment of PH assumption – STRIDE vs sorafenib

As per OS and PFS, the PH assessment for the STRIDE and sorafenib TTD outcomes from HIMALAYA was based on IPD from the trial. The formal assessment of the PH assumption, based on the visual inspection of the Kaplan-Meier curves, the log-log plot, the Schoenfeld residuals plot and the Grambsch and Therneau test, found that there was violation of the PH assumption demonstrates that the PH assumption does not hold.¹¹⁴⁻¹¹⁷ Further detail on the PHA for TTD can be found in Appendix D.

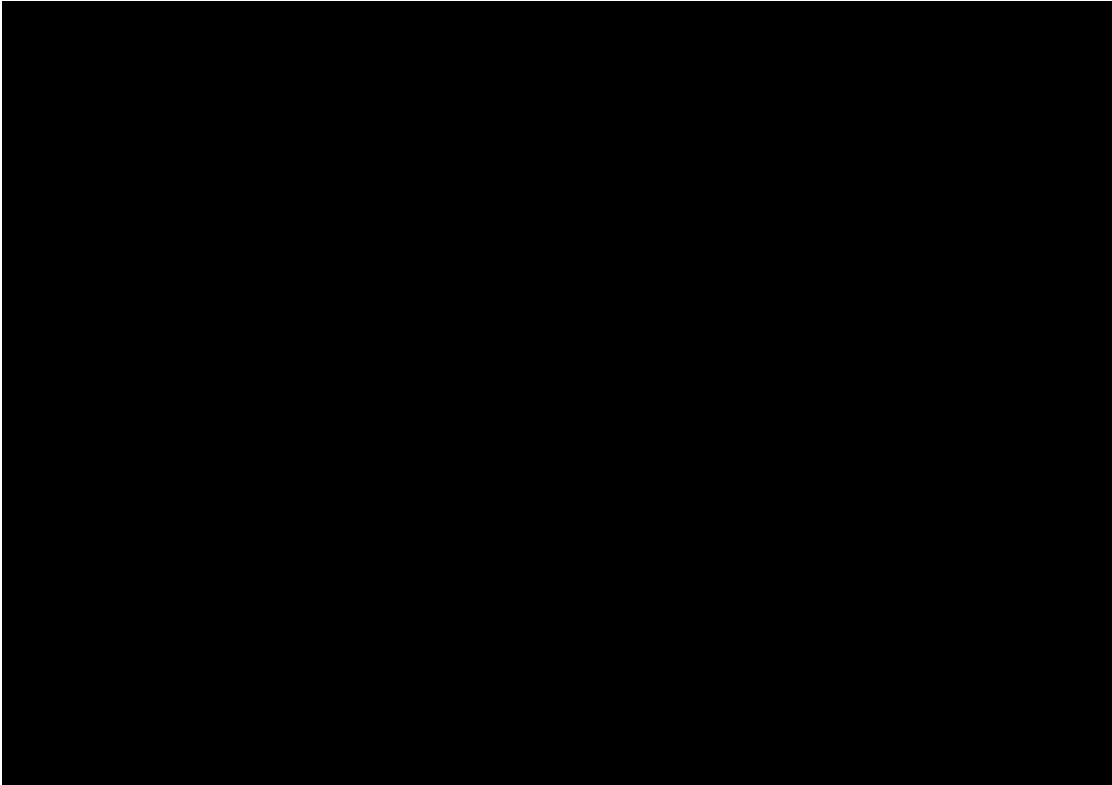
As the PH assumption had been violated, it was considered necessary to explore independently fitted models rather joint-fitting models.

B.3.3.5.2 Assessment of observed trial hazards – STRIDE vs sorafenib

Plots of the observed raw and smoothed hazards were assessed to judge the complexity of observed trial hazards and decide whether more flexible parametric models should be considered alongside the standard parametric models. [Error! Reference source not found.](#)

[REDACTED], standard parametric models were considered sufficiently flexible to model TTD.

Figure 48 Observed raw and smoothed hazards from the HIMALAYA trial



Abbreviations: ITT: intention-to-treat; sora: sorafenib; TREME 300 + DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE); TTD: time to treatment discontinuation.

B.3.3.5.3 STRIDE

As described above, independent fitting of standard-based models was considered the most appropriate approach to capturing TTD for STRIDE.

Statistical fit of parametric survival functions

The model fit statistics (AIC and BIC) for the parametric survival functions explored for TTD for STRIDE are presented in Table 46. Visual assessment of the parametric survival functions to the Kaplan-Meier data for STRIDE was assessed in Figure 49.

According to AIC and BIC statistics, the Weibull survival function had the best fit to the observed Kaplan-Meier data for the STRIDE (durvalumab only) treatment arm (Table 46). This is also reflected in the visual assessment of fit to the observed Kaplan-Meier data for STRIDE (durvalumab only) (Figure 49).

Table 46: Model fit statistics for TTD parametric survival functions for STRIDE

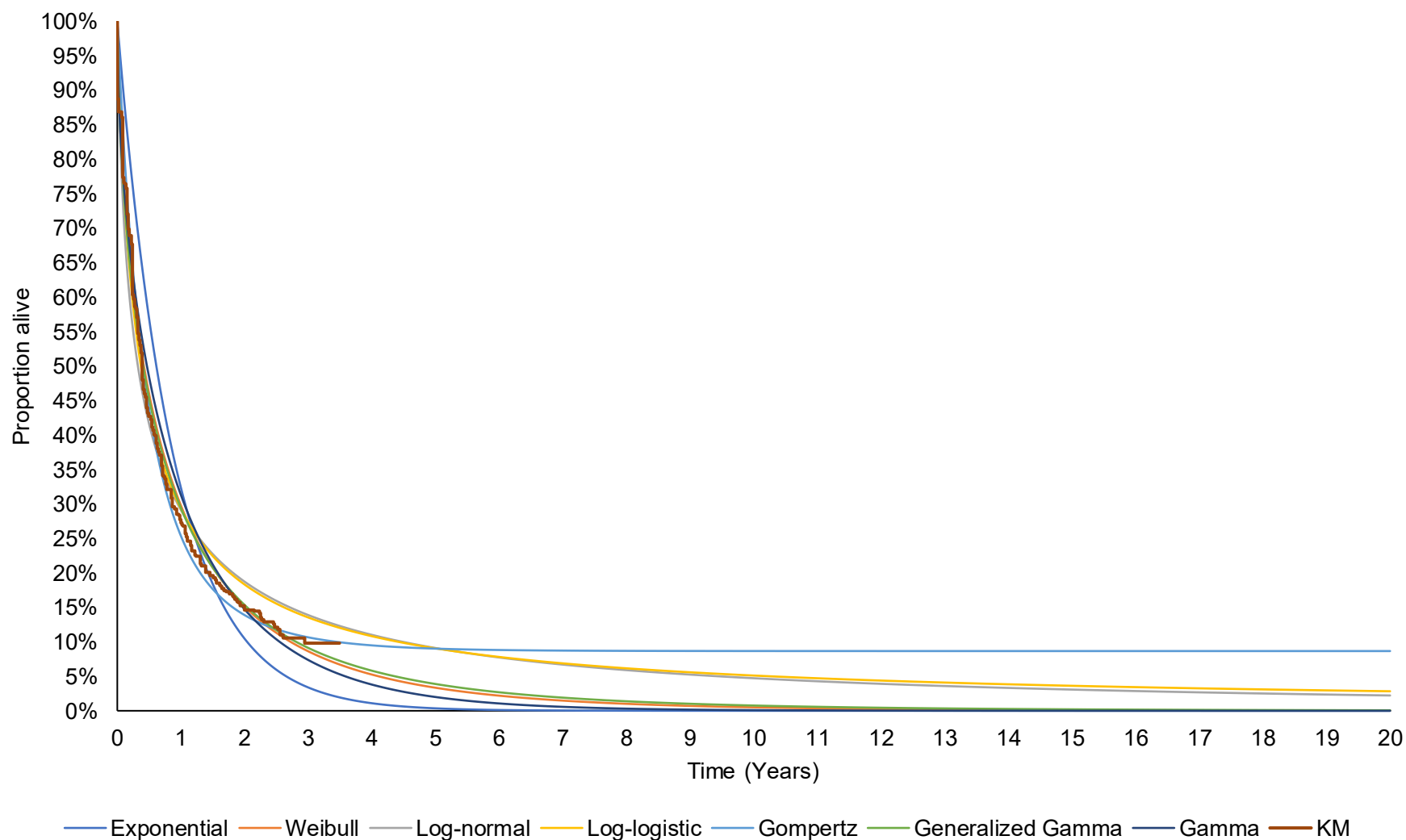
Function	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	2323.3	5	2327.27	5
Weibull	2203.4	1	2211.35	1
Log-normal	2231.53	6	2239.48	6
Log-logistic	2217.7	4	2225.65	4
Gompertz	2233.82	7	2241.77	7
Generalised gamma	2204.7	2	2216.62	2

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Function	AIC	Rank (AIC)	BIC	Rank (BIC)
Gamma	2211.29	3	2219.24	3

Footnote: The bolded function represents the best-fitting parametric survival function that was used in the model.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTD: time to treatment discontinuation.

Figure 49: STRIDE (durvalumab only) TTD parametric survival function extrapolations



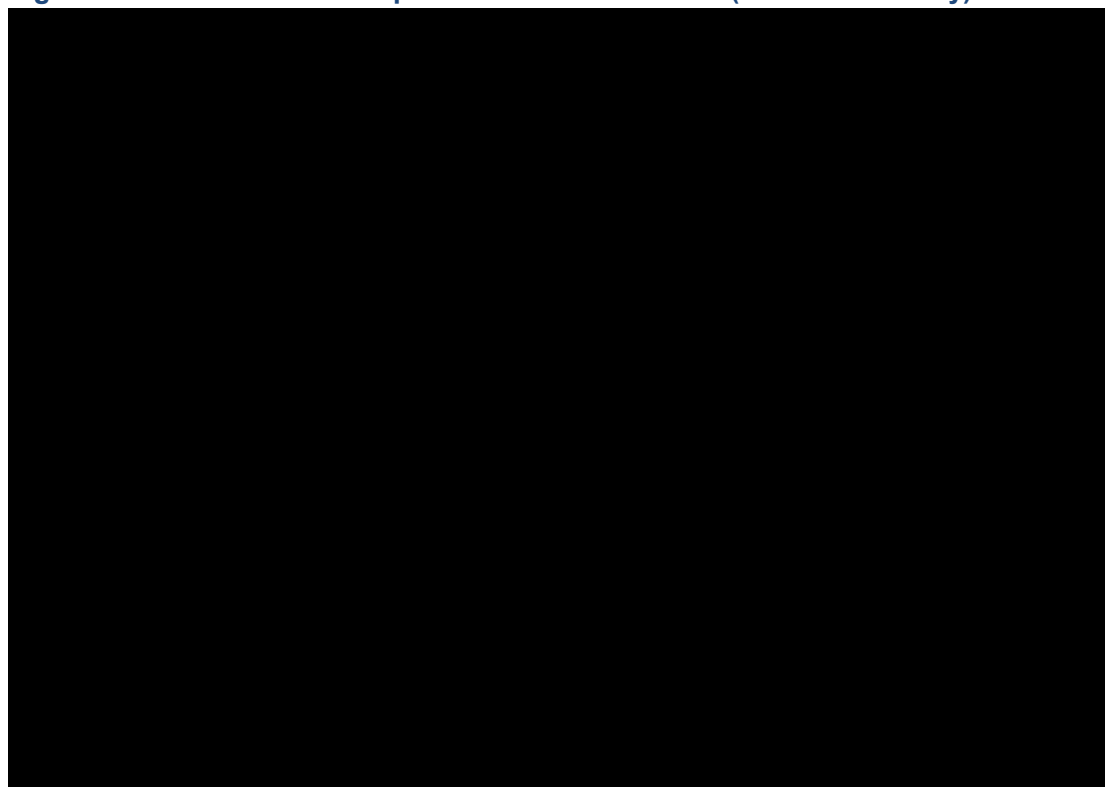
Abbreviations: KM: Kaplan-Meier; STRIDE: singular tremelimumab regular interval durvalumab; TTD: time to treatment discontinuation.

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Observed vs modelled hazard rate

The observed hazard of the STRIDE arm from HIMALAYA (durvalumab only) was compared with the hazard of the standard models in Figure 50. Aligned with the goodness of fit statistics, Weibull and generalised gamma appear to capture [REDACTED].

Figure 50: Smoothed hazard plots for TTD for STRIDE (durvalumab only)



Abbreviations: ITT: intention-to-treat; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TREME 300 DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE); TTD: time to treatment discontinuation.

In line with the AIC/BIC statistics and visual assessment of fit, the Weibull model was selected to model TTD for STRIDE (durvalumab only) in the base case. The second best-fitting curve, the generalised gamma, was selected in a scenario analysis.

B.3.3.5.4 Sorafenib

Sorafenib – Statistical fit of parametric survival functions

The model fit statistics (AIC and BIC) for the parametric survival functions explored for TTD for sorafenib are presented Table 47. Visual assessment of the parametric survival functions to the Kaplan-Meier data for sorafenib was assessed in Figure 51.

According to AIC and BIC statistics, the log-normal survival function had the best fit to the observed Kaplan-Meier data for the sorafenib treatment arm (Table 47). This is also reflected in the visual assessment of the fit of function to the observed Kaplan-Meier data.

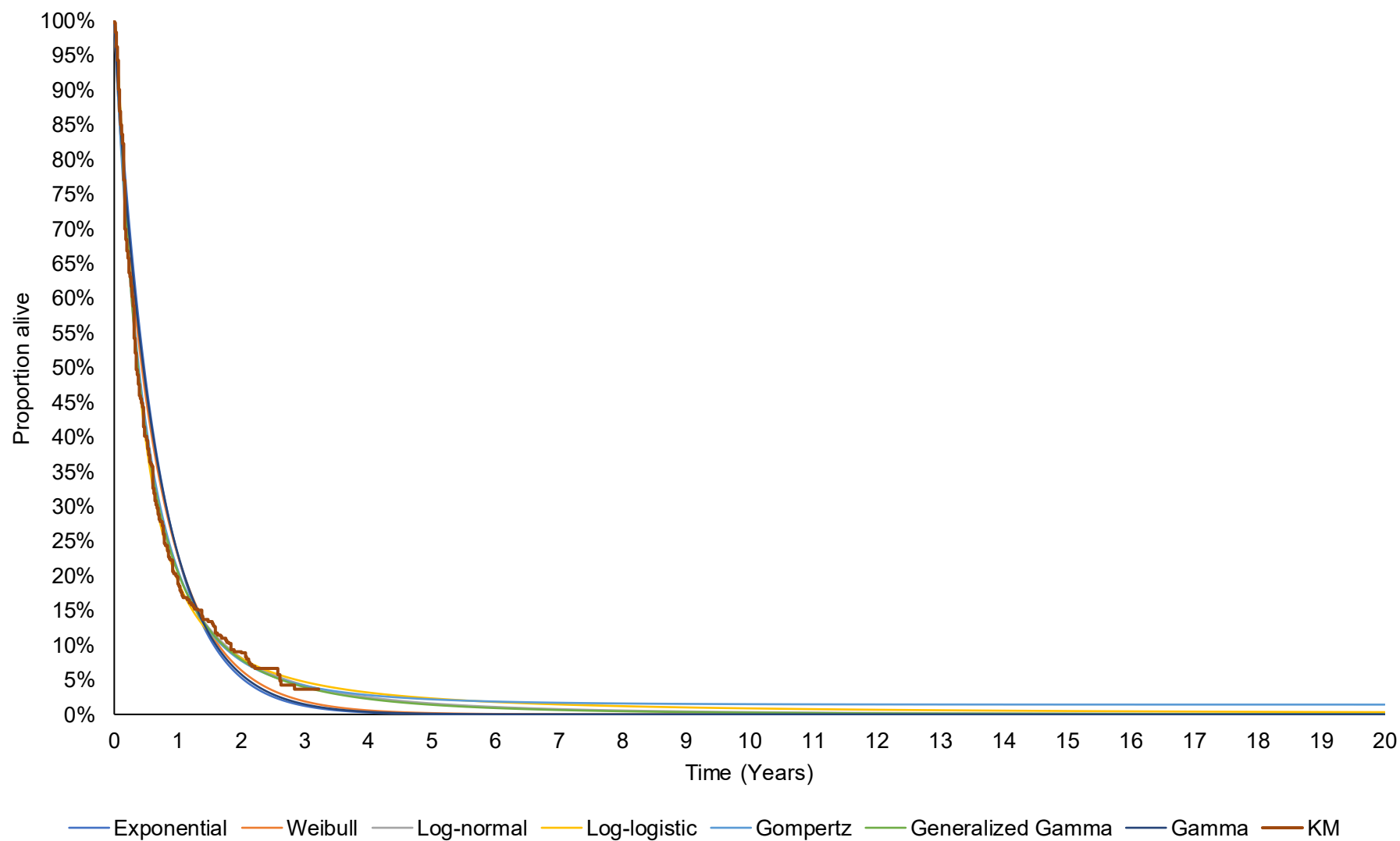
Table 47: Model fit statistics for TTD parametric survival functions for sorafenib

Function	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	2202.92	6	2206.88	6
Weibull	2198.5	5	2206.43	5
Log-normal	2159.57	1	2167.5	1
Log-logistic	2160.65	2	2168.58	2
Gompertz	2178.4	4	2186.33	4
Generalised gamma	2161.31	3	2173.2	3
Gamma	2203.46	7	2211.39	7

Footnote: The bolded function represents the best-fitting parametric survival function that was used in the model.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD; time to treatment discontinuation.

Figure 51: Sorafenib TTD parametric survival function extrapolations



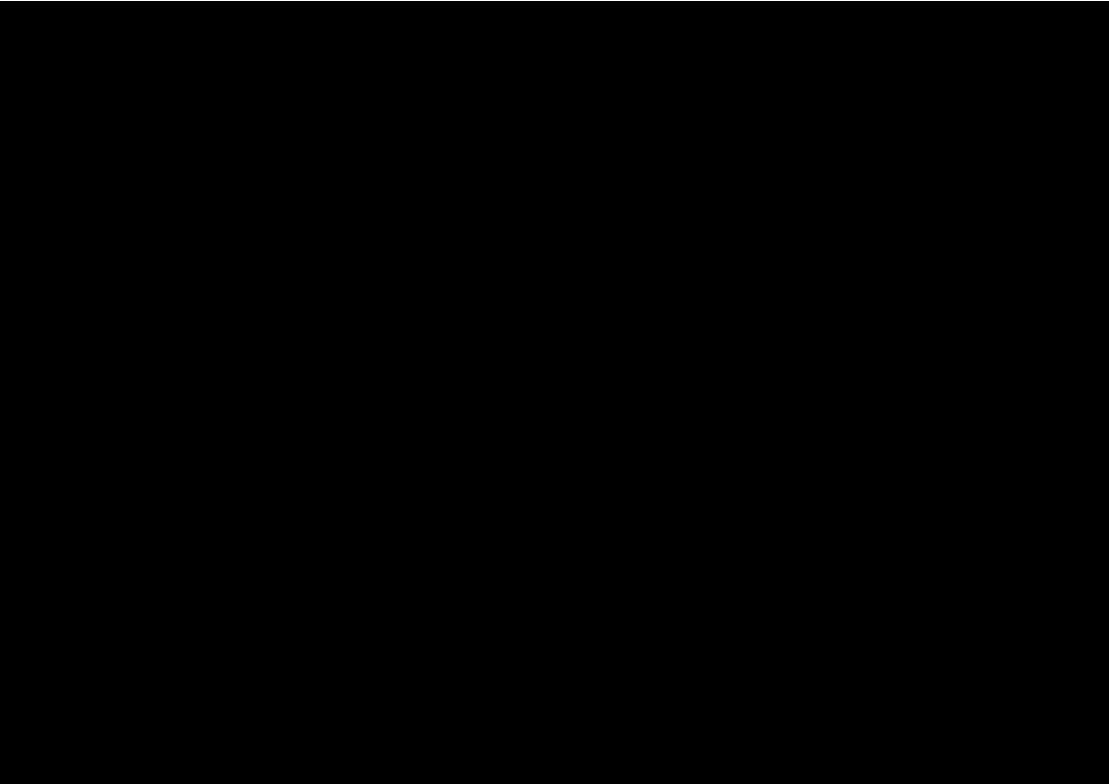
Footnotes: KM: Kaplan-Meier; TTD: time to treatment discontinuation.

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Observed vs modelled hazard rate

The observed hazard of the sorafenib arm from HIMALAYA was compared with the hazard of the standard models in Figure 52. Aligned with the goodness of fit statistics, log-logistic and log-normal appear to [REDACTED].

Figure 52: Smoothed hazard plots for TTD for STRIDE (durvalumab only)



Footnote: ITT: intention-to-treat; sora: sorafenib; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTD: time to treatment discontinuation.

In line with the AIC/BIC statistics and visual assessment of fit, the log-normal model was selected to model TTD for STRIDE (durvalumab only) in the base case. The second best-fitting curve, the log-logistic, was selected in a scenario analysis.

Base case parametric extrapolation selections

The base case parametric extrapolation selection was informed by the assessment above with the extrapolation choices included in the base case as well as a scenario presented in Table 38.

Table 48: Base case and scenario curve choices

Technologies	TTD extrapolation	
	Base case	Scenario
STRIDE	Weibull	Generalised gamma
Sorafenib	Log-normal	Log-logistic

Abbreviations: OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTD: time to treatment discontinuation.

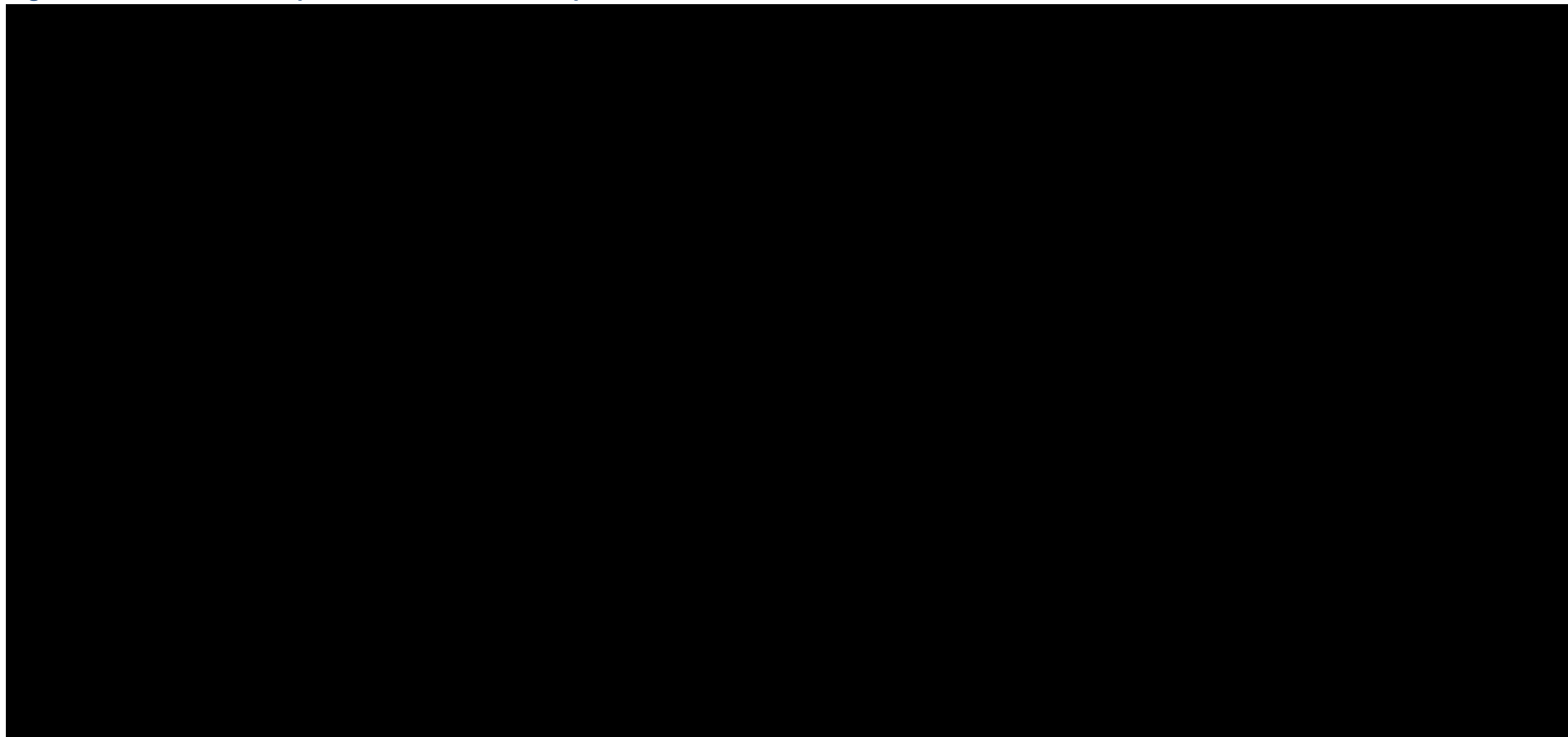
TTD for atezolizumab + bevacizumab and lenvatinib

As mentioned above, in the absence of data regarding TTD for atezolizumab + bevacizumab and lenvatinib and as a simplifying assumption, TTD for these comparators was assumed equal to PFS. Further information on the PFS extrapolations can be found in Section B.3.3.4.

TTD parametric survival extrapolations used within the model

The parametric survival extrapolations for TTD selected for the base case are presented in Figure 53 for STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib.

Figure 53: Base case TTD parametric survival extrapolations for STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib



Abbreviations: KM: Kaplan-Meier; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTD: time to treatment discontinuation.

B.3.3.6 Adverse events

Probabilities of individual AEs for each intervention were based on safety data from the respective clinical trials. All Grade 3+ AEs that occurred in $\geq 5\%$ of the patients within the relevant treatment arms in the HIMALAYA, IMbrave150 and REFLECT clinical trials were included.^{4, 73, 143, 144} The incidence of these AEs is presented in Table 49. The costs and disutilities applied to each AE can be found in Section B.3.5.3 and Section B.3.4.4, respectively.

Table 49: Incidence of Grade 3+ adverse events for STRIDE and relevant comparators

Adverse event; n (%)	STRIDE (HIMALAYA) N=388	Atezolizumab + bevacizumab (IMbrave150) N=329	Sorafenib (HIMALAYA) N=374	Lenvatinib (REFLECT) N=476
Aspartate aminotransferase increased	20 (5.2)	14 (4.3)	12 (3.2)	24 (5.0)
Blood bilirubin increased	3 (0.8)	2 (0.6)	8 (2.1)	31 (6.5)
Gamma-glutamyl transferase increased	8 (2.1)	4 (1.2)	7 (1.9)	26 (5.5)
Hypertension	7 (1.8)	34 (10.3)	23 (6.2)	111 (23.3)
Lipase increased	24 (6.2)	0 (0.0)	11 (2.9)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	0 (0.0)	0 (0.0)	34 (9.1)	14 (2.9)
Platelet count decreased	████	8 (2.4)	████	26 (5.5)
Proteinuria	████	9 (2.7)	████	<u>27 (5.7)</u>
Weight decreased	████	0 (0.0)	████	36 (7.6)

Abbreviations: STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Abou-Alfa et al. 2022.⁴ (Table 4, pg10); NICE TA666 2020.¹⁰ (Table 27, pg60); NICE TA551 2018.⁸ (Table 23, pg109); AstraZeneca Data on File: HIMALAYA CSR, Jan 2022.⁸⁹ (Table 14.3.2.7, Slide 37)

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Within the HIMALAYA trial, data were collected using two PRO measures: EORTC QLQ-C30 and EORTC QLQ-HCC18. EQ-5D-5L and EQ-VAS data were also reported as exploratory endpoints. HRQoL results from HIMALAYA are presented in Section B.2.6.3.

B.3.4.2 Mapping

No mapping methods were employed as part of this cost-effectiveness analysis given the availability of the EQ-5D data from the HIMALAYA trial, which aligns with NICE's preference.¹³² As EQ-5D-5L data were collected within the trial, these values were cross-walked to EQ-5D-3L; this is further described in Section B.3.4.5.

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B.3.4.3 Health-related quality-of-life studies

As described in a SLR was conducted to identify relevant economic, cost and healthcare resource use and HRQoL studies in adults with advanced or unresectable HCC. The original SLR was conducted in May 2020, and subsequently updated in September 2021 and June 2024.

An overview of the SLR methodology and results can be found in Appendix H. In total, 49 studies across 58 publications were identified across the original SLR and two updates, with 2 HRQoL studies identified in the latest update. However, as EQ-5D data were available from the HIMALAYA trial, representing data directly relevant to the patient population under consideration in this submission, these data were used to inform the economic model.

B.3.4.4 Adverse reactions

Given that treatment dependent utilities were applied in the model, separate disutilities associated with individual AEs were not applied in the base case.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Within the model, utility values were applied based on the treatments patients received.

EQ-5D-5L utility data were collected in the HIMALAYA trial (FAS; DCO: 27th August 2021). Utility values were derived using a mixed model for repeated measures (MMRM) analysis of all the post-baseline scores for each visit to estimate the statistical relationship between utilities and treatment (base case) and separately, utilities and health state (scenario).¹⁴⁵ This method accounts for the autocorrelation in utility score within each patient and is appropriate when handling data that are missing at random. Notably, a random intercept model assuming independent within-subject errors was fitted to account for the subject variability.

In the model, utilities were treatment-dependent, and it was assumed that atezolizumab + bevacizumab would have the same utility value as STRIDE, and lenvatinib would have the same utility value as sorafenib. This approach was adopted as it was considered to be the most robust way of capturing the impact of adverse events due to TKIs on patients, as evidenced in IMbrave150 and HIMALAYA, and a systematic review and meta-analysis of systemic therapies for advanced HCC which shows that patients treated with TKIs are almost twice as likely as those treated with immune checkpoint inhibitors to experience an adverse event that is Grade 3 or higher (69% vs. 35%).^{45, 146}

The EQ-5D-5L health utility value sets from the HIMALAYA trial were cross-walked to the EQ-5D-3L using the algorithm described in Hernández-Alava et al., as recommended by NICE.^{99, 130} Utility values in the model were age-adjusted using the age- and sex-matched general population utility values reported in Hernández-Alava et al. Age-adjustment of utility values was performed multiplicatively with the multiplier equal to one in the first cycle and gradually decreasing over time.¹¹⁹

The base case utility values based on the treatment model are provided in Table 50.

Table 50: Summary of utility values for cost-effectiveness analysis (base case)

Treatment	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
Utility values				

Abbreviations: STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

As described in Section B.3.2.2, the perspective on costs was that of the NHS and PSS, in line with the NICE reference case with costs sourced from NHS Reference Costs, PSSRU, the BNF and eMIT.^{8-10, 133} The cost categories considered in the model included:

- Drug acquisition costs
- Drug administration costs
- Subsequent treatment costs
- Health state resource use costs
- AE costs
- End-of-life costs

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition

The drug acquisition costs for STRIDE were provided by AstraZeneca, while comparator costs were based on list prices sourced from the BNF.^{133, 136} A confidential PAS discount for durvalumab was included in the model.

Comparator drugs (atezolizumab + bevacizumab, sorafenib, and lenvatinib) also have confidential PAS discounts (Section B.1.2), but as these discounts are not disclosed, list prices of the comparator treatments were used in the analyses (Table 51). First-line treatment costs (acquisition and administration) were applied in the cycle the treatment was received in.

For treatments with multiple pack options, the pack with the lowest cost per mg was used. For weight-based treatments, a method of moments - a statistical technique for estimating population parameters by equating sample moments to population moments - was applied to calculate the average number of vials received per administration.

Table 51: Treatment pack costs

Treatment	Available form	Pack size	Total mg per pack	Cost per pack
Durvalumab	50 mg/ml; 2.4 ml (vial)	1	120 mg	List: £592.00
Durvalumab	50 mg/ml; 10 ml (vial)	1	500 mg	List: £2,466.00

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Treatment	Available form	Pack size	Total mg per pack	Cost per pack
Tremelimumab ^a	20 mg/ml; 15 ml (vial)	1	300 mg	List: £20,610.00
Sorafenib	200 mg (per tablet)	112	22,400 mg	£552.40
Lenvatinib	10 mg (per capsule)	30	300 mg	£1,437.00
Atezolizumab	60 mg/ml; 20 ml (vial)	1	1,200 mg	£3,807.69
Bevacizumab	25 mg/ml; 4 ml (vial)	1	100 mg	£205.00
Bevacizumab	25 mg/ml; 16 ml (vial)	1	400 mg	£810.00

Footnote:

Source: AstraZeneca 2024; BNF 2024;¹³⁶ eMIT 2023.¹³³

Abbreviations: PAS: patient access scheme.

In the base case, drug wastage was assumed, meaning that the doses are rounded up to the full vial to account for wasted amounts of drug. Vial sharing was explored in a scenario analysis, in which the cost per mg of each treatment was multiplied by the exact dose in a cycle to derive acquisition costs.

Relative dose intensity (RDI) was set to 100% in the base case. In a scenario analysis, the RDI reported for each treatment was applied within the model using the percentages detailed in Table 52. For STRIDE and sorafenib, RDI was taken from the HIMALAYA trial.⁸⁹ For atezolizumab + bevacizumab and lenvatinib, RDI assumptions accepted within the TA666 evaluation were used.¹⁰

Table 52: RDI values used within the model in scenario analysis

Regimen	Treatment name	RDI	Source
STRIDE	Durvalumab	97.7%	HIMALAYA CSR ⁸⁹
	Tremelimumab	100.0%	HIMALAYA CSR ⁸⁹
Atezolizumab + bevacizumab	Atezolizumab	95.1%	TA666 ¹⁰
	Bevacizumab	93.3%	TA666 ¹⁰
Sorafenib	Sorafenib	78.3%	HIMALAYA CSR ⁸⁹
Lenvatinib	Lenvatinib	88.0%	TA666 ¹⁰

Abbreviations: CSR: clinical study report; RDI: relative dose intensity; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TA: technology appraisal.

Drug administration costs

As described in Section B.1.2, tremelimumab is administered as a priming single dose in combination with durvalumab at Cycle 1/Day 1. This is followed by durvalumab monotherapy Q4W. Both treatments are administered as separate IV infusions. Initial IV administration costs were therefore applied to the first doses for durvalumab and tremelimumab, with a subsequent IV administration cost applied for each subsequent administration of durvalumab monotherapy Q4W.^{1, 6} For the comparators, atezolizumab + bevacizumab is administered via IV infusion Q3W, sorafenib is administered orally BID, and lenvatinib is administered orally once daily, with

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administration costs applied accordingly.⁸⁻¹⁰ The dosing schedule for each treatment is provided in Table 53.

Table 53: Dosing schedules

Regimen	Treatment name	Prescribed dose	Dose per administration	Frequency	Administration method
STRIDE	Durvalumab	1500 mg	1500 mg	Q4W	IV
	Tremelimumab	300 mg	300 mg	One dose only	IV
Atezolizumab + bevacizumab	Atezolizumab	1200 mg	1200 mg	Q3W	IV
	Bevacizumab	15 mg/kg	1050 mg	Q3W	IV
Sorafenib	Sorafenib	400 mg	400 mg	Twice daily	Oral
Lenvatinib	Lenvatinib	12 mg	12 mg	Once daily	Oral

Abbreviations: IV: intravenous; Q3W: every three weeks; Q4W: every four weeks; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

The drug administration unit costs for IV drug infusion and oral administration are sourced from the NHS Reference Costs 2021/22 and are detailed in Table 54.^{10, 128}

Table 54: Drug administration costs

Method	Cost (2021/2022)	Source
First IV administration	£207.59	NHS Reference Costs 2021/22 (SB12Z, Chemotherapy, Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient)
Subsequent IV administration	£326.46	NHS Reference Costs 2021/22 (SB15Z, Chemotherapy, Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient)
Oral	£197.46	NHS Reference Costs 2021/22 (SB11Z, Chemotherapy, Deliver Exclusively Oral Chemotherapy, Outpatient)

Abbreviations: IV: intravenous; NHS: National Health Service.

Source: NHS Reference Costs 2021/22.¹²⁸ (SB12Z, SB15Z, SB14Z)¹⁰

Subsequent treatment costs

In the HIMALAYA trial, ■■■ of patients received a disease-related anticancer treatment after discontinuing treatment with STRIDE, and ■■■ after discontinuing treatment with sorafenib.⁴⁵ Whilst some of the subsequent treatments received are commonly used in UK clinical practice (e.g., regorafenib), there were also treatments not routinely used in the UK (e.g. ■■■ of patients received an IO after discontinuation from sorafenib, including ■■■ who received nivolumab).⁶⁴ Therefore, in order to align with UK clinical practice, the subsequent treatments within the model were informed by NICE recommendations and clinical expert feedback.^{7-9, 64}

The distribution of patients progressing to each subsequent treatment, based on the first-line therapy they received, are provided in Table 55. These distributions represent treatments received in the second-line only, as only a small proportion of patients receive third-line treatment for advanced or unresectable HCC as a result of the short disease prognosis and reducing fitness to receive active therapy with each treatment line. It was assumed that the distribution of Company evidence submission for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

subsequent treatments received by patients who received STRIDE and atezolizumab + bevacizumab arms in the first-line would be equivalent. Subsequent treatments available for patients who receive lenvatinib at first-line are limited; as such, it is assumed that a small proportion of patients receive off-label treatments due to the lack of further treatment options.

Table 55: Subsequent treatment distribution

Subsequent treatment	Primary treatment, %			
	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
BSC	■	■	■	■
Cabozantinib	■	■	■	■
Lenvatinib	■	■	■	■
Regorafenib	■	■	■	■
Sorafenib	■	■	■	■

Abbreviations: BSC: best supportive care; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

The costs of these subsequent treatments are modelled as an average of costs weighted by the distribution in Table 55, and then applied as a one-off treatment cost upon discontinuation of first-line treatment. Duration of therapy was based on the median progression-free survival reported in the most relevant clinical trial identified for the treatment given the setting (Table 56). Costs were based on list prices from the BNF or eMIT.^{133, 136}

Table 56: Subsequent treatment costs

Subsequent treatment	Drug cost per administration	Drug cost source	Admin cost per administration	Admin cost source	Dose schedule	Total drug cost	Total admin cost	Duration of therapy	Total one-off cost
BSC	NA	NA	NA	NA	NA	£0.00	£0.00	NA	£0.00
Cabozantinib	£171.43	BNF 2024 (Cabometyx 20mg tablets - Ipsen Plc)	£6.92	NHS Reference Costs 2021/22 (SB11Z, Chemotherapy, Deliver Exclusively Oral Chemotherapy)	60 mg QD ¹⁴⁷	£27,133.61	£1,095.22	5.2 months ¹⁴⁸	£28,228.83
Lenvatinib	£57.48	BNF 2024 (Lenvima 10 mg capsules - Eisai Ltd)	£6.92	NHS Reference Costs 2021/22 (SB11Z, Chemotherapy, Deliver Exclusively Oral Chemotherapy)	12 mg QD	£12,946.65	£1,558.58	7.4 months ⁷³	£14,505.23
Regorafenib	£178.29	BNF 2024 (Stivarga 40mg tablets - Bayer Plc)	£2.35	NHS Reference Costs 2021/22 (SB11Z, Chemotherapy, Deliver Exclusively Oral Chemotherapy)	160 mg once daily, for 21 of 28 day cycle ¹⁴⁷	£13,023.77	£171.53	3.2 months ¹⁴⁹	£13,195.30
Sorafenib	£9.86	eMIT 2023	£1.76	NHS Reference Costs 2021/22 (SB11Z, Chemotherapy, Deliver Exclusively Oral Chemotherapy)	400 mg BID	£2,462.00	£439.55	4.1 months ⁷¹	£2,901.56

Footnotes: BID: twice per day; BNF: British National Formulary; BSC: best supportive care; eMIT: electronic Market Information Tool; NA: not applicable; NHS: National Health Service; QD: once daily; SmPC: Summary of Product Characteristics; assumed same as primary treatment

Source: BNF 2024;¹³⁶ eMIT 2023;¹³³ NHS Reference Costs 2021/22 (SB11Z, SB12Z);¹³⁵ Rimassa and Wörns (2020).¹⁴⁷

B.3.5.2 Health state unit costs and resource use

The proportion of patients receiving each healthcare resource use item by treatment and health state are provided in Table 57 and the frequency per week are presented in Table 58. The proportion multiplied by the frequency is presented in Table 59, and this forms the model input. Uncertainty is modelled around proportion multiplied by frequency, rather than separately on the proportion and frequency as individual inputs. These values were calculated based on resource use estimates reported in previous technology appraisals (TA666 and TA551) and adjustments were made based on a validation exercise with clinicians.^{7, 8, 10}

Costs were taken from the NHS Reference Costs 2021/2022 and PSSRU Unit Costs of Health and Social Care 2022/23.^{8, 10, 127, 128} The itemised costs for each type of resource use is presented in Table 60.

Costs were higher for patients who received atezolizumab + bevacizumab in the progression-free health state due to the requirement for every patient to receive an initial endoscopy and treatment and laboratory tests every three weeks.

Resource use was assumed to be higher for patients in the progressed disease health state who had received sorafenib at first-line, accounting for the high proportion of patients receiving subsequent active treatment as opposed to best supportive care (BSC), and extensive duration of subsequent treatment received (e.g. cabozantinib). Clinicians also provided feedback which suggested that use of TKIs in first-line is typically a second choice to IO, and is most often given if a patient is contraindicated to IO treatment due to comorbidities such as hypertension or cardiovascular/metabolic abnormalities.⁷ As such, it is likely that when these patients progress, they will require more monitoring and may be more likely to be hospitalised, compared to patients who receive IO in first-line.

Finally, the total costs per health state per cycle for the PF and PD health state are presented in Table 61.

Table 57: Resource use by treatment and health state (proportion of patients receiving)

Resource use		STRIDE			Atezolizumab + bevacizumab			Sorafenib			Lenvatinib		
		PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD
Physician visits	Appointment with oncologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with hepatologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with Gastroenterologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment within clinician nurse specialist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with palliative care physician/nurse	■	■	■	■	■	■	■	■	■	■	■	■
Laboratory tests	AFP test	■	■	■	■	■	■	■	■	■	■	■	■
	Liver function test	■	■	■	■	■	■	■	■	■	■	■	■
	INR	■	■	■	■	■	■	■	■	■	■	■	■
	Complete blood count	■	■	■	■	■	■	■	■	■	■	■	■
	Biochemistry	■	■	■	■	■	■	■	■	■	■	■	■

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Resource use		STRIDE			Atezolizumab + bevacizumab			Sorafenib			Lenvatinib		
		PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD
	Endoscopy	■	■	■	■	■	■	■	■	■	■	■	■
Radiological tests	Abdominal CT	■	■	■	■	■	■	■	■	■	■	■	■
	Abdominal MRI	■	■	■	■	■	■	■	■	■	■	■	■
Hospitalisation	Hospitalisation	■	■	■	■	■	■	■	■	■	■	■	■
	Hospital follow-up: Specialist	■	■	■	■	■	■	■	■	■	■	■	■
	Hospital follow-up: Nurse	■	■	■	■	■	■	■	■	■	■	■	■

Abbreviations: INR: international normalised ratio; PD: progressed disease; PF: progression free.

Table 58: Resource use by treatment and health state (frequency per week)

Resource use		STRIDE			Atezolizumab + bevacizumab			Sorafenib			Lenvatinib		
		PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD
Physician visits	Appointment with oncologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with hepatologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with	■	■	■	■	■	■	■	■	■	■	■	■

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Resource use		STRIDE			Atezolizumab + bevacizumab			Sorafenib			Lenvatinib		
		PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD
	Gastroenterologist												
	Appointment within clinician nurse specialist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with palliative care physician/nurse	■	■	■	■	■	■	■	■	■	■	■	■
Laboratory tests	AFP test	■	■	■	■	■	■	■	■	■	■	■	■
	Liver function test	■	■	■	■	■	■	■	■	■	■	■	■
	INR	■	■	■	■	■	■	■	■	■	■	■	■
	Complete blood count	■	■	■	■	■	■	■	■	■	■	■	■
	Biochemistry	■	■	■	■	■	■	■	■	■	■	■	■
	Endoscopy	■	■	■	■	■	■	■	■	■	■	■	■
Radiological tests	Abdominal CT	■	■	■	■	■	■	■	■	■	■	■	■
	Abdominal MRI	■	■	■	■	■	■	■	■	■	■	■	■
Hospitalisation	Hospitalisation	■	■	■	■	■	■	■	■	■	■	■	■

Resource use		STRIDE			Atezolizumab + bevacizumab			Sorafenib			Lenvatinib		
		PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD
	Hospital follow-up: Specialist	■	■	■	■	■	■	■	■	■	■	■	■
	Hospital follow-up: Nurse	■	■	■	■	■	■	■	■	■	■	■	■

Abbreviations: INR: international normalised ratio; PD: progressed disease; PF: progression free.

Table 59: Resource use by treatment and health state (proportion multiplied by weekly frequency)

Resource use		STRIDE			Atezolizumab + bevacizumab			Sorafenib			Lenvatinib		
		PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD
Physician visits	Appointment with oncologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with hepatologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with Gastroenterologist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment within clinician nurse specialist	■	■	■	■	■	■	■	■	■	■	■	■
	Appointment with	■	■	■	■	■	■	■	■	■	■	■	■

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Resource use		STRIDE			Atezolizumab + bevacizumab			Sorafenib			Lenvatinib		
		PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD	PF (first cycle)	PF (subsequent cycles)	PD
	palliative care physician/nurse												
Laboratory tests	AFP test	■	■	■	■	■	■	■	■	■	■	■	■
	Liver function test	■	■	■	■	■	■	■	■	■	■	■	■
	INR	■	■	■	■	■	■	■	■	■	■	■	■
	Complete blood count	■	■	■	■	■	■	■	■	■	■	■	■
	Biochemistry	■	■	■	■	■	■	■	■	■	■	■	■
	Endoscopy	■	■	■	■	■	■	■	■	■	■	■	■
Radiological tests	Abdominal CT	■	■	■	■	■	■	■	■	■	■	■	■
	Abdominal MRI	■	■	■	■	■	■	■	■	■	■	■	■
Hospitalisation	Hospitalisation	■	■	■	■	■	■	■	■	■	■	■	■
	Hospital follow-up: Specialist	■	■	■	■	■	■	■	■	■	■	■	■
	Hospital follow-up: Nurse	■	■	■	■	■	■	■	■	■	■	■	■

The health states are assumed to be comparable between STRIDE and atezolizumab + bevacizumab (except for endoscopy) and sorafenib and lenvatinib.

Abbreviations: AFP: alpha fetoprotein; CT: computerised tomography; GP: general practitioner; INR: international normalised ratio; MRI: magnetic resonance imaging; PD: progressed disease; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TA: technology appraisal.

Table 60: Itemised costs per week, by individual unit

Resource use		Cost inputs	Cost year
Physician visits	Appointment with oncologist	£221.48	2021/22
	Appointment with hepatologist	£200.68	2021/22
	Appointment with gastroenterologist	£182.93	2021/22
	Appointment with radiologist	£184.97	2021/22
	Appointment within clinician nurse specialist	£82.66	2022/23
	Appointment with palliative care physician/nurse	£82.66	2022/23
Laboratory tests	AFP test	£10.61	2021/22
	Liver function test	£10.61	2021/22
	INR	£2.86	2021/22
	Complete blood count	£2.86	2021/22
	Biochemistry	£1.55	2021/22
	Endoscopy	£146.00	2021/22
Radiological tests	Abdominal CT	£135.37	2021/22
	Abdominal MRI	£207.91	2021/22
Hospitalisation	Hospitalisation	£878.40	2021/22
	Hospital follow-up: Specialist	£200.68	2021/22
	Hospital follow-up: Nurse	£82.66	2022/23

Source: Approach was aligned with TA666¹⁰ and TA551;⁸ NHS Reference Costs 2021/22;¹²⁸ PSSRU Unit Costs of Health and Social Care 2022/23¹²⁷ and also informed by clinician feedback⁷

Abbreviations: AFP: alpha fetoprotein; CT: computerised tomography; GP: general practitioner; INR: international normalised ratio; MRI: magnetic resonance imaging; PSSRU: Personal Social Services Research Unit; TA: technology appraisal

Table 61: Total resource use costs per health state per cycle

Health state	Cost			
	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
PF (first cycle)	████	████	████	████
PF (subsequent cycles)	████	████	████	████
PD	████	████	████	████

Abbreviation: PD: progressed disease; PFS: progression free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.3.5.3 Adverse reaction unit costs and resource use

As outlined in Section B.3.3.6, AE probabilities for each treatment arm were informed by the HIMALAYA, IMbrave150 and REFLECT trials, with a summary of AE incidence rates provided in Table 49.^{4, 44, 73} By multiplying the rate of AEs by the AE costs (per event), the total AE costs per treatment arm can be calculated and applied in each cycle.

The unit cost for each AE is presented in Table 62, with the total cost per treatment arm presented in Table 63.

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Table 62: Adverse event costs, cost per event

Adverse event	Unit cost	Source
Aspartate aminotransferase increased	£801.11	Aligned with TA666 and TA551; NHS Reference Costs 2021/22 (Average of Non-elective Inpatient – Short Stay)
Blood bilirubin increased	£1,157.96	Aligned with TA666 and TA551; NHS Reference Costs 2021/22 (Average of Non-elective Inpatient – Short Stay; WF01A, Consultant Led, Medical Oncology Service, Non-Admitted Face-to-Face Attendance, Follow-up; Weighted average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z and RD27Z, Computerised Tomography Scan [19 years and over only])
Gamma-glutamyl transferase increased	£801.11	Aligned with TA551; NHS Reference Costs 2021/22 (Average of Non-elective Inpatient – Short Stay)
Hypertension	£1,077.59	Aligned with TA666; NHS Reference Costs 2021/22 (Average of Non-elective Inpatient – Short Stay; WF01A, Consultant Led, Medical Oncology Service, Non-Admitted Face-to-Face Attendance, Follow-up); PSSRU Unit Costs of Health and Social Care 2022/23 (GP Cost per Surgery Consultation Lasting 10 Minutes including direct care staff and qualification costs)
Lipase increased	£801.11	Assumed the same as other increased enzyme AEs
Palmar-plantar erythrodysesthesia syndrome	£481.77	Aligned with TA666 and TA551; NHS Reference Costs 2021/22 (JD07J, Non-elective Short Stay, Skin Disorders without Interventions with CC Score 2-5)
Platelet count decreased	£801.11	Aligned with TA551; NHS Reference Costs 2021/22 (Average of Non-elective Inpatient – Short Stay)
Proteinuria	£1,022.59	Aligned with TA551; NHS Reference Costs 2021/22 (Average of Non-elective Inpatient – Short Stay; WF01A, Consultant Led, Medical Oncology Service, Non-Admitted Face-to-Face Attendance, Follow-up)
Weight decreased	£837.11	Aligned with TA551; NHS Reference Costs 2021/22 (Average of Non-elective Inpatient – Short Stay); PSSRU Unit Costs of Health and Social Care 2022/23 (Hospital-based Scientific and Professional Staff, Cost per Working Hour [Band 4])

Source: TA551;⁸ TA666;¹⁰ NHS Reference Costs 2021/22.¹²⁸

Abbreviation: NHS: National Health Service; PSSRU: Personal Social Services Research Unit; TA: technology appraisal.

Table 63: Adverse event costs, costs per treatment arm

Adverse events	Costs per treatment arm			
	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
Aspartate aminotransferase increased	■	£55.28	■	£85.04
Blood bilirubin increased	■	£11.42	■	£158.76
Gamma-glutamyl transferase increased	■	£15.79	■	£92.12

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Adverse events	Costs per treatment arm			
	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
Hypertension	████	£180.59	████	£529.02
Lipase increased	████	£0.00	████	£0.00
Palmar-plantar erythrodysesthesia syndrome	████	£0.00	████	£29.83
Platelet count decreased	████	£31.59	████	£92.12
Proteinuria	████	£45.36	████	£122.11
Weight decreased	████	£0.00	████	£133.29
Total	████	£189.28	████	£340.03

Abbreviations: STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.3.5.4 Miscellaneous unit costs and resource use

The model includes a cost for end-of-life care, which is applied upon death. Aligned with TA666 and TA551, as well as the findings from Georgiou and Bardsley 2014, it is estimated that this cost amounts to £8,249.15 for individuals with advanced or unresectable HCC.^{8, 10, 150}

B.3.6 Severity

Survival for patients with advanced or unresectable HCC is poor, with an average life expectancy is less than two years despite the treatments currently available in the UK.³³ Disease symptoms in individuals with advanced or unresectable HCC have profound humanistic and HRQoL impacts.³⁷ As such, individuals report significantly lower physical wellbeing and overall HRQoL than the general population, patients with chronic liver disease, and patients with other cancers.²⁹

The severity modifier tool developed by SchAAR and Lumanity was used to calculate the absolute and proportional severity modifiers, using the reference case Measurement of Valuation of Health (MVH) value set and Health Survey for England (HSE) 2014 Adjusted Limited Dependent Variable Mixture Model (ALDVMM).¹⁵¹ A summary of the features of the QALY shortfall analysis is provided in Table 64. Based on this QALY shortfall analysis, the proportional QALY shortfall for the base case meets the threshold for applying a severity modifier of x1.2 to the incremental QALYs for the comparisons against lenvatinib and sorafenib.

The model predicts median OS is ~22 months for atezolizumab + bevacizumab, and ~13 months for sorafenib and lenvatinib. Therefore, advanced or unresectable HCC would have previously met end of life criteria. As highlighted by the external evidence cited in Section B.3.3.3.4, median OS for patients treated with sorafenib may be even lower (~10 months).

Table 64: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution, % Male	■	Section B.3.3.1
Starting age, year	■	

Abbreviations: QALY: quality-adjusted life year.

Table 65: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Current treatment	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute shortfall	Proportional shortfall	QALY weight
■	Atezolizumab + bevacizumab	2.42	■	■	x1.0
	Sorafenib	1.48	■	■	x1.2
	Lenvatinib	1.48	■	■	x1.2

Abbreviations: QALY: quality-adjusted life year.

B.3.7 *Uncertainty*

Comprehensive five-year overall survival data is available from the HIMALAYA trial. With the availability of highly mature data, long-term survival extrapolations can be generated with greater certainty. Any remaining uncertainty has been mitigated through detailed consultations with UK specialists regarding the anticipated long-term survival of adults with advanced or unresectable HCC in the UK.

B.3.8 *Managed access proposal*

The HIMALAYA trial provides highly mature OS data from a median follow-up of 5 years, thereby minimising uncertainty in the resulting long-term survival extrapolations. In line with recommendations from NICE TSD 14, clinical feedback was sought from UK-based oncologists on the long-term clinical validity of the modelled parametric survival extrapolations for sorafenib and STRIDE.¹¹⁸ Given the availability of mature, long-term survival data, validated by clinicians, decision uncertainty for this evaluation is greatly minimised. As a result, AstraZeneca do not intend to submit a managed access proposal.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 *Summary of base-case analysis inputs*

A summary of inputs for the base case analysis is presented in Table 66.

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Table 66: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Controls			
Discount rate, Lys	3.5%		Section B.3.2.2
Discount rate, QALYs	3.5%		
Discount rate, Costs	3.5%		
Time horizon	40		
Percentage of male patients, %	■		Section B.3.3.1
Patient age, years	■		
Patient weight; kg	■	Normal	
Patient height, cm	■		
Efficacy inputs			
Overall survival			
Approach – STRIDE	Splines and knots: Normal - 1 knot		Section B.3.3.3
Approach – Sorafenib	Splines and knots: Hazard - 1 knot		
Approach – Lenvatinib	Constant HR		
Approach - Atezolizumab + bevacizumab	Constant HR		
HR vs. sorafenib – Lenvatinib	1.00	Log-normal	
HR vs. sorafenib - atezolizumab + bevacizumab	■	Log-normal	
PFS			
Approach – STRIDE	Splines and knots: Hazard - 3 knots		Section B.3.3.4
Approach – Sorafenib	Splines and knots: Hazard - 2 knots		
Approach – Lenvatinib	Constant HR		
Approach - Atezolizumab + bevacizumab	Constant HR		
HR vs. sorafenib – Lenvatinib	■	Log-normal	
HR vs. sorafenib - atezolizumab + bevacizumab	■	Log-normal	
TTD			
Approach – STRIDE	One piece (Separately fitted): Weibull		Section B.3.3.5

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Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Approach – Sorafenib	One piece (Separately fitted): Log-normal		
Approach – Lenvatinib	Constant HR (1.00) vs. PFS		
Approach - Atezolizumab + bevacizumab	Constant HR (1.00) vs. PFS		
Drug costs			
Drug acquisition costs			
Durvalumab [50 mg/ml; 2.4 ml (vial)] – PAS price	██████	Gamma	Section B.3.5.1
Durvalumab [50 mg/ml; 10 ml (vial)] – PAS price	██████	Gamma	
Tremelimumab [20 mg/ml; 15 ml (vial)]	£20,610.00	Gamma	
Sorafenib [200 mg (per tablet)]	£552.40	Gamma	
Lenvatinib [10 mg (per capsule)]	£1,437.00	Gamma	
Atezolizumab [60 mg/ml; 20 ml (vial)]	£3,807.69	Gamma	
Bevacizumab [25 mg/ml; 4 ml (vial)]	£205.00	Gamma	
Bevacizumab [25 mg/ml; 16 ml (vial)]	£810.00	Gamma	
Regorafenib [40 mg (per tablet)]	£3,744.00	Gamma	
Cabozantinib [20 mg (per tablet)]	£5,143.00	Gamma	
Cabozantinib [40 mg (per tablet)]	£5,143.00	Gamma	
Cabozantinib [60 mg (per tablet)]	£5,143.00	Gamma	
Administration Costs			
Oral	£197.25	Gamma	Section B.3.5.1
IV (Simple, first)	£207.59	Gamma	
IV (Simple, subsequent)	£326.46	Gamma	
Relative dose intensity			
Durvalumab	100%	Beta	Section B.3.5.1
Sorafenib	100%	Beta	
Lenvatinib	100%	Beta	
Atezolizumab	100%	Beta	
Tremelimumab	100%	Beta	

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Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Bevacizumab	100%	Beta	
Subsequent treatment (mean time on treatment)			
BSC alone	NA		Section B.3.5.1
Cabozantinib	183.50	Normal	
Lenvatinib	312.10	Normal	
Regorafenib	167.80	Normal	
Sorafenib	242.60	Normal	
Resource use costs			
Appointment with oncologist	£221.48	Gamma	Section B.3.5.2
Appointment with hepatologist	£200.68	Gamma	
Appointment with Gastroenterologist	£182.93	Gamma	
Appointment with Radiologist	£184.97	Gamma	
Appointment within clinician nurse specialist	£82.66	Gamma	
Appointment with palliative care physician/nurse	£82.66	Gamma	
AFP test	£10.61	Gamma	
Liver function test	£10.61	Gamma	
INR	£2.86	Gamma	
Complete blood count	£2.86	Gamma	
Biochemistry	£1.55	Gamma	
Endoscopy	£146.00	Gamma	
Abdominal CT	£135.37	Gamma	
Abdominal MRI	£207.91	Gamma	
Hospitalisation	£878.40	Gamma	
Hospital follow-up: Specialist	£200.68	Gamma	
Hospital follow-up: Nurse	£82.66	Gamma	
End of Life Costs	£8,249.15	Gamma	
Adverse event costs			
Aspartate aminotransferase increased	£801.11	Gamma	Section B.3.5.3
Blood bilirubin increased	£1,157.96	Gamma	

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Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Gamma-glutamyl transferase increased	£801.11	Gamma	
Hypertension	£1,077.59	Gamma	
Lipase increased	£801.11	Gamma	
Palmar-plantar erythrodysaesthesia syndrome	£481.77	Gamma	
Platelet count decreased	£801.11	Gamma	
Proteinuria	£1,022.59	Gamma	
Weight decreased	£837.11	Gamma	
Utilities			
Treatment: sorafenib	██████	Beta	Section B.3.4.5
Treatment: STRIDE	██████	Beta	

Abbreviations: AFP: alpha-fetoprotein; BSC: best supportive care; CI: confidence interval; CT: computerised tomography; GP: general practitioner; HR: hazard ratio; INR: International normalised ratio; IV: intravenous; LYs: life years; MRI: magnetic resonance imaging; PAS: patient access scheme; PFS: progression-free survival; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTD: time to treatment discontinuation.

B.3.9.2 Assumptions

The key assumptions used in the base case analysis are detailed in Table 67.

Table 67: Modelling assumptions

Category	Assumption	Justification	Addressed in scenario analysis
Time horizon	A time horizon of 40 years is considered sufficient to capture the relevant consequences of first-line HCC treatment in terms of costs and QALYs.	7% of patients remain alive in the intervention arm after a 20-year period and hence a longer timeframe was required	A scenario analysis with a 20-year time horizon has been performed for completeness.
Time to treatment discontinuation	For atezolizumab + bevacizumab and lenvatinib TTD is assumed equal to PFS.	This is a conservative assumption as both treatments are recommended until loss of clinical benefit and as such, treatment may continue beyond progression in clinical practice.	N/A
Subsequent treatments	Within the model, patients will not receive the same treatment again in later lines.	As the model only considers the patient's first and second line of therapy, it is assumed that they will not continue their first	N/A

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Category	Assumption	Justification	Addressed in scenario analysis
		treatment as a subsequent therapy.	
	A one-off cost for subsequent therapies (drug costs plus administration costs) is applied upon treatment discontinuation.	Simplifying assumption to avoid undue complexity through introducing multiple treatment lines in the model.	N/A
Utilities	A general population utility multiplier is applied in the model base case.	To account for age and sex related decline in health-related quality of life.	N/A
	In the base case it is assumed that HRQoL (utilities) is treatment-dependent.	This approach was selected as it was considered to be the most robust way of capturing the impact of adverse events due to TKIs on patients.	N/A
Costs	No vial sharing is allowed.	This assumption reflects clinical practice and NHS guidelines.	A scenario including vial sharing is explored in a scenario analysis.

Abbreviations: AE: adverse event; HCC: hepatocellular carcinoma; NHS: National Health Service; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.3.10 *Base-case results*

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic and probabilistic cost-effectiveness results for STRIDE vs. atezolizumab + bevacizumab, sorafenib and lenvatinib are presented in Table 68 and Table 69, respectively. The fully incremental results for the deterministic and probabilistic analyses are presented in Table 70 and Table 71, respectively. In the deterministic base case, STRIDE dominated atezolizumab + bevacizumab, accumulating fewer costs and greater QALYs over a lifetime horizon. Relative to sorafenib and lenvatinib, STRIDE was associated with deterministic, pairwise ICERs of [REDACTED] and [REDACTED] per QALY, respectively; this also includes the application of a 1.2x severity modifier to the incremental QALYs for these two comparisons (see Section B.3.6)

In the probabilistic analysis, the NHB results are similar to those in the deterministic analyses. Pairwise probabilistic ICERs for the comparison between STRIDE and sorafenib and STRIDE and lenvatinib were consistent with the deterministic ICERs. For the comparison of STRIDE and atezolizumab + bevacizumab, the incremental QALYs are close to zero for both the deterministic and probabilistic analysis, but for the probabilistic analysis the ICERs fall in the southwest (SW) quadrant of the cost-effectiveness plane, meaning that the results show cost saved per QALY forgone.

At a willingness-to-pay (WTP) threshold of £30,000/QALY gained, STRIDE represents a cost-effective use of NHS resources vs. the principal comparator, and SoC in NHS clinical practice, atezolizumab + bevacizumab, in both the deterministic and probabilistic analysis.

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The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

Table 68: 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	██████	██	██	-	-	-	-	-	-
Atezolizumab + bevacizumab	£244,087	3.02	2.42	██████	██	██	STRIDE is dominant	██	██
Sorafenib	£36,799	1.92	1.48	██████	██	██	██████	██	██
Lenvatinib	£48,445	1.92	1.48	██████	██	██	██████	██	██

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 69: Probabilistic 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	██████	██	██	-	-	-	-	-	-
Atezolizumab + bevacizumab	£249,037	3.10	2.47	██████	██	██	██████ ^a	██	██
Sorafenib	£36,790	1.92	1.47	██████	██	██	██████	██	██
Lenvatinib	£49,648	1.92	1.47	██████	██	██	██████	██	██

Footnotes: All results include the commercial access agreement in place for durvalumab. ^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; WPT: willingness to pay.

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Table 70: Deterministic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER
Sorafenib	£36,798.68	1.92	1.48	-	-	-	-
Lenvatinib	£48,444.96	1.92	1.48	-	-	-	
STRIDE							
Atezolizumab + bevacizumab	£244,087.04	3.02	2.42	-	-	-	

Footnotes: All results include the commercial access agreement in place for durvalumab. ^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; WTP: willingness to pay.

Table 71: Probabilistic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER
Sorafenib				-	-	-	-
Lenvatinib	£49,648.43	1.92	1.47	-	-	-	
STRIDE	£103,904.23	3.09	2.44				
Atezolizumab + bevacizumab	£249,036.81	3.10	2.47				

Footnotes: All results include the commercial access agreement in place for durvalumab. ^aICER in the southwest (SW) quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; WTP: willingness to pay.

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B.3.11 *Exploring uncertainty*

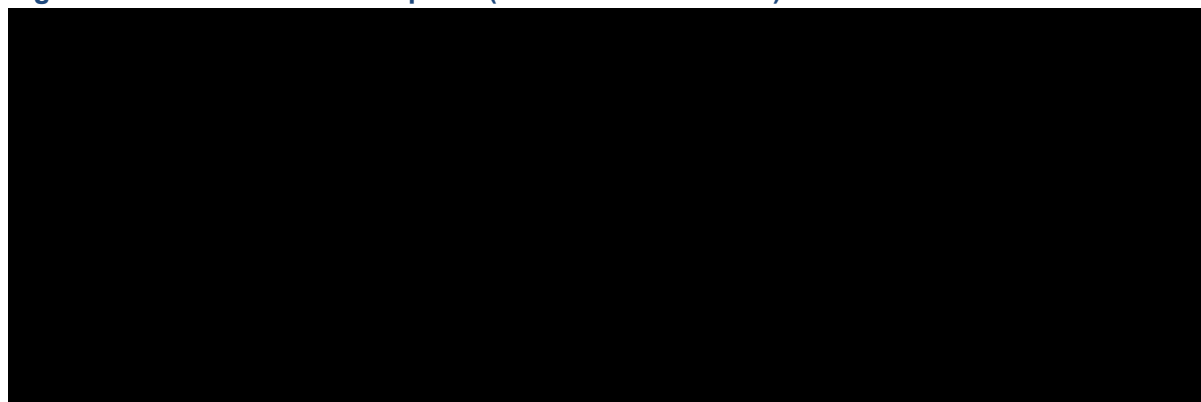
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections B.3.11.1 and B.3.11.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.11.4. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for, and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were run with 1,000 iterations, with estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Beta distributions were assumed for uncertain parameters bound by zero and one, including utilities, proportions, and probabilities. Log-normal distributions were assumed for hazard ratios. Gamma distributions were assumed for costs. Normal distributions were assumed for other uncertain parameters including resource use frequencies, with capping in place to ensure positivity for parameters which must be non-negative.

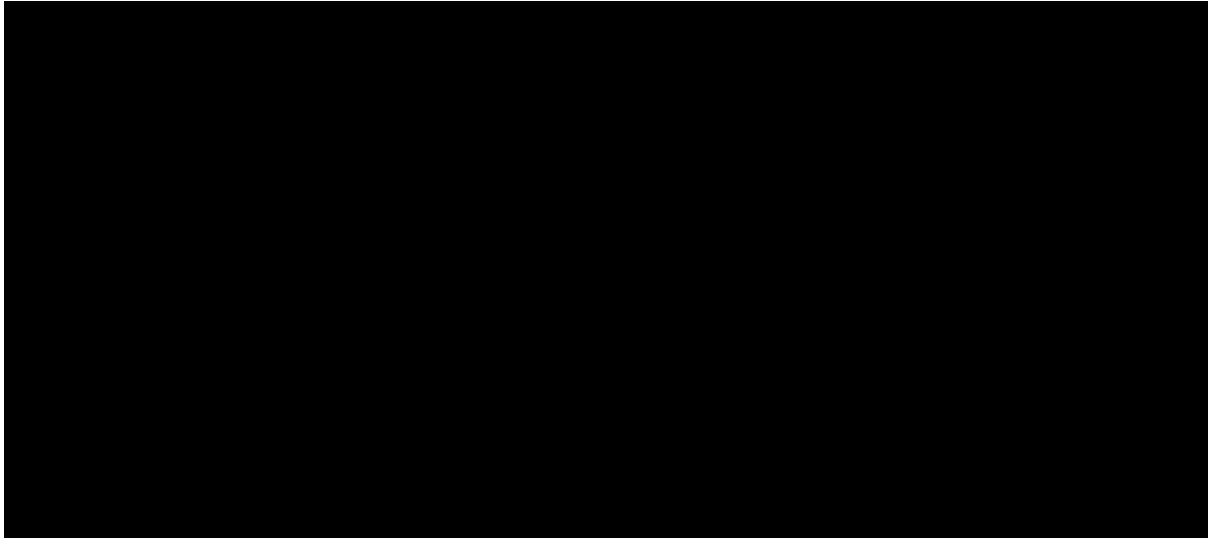
The probabilistic pairwise cost-effectiveness planes for STRIDE vs. relevant comparators are presented in Figure 54 to Figure 56. The cost-effectiveness acceptability curve is presented in Figure 57.

Figure 54: Cost-effectiveness plane (STRIDE vs sorafenib)



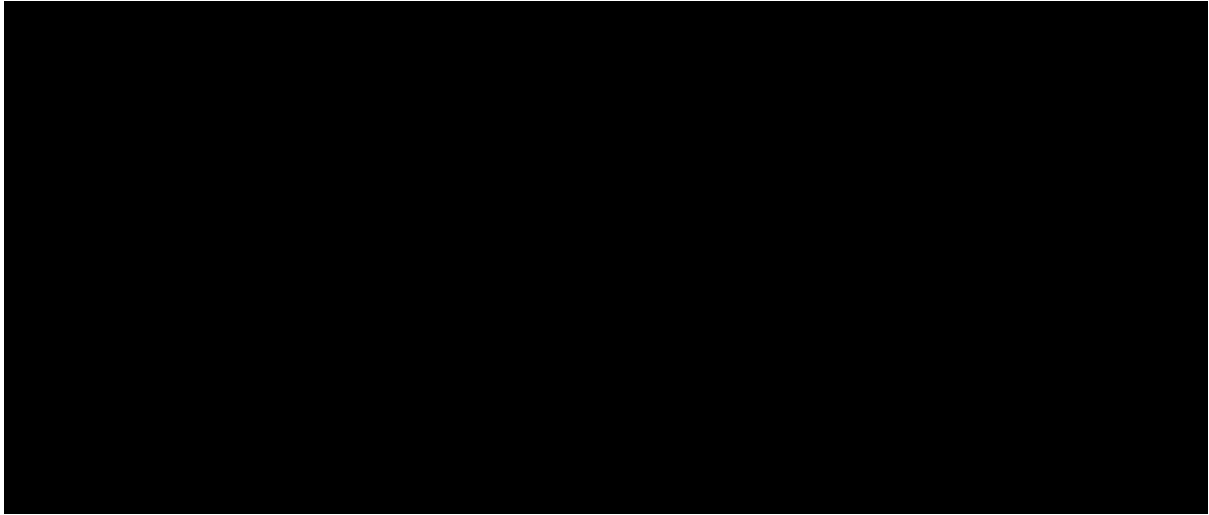
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 55: Cost-effectiveness plane (STRIDE vs lenvatinib)



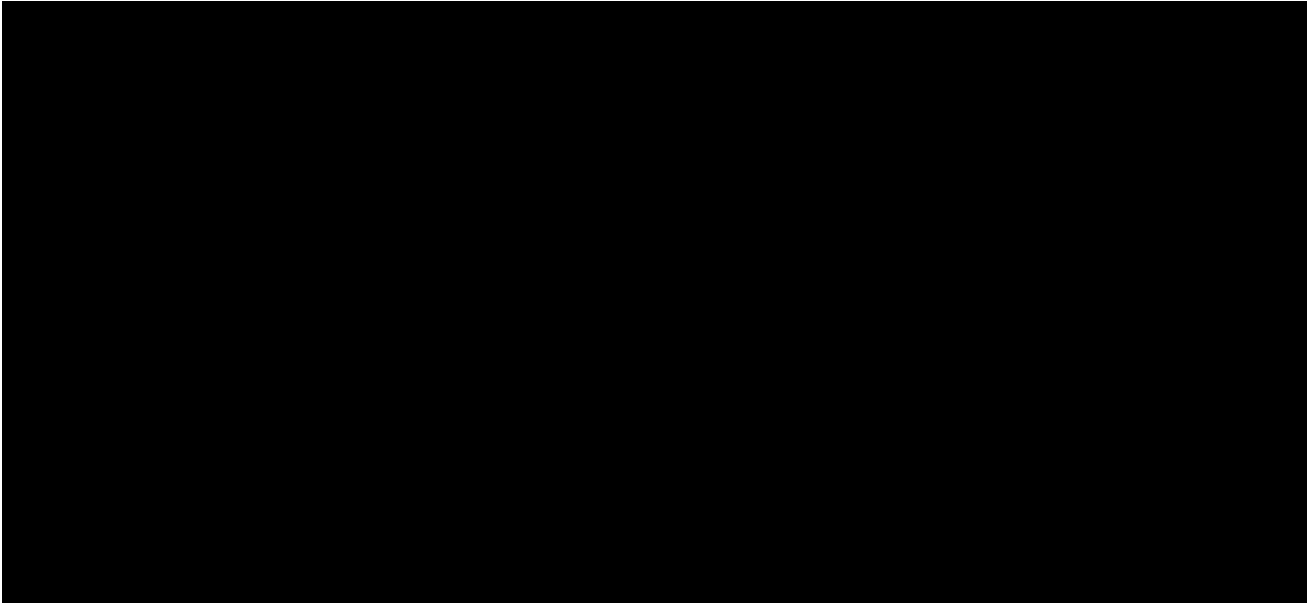
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 56: Cost-effectiveness plane (STRIDE vs atezolizumab + bevacizumab)



Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 57: Cost-effectiveness acceptability curve



Abbreviations: WTP: willingness to pay.

B.3.11.2 Cost comparison vs. atezolizumab + bevacizumab

The deterministic and probabilistic base case results show that incremental QALYs for the comparison between STRIDE and atezolizumab + bevacizumab fall either side of zero. This can be observed in Figure 56. This indicates, at a minimum, likely clinical equivalence between the two interventions, which is further supported by the results of the NMA presented in Section B.2.9, where no statistically significant difference was observed between STRIDE and atezolizumab + bevacizumab in terms of OS and PFS. To investigate this equivalence, a cost comparison was conducted where incremental QALYs were manually set equal for the two therapies. The results of this scenario analysis are presented in Table 72 and show that STRIDE is associated with cost-savings when compared to atezolizumab + bevacizumab.

Table 72: Cost comparison for STRIDE vs atezolizumab + bevacizumab (deterministic)

Scenario		STRIDE vs atezolizumab + bevacizumab		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Base case		██████	██	Dominant
1	Cost-minimisation analysis, assuming equal efficacy	██████	0.00	NA

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.3.11.3 Deterministic sensitivity analysis

To assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted. The tornado diagrams for STRIDE vs. relevant comparators are presented in Figure 58, Figure 59 and Figure 60. The top 10 most influential parameters on the base case are presented in each case. In the comparison of STRIDE vs. sorafenib, the model was robust to variation in inputs. In the comparison of STRIDE vs. lenvatinib, results were most influenced by the PFS HR. Given PFS informs treatment duration for lenvatinib, and therefore drug costs, this likely explains the level of influence of this input. In the comparison of STRIDE

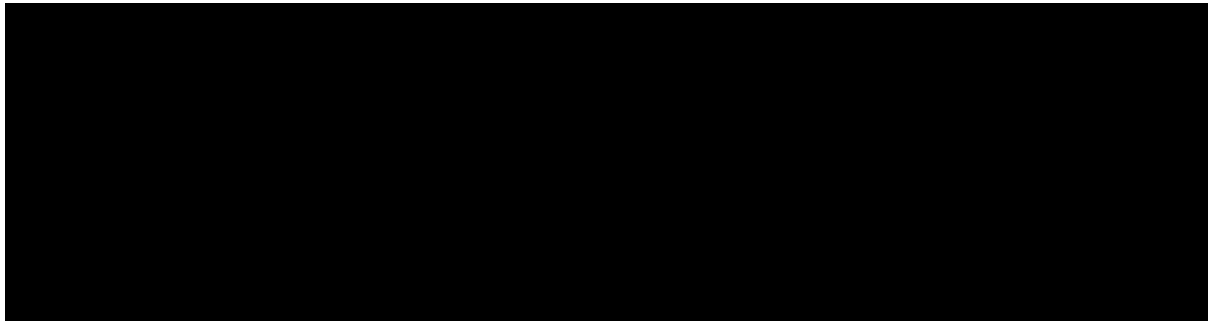
vs. atezolizumab + bevacizumab, the PFS HR was again influential, and otherwise the model was robust to input variation.

Figure 58: Tornado diagram (STRIDE vs sorafenib; INHB at £30,000 WTP)



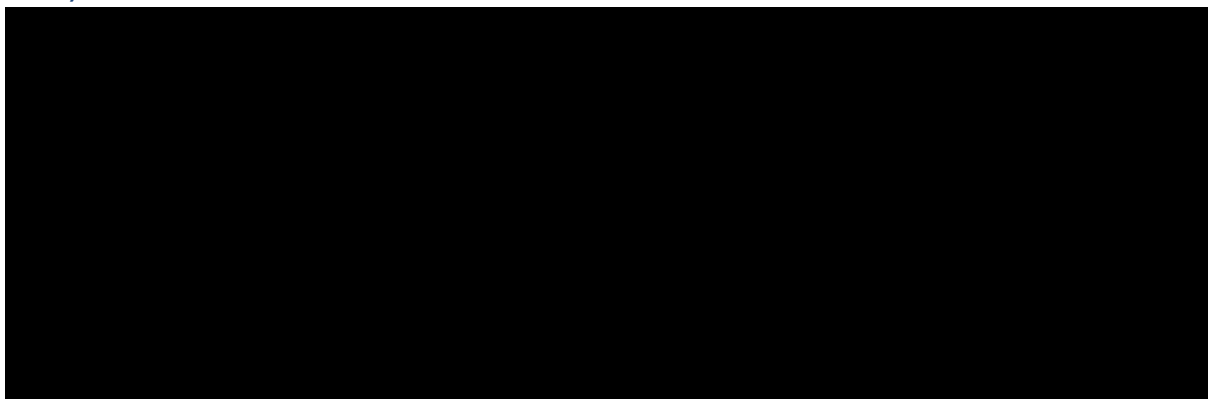
Abbreviations: DurvTrem: durvalumab with tremelimumab (otherwise referred to as STRIDE); IV: intravenous; INHB: incremental net health benefit; PD: progressed disease; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness-to-pay.

Figure 59: Tornado diagram (STRIDE vs lenvatinib; INHB at £30,000 WTP)



Abbreviations: DurvTrem: durvalumab with tremelimumab (otherwise referred to as STRIDE); IV: intravenous; INHB: incremental net health benefit; PD: progressed disease; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness-to-pay.

Figure 60: Tornado diagram (STRIDE vs atezolizumab + bevacizumab; INHB at £30,000 WTP)



Abbreviations: AtezoBev: atezolizumab + bevacizumab; DurvTrem: durvalumab with tremelimumab (otherwise referred to as STRIDE); IV: intravenous; INHB: incremental net health benefit; PD: progressed disease; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness-to-pay.

B.3.11.4 Scenario analysis

A number of scenario analyses were conducted to explore the impact of certain assumptions and alternative inputs on the results of the economic analysis. Each scenario analysis is described in turn below and full results of the scenario analysis are presented in Table 73. In the majority of scenarios, STRIDE remains dominant vs. atezolizumab + bevacizumab. In the two non-dominant scenarios, the ICER falls within the SW quadrant, where STRIDE remains cost-effective. The ICERs vs. sorafenib and lenvatinib remain relatively stable between scenarios, illustrating the robustness of the model to uncertainty.

Table 73: Scenario analysis results for STRIDE vs relevant comparators (deterministic)

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Base case		██████	██	Dominant	██████	██	██████	██████	██	██████
1	20-year time horizon	██████	██	██████	██████	██	██████	██████	██	██████
2	Inclusion of vial sharing	██████	██	Dominant	██████	██	██████	██████	██	██████
3	Treatment-specific RDIs	██████	██	Dominant	██████	██	██████	██████	██	██████
4	OS extrapolation choice for STRIDE: generalised gamma	██████	██	Dominant	██████	██	██████	██████	██	██████
5	OS extrapolation choice for sorafenib: generalised gamma	██████	██	██████	██████	██	██████	██████	██	██████
6	PFS extrapolation choice for STRIDE: generalised gamma	██████	██	Dominant	██████	██	██████	██████	██	██████
7	PFS extrapolation choice for sorafenib: log-normal	██████	██	Dominant	██████	██	██████	██████	██	██████
8	TTD extrapolation choice for STRIDE: generalised gamma	██████	██	Dominant	██████	██	██████	██████	██	██████

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
9	TTD extrapolation choice for sorafenib: log-logistic			Dominant						

Footnotes: ^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: ICER: incremental cost-effectiveness ratio; PFS: progression-free survival; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; TTD: time to treatment discontinuation.

B.3.12 Subgroup analysis

No subgroup analyses were considered relevant to this appraisal and as such no subgroup analyses were included in the cost-effectiveness analysis.

B.3.13 Benefits not captured in the QALY calculation

Although this evaluation considers the cost-saving advantage of STRIDE not requiring endoscopy compared to atezolizumab + bevacizumab, it does not capture the benefits of reduced amount of time before a patient can commence starting life-extending treatment, nor the reduced capacity burden for the NHS that would be realised if STRIDE was recommended through reduced endoscopy, reduced dosing admin and laboratory tests and monitoring.

Furthermore, the potential positive impact on carers and/or relatives associated with the improved outcomes of patients that receive treatment with STRIDE is not considered in the economic analysis. The impact of improved outcomes on the productivity of patients, carers and/or relatives is also not considered.

Given the highly mature long-term survival data available for STRIDE, clinicians can have greater confidence in the long-term efficacy of STIDE for their patients.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Internal validation

A thorough quality control check and technical validation was conducted by health economic modellers, in line with Drummond et al. (2015),¹⁵² Philips et al. (2004),¹⁵³ and TECH-VER.¹⁵⁴

These checks include, but are not limited to the following criteria:

- A manual review of all programming using formulae within Microsoft Excel and code in Visual Basis for Applications (VBA)
- Confirmation that the mathematical calculations, programming, and formulae are consistent with the specification and are logically applied
- A review of the patient flow sheets, scope, results, and sensitivity analysis functionality
- Validity checks to ensure consistency between the clinical trial data and model outcomes
- Extreme value testing (setting in zero values to parameters and stress testing the model in general) to assess whether the outcomes, and changes in outcomes, make intuitive sense for the options selected – in addition to editorial checks (text descriptions, referencing, navigation and graphical outputs) within the model

External validation

Long-term survival expectations in advanced or unresectable HCC are detailed in Section B.3.2.2. It demonstrates that the extrapolations have reasonable visual fit to the short-term observed trial Kaplan-Meier data for the FAS population.

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Clinical feedback was also used to validate the inputs and results from the model, including the treatment pathway and validation of long-term survival extrapolations. Where possible, UK sources were used for model inputs to ensure the outputs are representative of NHS clinical practice.

B.3.15 Interpretation and conclusions of economic evidence

Principal results from economic analysis

To assess the cost-effectiveness of STRIDE vs. relevant comparators in patients with advanced or unresectable HCC, a *de novo* cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England.

In the deterministic base case, STRIDE dominated atezolizumab + bevacizumab, accumulating fewer costs and greater QALYs over a lifetime horizon. Relative to sorafenib and lenvatinib, STRIDE was associated with deterministic, pairwise ICERs of [REDACTED] and [REDACTED] per QALY, respectively. At a willingness-to-pay (WTP) threshold of £30,000/QALY gained, STRIDE therefore represents a cost-effective use of NHS resources vs. the principal comparator, and SoC in NHS clinical practice, atezolizumab + bevacizumab. The probabilistic base case analysis supports this conclusion, with average results being close to the deterministic base case outcomes and therefore sufficiently robust to uncertainty in parameter estimates. The results of an exploratory cost comparison demonstrate that STRIDE still remains cost-saving when compared to atezolizumab + bevacizumab when assuming equal efficacy across the two treatments.

The results of the deterministic sensitivity analyses identified respective treatment acquisition costs and NMA-derived hazard ratios for OS and PFS, where applicable, as the main drivers of the model outcomes (i.e. INHB); these parameters were therefore also further tested as part of additional scenario analyses, by varying assumptions around vial sharing and RDI, as well as different survival extrapolations. Results remained overall stable across all tested scenarios, with STRIDE remaining dominant across the majority of scenarios, or otherwise cost-effective, against atezolizumab + bevacizumab in particular.

Strengths and limitations

Efficacy data for the model was sourced from the HIMALAYA trial, a methodologically robust Phase III RCT in the patient population of interest to this evaluation. The HIMALAYA trial provides long-term data for STRIDE as well as one of the relevant comparators (sorafenib); most notably providing highly mature five-year OS data. Extrapolations were fit directly to these data which, due to the maturity of the data, reduces ambiguity in efficacy extrapolations and as such, is anticipated to significantly minimise decision uncertainty for the NICE Committee. However, the comparator trials spanned a shorter time period and as such, there is increased uncertainty in the long-term survival extrapolations for these comparators.

Comprehensive clinical validation was performed to validate long-term survival estimates as well as the key assumptions made in the analysis. Baseline characteristics of patients within the HIMALAYA trial are used within the model have been validated by UK clinical experts to be representative of UK clinical practice.

As the HIMALAYA trial compared STRIDE to sorafenib, an NMA was required to obtain comparative efficacy evidence for the remaining two comparators (atezolizumab + bevacizumab Company evidence submission for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

and lenvatinib). Trials included in the NMA had notably different lengths of follow-up, with comparator trials spanning a much shorter duration relative to HIMALAYA. Therefore, although the NMA used robust methodologies, there is inherent and unavoidable uncertainty in the model outputs for the long-term efficacy of the comparators. Furthermore, the PH assumption was violated for HIMALAYA and REFLECT. For HIMALAYA, this was addressed in the economic model by independently fitting curves to the patient-level data from the HIMALAYA study, as recommended in NICE DSU TSD 14.¹¹⁸ For REFLECT, an analysis investigating a time-varying treatment effect for the efficacy of lenvatinib vs. sorafenib was conducted to evaluate the impact of the PH violation identified, which found that use of the NMA results within the model was a conservative choice (Section B.3.3.2). As explained above, lenvatinib and sorafenib were considered to have equivalent OS efficacy given the result of the REFLECT study, which showed that lenvatinib was non-inferior to sorafenib but that superiority could not be established. This equivalence was achieved through setting the HR equivalent to 1. There was no violation of the PH assumption for IMbrave150.

The model closely aligns to the NICE reference case, adopting an NHS and PSS perspective as well as utilising a lifetime horizon of 40 years to ensure all costs and QALY gains associated with the interventions are fully captured and discounting costs and benefits at a rate of 3.5% per annum. Furthermore, learnings and committee preferences were adopted from previous evaluations in this disease area to ensure the trial and evaluation are reflective of current best practices.

The results of the economic analysis are therefore considered highly relevant to decision-making on the introduction of STRIDE into NHS clinical practice for adults with advanced or unresectable HCC.⁸⁻¹⁰

Overall conclusions

There remains a significant unmet need for an efficacious and tolerable treatment option for adults with advanced or unresectable HCC that does not carry an associated increase in bleeding risk. STRIDE offers an efficacious and safe alternative to atezolizumab + bevacizumab, sorafenib and lenvatinib, and is supported by unprecedented, highly mature OS data, which aid in the minimisation of uncertainty associated with the long-term extrapolation of survival outcomes. In the base case, STRIDE was associated with a dominant deterministic incremental ICER relative to atezolizumab + bevacizumab, the principal comparator and current SoC in NHS clinical practice (Section B.3.10). STRIDE can therefore be considered a cost-effective use of NHS resources, whilst fulfilling a significant unmet need for patients with advanced or unresectable HCC in the UK for an effective treatment that does not increase risk of bleeding.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma

[ID2725]

Summary of Information for Patients (SIP)

13th August 2024

File name	Version	Contains confidential information	Date
ID2725_STRIDE IN HCC_SIP_12Aug24 [NoCIC]	V1	No	13 th August 2024

Summary of information for patients for durvalumab with tremelimumab for untreated
advanced or unresectable hepatocellular carcinoma [ID2725]

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from **National Institute for Health and Care Excellence (NICE)** for their treatment to be sold to the **National Health Service (NHS)** for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [JTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: durvalumab in combination with tremelimumab. The combined name for this treatment is called **STRIDE**, which is short for Single Tremelimumab Regular Interval Durvalumab

Brand name: IMFINZI® in combination with IMJUDO®

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is adults with **advanced or unresectable** hepatocellular carcinoma (HCC). These individuals must be ineligible for **locoregional** therapy and have not undergone **systemic therapy** during their current disease **stage**.

Please note: Further explanations for the words and phrases highlighted in **blue bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections or documents are highlighted in **orange**.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state

Summary of information for patients for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is a licence that sets out the conditions for the use of a treatment based on evidence supporting its safety and effectiveness. Durvalumab in combination with tremelimumab currently holds a marketing authorisation for the treatment of adults with advanced or unresectable HCC, which was granted by the **European Medicines Agency (EMA)**.¹

A marketing authorisation application was subsequently approved by the United Kingdom (UK) **Medicines and Healthcare Products Regulatory Agency (MHRA)** on the 6th June 2023 for the use of durvalumab in combination with tremelimumab in patients with advanced with advanced or unresectable HCC.² This is the indication under consideration for this evaluation.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK engages the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information. The Alan Morement Memorial Fund (AMMF), the Cholangiocarcinoma Charity and Liver Cancer UK are all part of the British Liver Trust.

- AMMF - The Cholangiocarcinoma Charity: £5,000 grant contribution towards AMMF Centres of Expertise Program Management (2024)
- AMMF - The Cholangiocarcinoma Charity: £45,000 AMMF European Cholangiocarcinoma Conference (2024)
- Liver Cancer UK: £10,500 (2023)
- Liver Cancer UK: £5,000 (2022)

All patient group contributions are published annually on AstraZeneca UK's website: <https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups>

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Summary of information for patients for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

STRIDE is intended to treat advanced or unresectable hepatocellular carcinoma (HCC)

What is hepatocellular carcinoma?

Hepatocellular carcinoma, also called HCC, is a type of liver cancer that develops from liver cells called hepatocytes.³ HCC accounts for about 50% of all liver cancer cases and is the most common type of primary liver cancer, i.e. where the cancer originates within the liver itself.⁴ In the UK, approximately 6,100 people are diagnosed with HCC each year, and nearly 6,000 people die from it annually. This means HCC makes up 3% of all cancer deaths in the UK.^{5, 6}

What are the signs and symptoms of HCC?

For patients in the early stages of HCC, there might not be any symptoms, or they might be hard to spot. Some common symptoms include:⁷

- Extreme tiredness
- Weakness
- Loss of appetite
- Unintended weight loss
- Nausea or vomiting
- Pain in the area of the liver
- General feeling of being unwell

Because these symptoms are so general, HCC is often diagnosed late. About 41% of patients are diagnosed when the cancer is already advanced or cannot be removed with surgery.^{8, 9} Furthermore, up to half of the patients who do have surgery to remove the cancer find that it comes back within two years.¹⁰

What causes HCC?

HCC often develops in people who have **cirrhosis**, a condition where the liver becomes severely scarred. There are many risk factors that contribute to developing cirrhosis, including:

- Infections with hepatitis B or C viruses
- Long-term heavy drinking
- Obesity
- Diabetes

There are also additional factors that can increase the likelihood of have HCC. For instance, individuals aged over 60 (especially those over 85), men, and those with a family history of primary liver cancer are at higher risk. Additionally, individuals with medical conditions such as

gallstones, liver flukes (parasites in the liver), or human immunodeficiency virus (HIV) also have an increased likelihood of developing HCC.¹¹

What is advanced or unresectable HCC?

HCC initially progresses slowly.¹² In its early stages, it can often be treated effectively with surgery to remove the tumour or through a liver transplant.⁷ However, symptoms of HCC are typically scarce and non-specific, which means many people may not realise they have liver cancer until it has advanced.

As the cancer progresses, it can become more challenging to treat and it may spread to other parts of the liver or to other organs. Doctors use the **Barcelona Clinic Liver Cancer (BCLC) Staging System** to describe how far the cancer has progressed, from very early (Stage 0) to terminal (Stage D). You can find more details about staging in [Section 2b](#). When HCC reaches an advanced stage (Stage C), it may no longer be possible to remove the tumour surgically. This stage is referred to as advanced or unresectable HCC. At this point, treatment options focus on managing symptoms and trying to slow the progression of the disease, often involving systemic therapies such as targeted treatments, immunotherapy, or chemotherapy.

What is the impact of advanced or unresectable HCC (disease burden)?

Physically, advanced or unresectable HCC can cause severe symptoms that make everyday activities difficult, with symptoms like diarrhoea, fatigue, skin toxicity and appetite loss reported to have a significant impact.¹³

Emotionally, both patients and caregivers often experience stress, anxiety, and depression due to the diagnosis and ongoing treatment. Frequent medical visits and treatments can disrupt daily routines, making it challenging for patients to engage in social activities or maintain their independence.⁸

Families and caregivers also bear considerable emotional and financial stress. Balancing work, personal life, and caregiving duties can lead to neglecting their own care and reduced well-being.¹⁴ The financial strain of caregiving, such as lost income and extra expenses, can further impact family resources and everyone's **quality of life**.

What is the personal, financial and societal cost of advanced or unresectable HCC?

HCC has significant costs that affect patients, caregivers, and society as a whole. For patients, living with HCC means dealing with symptoms like pain, fatigue, and liver problems, which can disrupt daily life and frequently lead to time off work or long-term disability.¹⁵ Caregivers also face financial challenges, often providing unpaid assistance in managing their loved one's health.¹⁴

Treating HCC is also expensive. In England, the cost to treat 15,684 patients over six years was about £245 million, with an average cost of around £9,065 per patient over two years.¹⁶ The NHS bears a significant financial burden due to the rising number of HCC cases, which in turn affects the overall economy and workforce. Besides these direct medical costs, there are also indirect costs such as lost income and additional expenses for travel and caregiving responsibilities.¹⁴

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is HCC diagnosed?

When diagnosing HCC, doctors use various methods to assess the liver function. Imaging tests, such as **computerised tomography (CT)**, **magnetic resonance imaging (MRI)**, **ultrasounds** and **PET (positron emission tomography)** scans, can be used to look for any tumours within the liver. Tissue **biopsies** can be examined under a microscope for signs of damage or disease. Blood tests can also be taken to look for tumour **markers**, which doctors can look for to diagnose cancers.^{11, 17}

Staging

Once diagnosed, the next important step is determining the stage of the cancer. The stage of a cancer describes its size and whether it has spread from where it first started. By analysing the stage, clinicians can discuss the best treatment options available for patients. In the UK, the staging depends on factors such as:⁷

- Where the cancer is in the liver
- The size of the tumour or tumours
- How many tumours there are
- Whether the cancer has spread outside the liver
- Whether any important **blood vessels** in the liver are affected
- How well your liver is working
- Your general health

These evaluations use the BCLC staging system to categorise patients, from Stage 0 (very early HCC) to Stage D (**terminal** HCC), and can inform the type of treatments patients are likely to be recommended. In this evaluation, we are particularly focussed on intermediate (Stage B) and advanced or unresectable (Stage C) HCC.

Intermediate HCC (Stage B) means there are multiple tumours in the liver, but they haven't spread outside the liver or into major blood vessels.^{18, 19} Advanced HCC (Stage C) is when tumours have started to invade blood vessels or spread beyond the liver to other parts of the body.^{18, 19} Patients at this stage might have more severe symptoms and may need treatments like targeted therapies or immunotherapy to help control the disease and improve their quality of life. Understanding these stages is crucial as it helps doctors choose the optimal treatment options for different patients.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for advanced or unresectable HCC?

In England and Wales, three **first-line therapies** are currently recommended by NICE for the systemic treatment of adults with advanced or unresectable HCC.²⁰⁻²³

Atezolizumab + bevacizumab

The **combination therapy** atezolizumab + bevacizumab is the preferred treatment option for individuals with advanced or unresectable HCC. It is given to patients every three weeks through an **intravenous** (IV) line, which is where the medicine is administered directly into the vein.²¹ These medicines help the **immune system** fight cancer and can slow down the growth of blood vessels that feed tumours.²⁴

Since bevacizumab can increase the risk of bleeding, all patients need to have an endoscopy before starting the treatment.^{25, 26} This test helps doctors check for any potential bleeding risks. Unfortunately, the procedure can be uncomfortable for patients, it might delay the start of cancer treatment and may put a strain on the healthcare services.

Sorafenib and lenvatinib

Some people might not be able to take atezolizumab + bevacizumab. This could be because the treatment needs to be given through an IV or because they are allergic to some of the ingredients. For these individuals, there are two alternative therapies that can be taken: sorafenib or lenvatinib.

Sorafenib and lenvatinib are both administered orally, with sorafenib taken twice a day and lenvatinib taken once a day.^{22, 23} They work by blocking **proteins** needed for cancer **cell** growth and creating new blood vessels.²⁷⁻²⁹ Both medications are recommended by NICE for those with advanced HCC and good liver function.

Unmet need

Although atezolizumab + bevacizumab is often the first systemic treatment offered to patients with HCC, the requirement for an endoscopy can delay the start of therapy and put extra strain on healthcare services. Additionally, some patients may not be suitable for this treatment due to risks like treatment-related bleeding, other co-existing limiting conditions or allergies to the

Summary of information for patients for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

ingredients. Therefore, there is a significant need for more treatment options that can help a large number of patients live longer.

STRIDE

STRIDE is a new combination treatment of durvalumab and tremelimumab. Tremelimumab is given as a one-off dose, administered to patients via IV. Durvalumab is administered to patients via IV every four weeks. This combination therapy works by improving the immune system's ability to attack cancer cells without increasing the risk of treatment-related bleeding.³⁰

Recent treatment guidelines developed by experts in liver disease support the use of STRIDE as a first-line treatment alongside atezolizumab + bevacizumab for patients with advanced or unresectable HCC.⁵ Alternative options, for example if patients do not want an IV treatment or have an allergy to one of the first-line treatment options, include lenvatinib or sorafenib.⁵ This positioning has also been supported by feedback from UK clinical experts.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

HCC from the patient perspective

Integrating the patient voice with clinician reports to identify hepatocellular carcinoma-specific treatment-related symptomatic adverse events³¹

A study was conducted to improve how patients report side effects during clinical trials for HCC. The study used a special system called the **Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)** to gather side effect information from both patients and doctors. Five medical oncologists from different countries and 17 patients with HCC participated. They worked together to identify the most important side effects to monitor during these trials. Doctors highlighted serious side effects like hand-foot syndrome, diarrhoea, fatigue, decreased appetite, rash, vomiting, and weight loss. They also noted concerns such as chills, difficulty swallowing, and loss of bowel control. Patients pointed out that loss of appetite, pain at injection sites, fatigue, nausea, and hair loss were particularly bothersome. The study concluded that combining patient and doctor perspectives is crucial. This helps create a useful list of side effects to monitor, making treatments more tolerable for patients.

Unmet need and value of STRIDE

Patients with HCC face significant unmet needs, including insufficient information at diagnosis and treatments that often impair their quality of life. Common side effects such as fatigue, nausea, and hair loss are major concerns. There is a need for better communication and more accessible information, as well as treatments that prioritise maintaining and improving quality of life.

How STRIDE addresses these needs

STRIDE shows great promise in addressing the needs of patients with HCC. In the HIMALAYA trial, patients answered quality of life and health questions using special questionnaires.³² Patients on STRIDE experienced longer times before symptoms worsened and showed better overall health, physical functioning, and improvements in specific symptoms like fatigue, nausea, and appetite loss compared to those on sorafenib. STRIDE also improved abdominal pain and swelling more effectively.

Additionally, patients reported better daily functioning, emotions, and social interactions. Quality of life remained stable and even slightly improved over time for STRIDE patients. Overall, STRIDE leads to better health outcomes and significantly improves the quality of life for patients with HCC, effectively addressing the key areas where patients had highlighted the need for improvement.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating

Summary of information for patients for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

STRIDE is a combination therapy consisting of two treatments: durvalumab and tremelimumab.

Durvalumab is a specially designed **antibody** that helps your immune system fight cancer by blocking a protein called **PD-L1**. PD-L1 is a protein that some cancer cells use to hide from your immune cells. By blocking PD-L1, durvalumab enables your immune system's white blood cells to recognise and attack the cancer cells more effectively.³³⁻³⁵

Tremelimumab is another antibody that supports your immune system by targeting a different protein known as **CTLA-4**, which is found on activated **T-cells**. Normally, CTLA-4 can inhibit white blood cell activation, which can limit your **immune response**. By blocking CTLA-4, tremelimumab keeps white blood cells activated and enhances their ability to combat cancer cells.^{36, 37}

When used together, these two treatments offer a complementary approach to combating cancer. Durvalumab stops cancer cells from hiding by inhibiting PD-L1, while tremelimumab ensures that white blood cells stay activated by blocking CTLA-4. Compared to using either treatment alone, this combination results in a stronger and more prolonged immune response against the cancer cells, improving the chances of stopping the cancer.³⁰

Importantly, this treatment avoids using drugs that affect the growth of new blood vessel, and avoiding such drugs can reduce the risk of serious treatment-related bleeding. This is particularly beneficial for patients with advanced liver cancer, who are more likely to experience bleeding complications.⁵

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, STRIDE is not intended to be used with any other treatment for advanced or unresectable HCC.

Summary of information for patients for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is STRIDE taken?

The STRIDE regimen involves two medicines: tremelimumab and durvalumab. Treatment begins with a single dose of 300 mg of tremelimumab given through an IV. This happens on the first day of the first treatment cycle (**Cycle 1, Day 1**). Immediately after, patients receive 1,500 mg of durvalumab, also given through an IV infusion on the same day. After the initial treatment, patients continue to receive 1,500 mg durvalumab alone every four weeks via an IV infusion.³² The treatment typically continues long-term, but the exact duration will be determined by the doctor based on how the cancer responds to the treatment and if the patient experiences any adverse events.

Further details on the administration and dosing requirements for STRIDE can be found in the **Summary of Product Characteristics (SmPC)** for STRIDE for the treatment of advanced or unresectable HCC.^{38, 39}

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of STRIDE in advanced or unresectable HCC

The key **clinical trial** providing clinical evidence for STRIDE in patients with advanced or unresectable HCC is the **Phase III HIMALAYA** trial.^{32, 40}

The HIMALAYA trial assesses how well STRIDE worked to improve patient survival and reduce or stop tumour growth compared to sorafenib. More details on the exact measurements used can be found in **Section 3e**. The trial also assesses the safety and tolerability of STRIDE compared to sorafenib, including the frequency and severity of side effects, and whether patients had to stop treatment. Finally, the trial considers the impact of STRIDE on patients' quality of life.

The HIMALAYA trial is being conducted in 170 countries and includes 1,324 participants. The initial phase of the trial was completed on August 27, 2021, and the entire study is expected to be finished by August 27, 2024. Data collected from HIMALAYA has been reported in the New England Journal of Medicine by Abou-Alfa 2022, and the latest information on the trial is available at ClinicalTrials.gov.^{32, 40}

More information on this trial can be found in **Document B** in **Section B.3.1**.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

There are six key clinical outcomes that were used to assess the efficacy of STRIDE compared to sorafenib. The outcomes used, their respective definitions, and the results from the HIMALAYA trial are listed below:

- **Overall survival (OS):** the duration from the start of the trial until death of any cause
- **Progression-free survival (PFS):** the time from the start of the trial until the tumour progresses or until death of any cause
- **Time to progression (TTP):** the time from the start of the trial until the tumour progresses
- **Objective response rate (ORR):** the number of patients showing **complete** or **partial response** from the treatment
- **Disease control rate (DCR):** the number of individuals who had a complete or partial response, or whose disease had stabilised
- **Duration of response (DoR):** the percentage of patients still responding to treatment

Efficacy measure	STRIDE	Sorafenib
OS ^a , months	16.4	13.8
PFS ^a , months	3.8 ^b	4.1 ^b
TTP ^a , months	5.4	5.6
ORR, %	20.1	5.1
DCR, %	60.1	60.7
DoR ^a , months	22.3	18.4

Footnote: ^aThe OS, PFS, TTP and DoR efficacy measures refer to the **median** value; ^bA higher percentage of patients in the STRIDE group (12.5%) remained progression-free compared to the sorafenib group (4.9%), indicating that there is a benefit of the STRIDE treatment to patient despite having similar PFS values.

In summary, STRIDE demonstrated a statistically significant and clinically meaningful improvement in OS compared to sorafenib, which was the main clinical outcome assessed. Additionally, improvements were observed in ORR and DCR, with comparable PFS, TTP, and DCR to sorafenib.

Indirect treatment comparison

No data are available for **direct comparisons** of STRIDE versus atezolizumab + bevacizumab and lenvatinib from the HIMALAYA trial. Therefore, an analysis called an **indirect comparison** was used. This method allows researchers to compare data from different clinical trials by using a common treatment that was assessed in both trials, in this case sorafenib.

This analysis revealed that OS and PFS were improved for STRIDE, atezolizumab + bevacizumab, and lenvatinib compared to sorafenib. It also revealed that there was no significant difference in effectiveness between STRIDE and atezolizumab + bevacizumab, which is currently the treatment option that offers patients the best chance of survival.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of STRIDE

During HIMALAYA, patients were asked to answer questions about their quality of life and health, using the three questionnaires below:

- **EORTC QLQ-C30:** This is a questionnaire designed to evaluate the overall quality of life of patients with cancer participating in clinical trials. The questionnaire addresses a wide range of health and well-being aspects
- **EORTC QLQ-HCC18:** This is a specialised questionnaire aimed at assessing the quality of life specifically in patients with HCC involved in clinical trials
- **EQ-5D-5L:** This is a standardised questionnaire that is non-specific to any disease area which provides a general measure of health and well-being by examining five key areas of daily functioning and health status

Before treatment began, patients in both the STRIDE and sorafenib groups had similar health scores, but there were some small differences. STRIDE patients had high physical functioning scores but lower overall health and quality of life scores. On the other hand, those starting on sorafenib reported more severe symptoms, including fatigue, loss of appetite, abdominal pain, and shoulder pain.

Treatment with STRIDE resulted in a longer amount of time before symptoms worsened compared to sorafenib. Patients who received STRIDE showed better results in overall health, physical functioning, and specific symptoms such as fatigue, nausea, and appetite loss. STRIDE also led to greater improvements in abdominal pain and swelling compared to sorafenib. Moreover, patients on STRIDE experienced greater improvements in daily roles, cognitive abilities, emotions and social interactions.⁴¹

Quality of life, measured by the EQ-5D-5L questionnaire, remained stable and even improved slightly over time for patients who received STRIDE, compared to patients who received sorafenib. Additionally, patients on STRIDE reported fewer severe problems compared to those on sorafenib, even after stopping treatment.

Overall, all three questionnaires indicated that STRIDE leads to better health outcomes and improved quality of life for patients. Additionally, treatment with STRIDE allowed patients to maintain their daily functioning and manage disease symptoms for a longer period compared to those who were treated with sorafenib.⁴¹

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own **side effects** and the same medicine can produce different reactions in different people. The SmPC for STRIDE reports side effects which are categorised as very common (occurring in more than 1 in 10 people) and common (occurring in more than 1 in 100 but less than 1 in 10 people).^{38, 39} Detailed information about any side effects can be found in the patient leaflets on the EMC website.^{42, 43}

In HIMALAYA, STRIDE was generally well **tolerated**. No new side effects were discovered for STRIDE compared to the already known side effects for the two medicines within the regimen.⁴⁴

When compared to sorafenib, a similar number of patients experienced serious side effects: 196 patients (50.5%) who received STRIDE and 196 patients (52.4%) who received sorafenib. Additionally, 53 patients (13.7%) receiving STRIDE and 63 patients (16.8%) receiving sorafenib had to stop treatment due to side effects. This suggests that STRIDE and sorafenib have similar safety profiles.

The most common side effects seen in patients receiving STRIDE were rashes (22.4%), itching (22.9%) and diarrhoea (26.5%). Importantly, there were low levels of bleeding-related side effects in patients treated with STRIDE.³² There was also no difference in liver-related side effects between STRIDE and sorafenib, indicating that treatment with STRIDE is not associated with increased liver problems.³²

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of STRIDE to patients with advanced or unresectable HCC include:



STRIDE is associated with improved overall survival compared to sorafenib



STRIDE offers another treatment option for all individuals, reducing the clinical and health-related quality of life burden



STRIDE does not result in an increased risk of bleeding in the stomach, intestines or oesophagus related to the treatment



To be eligible for STRIDE, patients do not require an endoscopy to screen for an increased risk of bleeding, reducing clinical burden and the associated impact on patients' wellbeing, and reducing time to the start of treatment

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

STRIDE is generally a well-tolerated and effective treatment, leading to improved OS compared to sorafenib. However, like all therapies STRIDE does not work for everyone and some patients might not experience any improvement in HCC. Patients for whom STRIDE does not work may still experience side effects, which are detailed in **Section 3g**.

The tremelimumab component of STRIDE is given as a one-off dose at the beginning of the treatment, whereas the durvalumab component is given through an IV every four weeks, and patients need to visit the hospital for these appointments. However, unlike some other treatments, most patients don't need an endoscopy, and the hospital visits are less frequent. This makes it easier for both patients and the healthcare system.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicine provides this information to healthcare administrators using a **health economic model**. The health economic model developed for this NICE submission will be used to perform an analysis comparing the costs and benefits of the new treatment (STRIDE) with each of the three existing therapies offered as a first-choice therapy to patients: atezolizumab + bevacizumab, lenvatinib and sorafenib.

How the model reflects advanced or unresectable HCC

The economic model was designed to reflect the key features of advanced or unresectable HCC and **clinical practice** in the UK. To do this, a model structure called a **partitioned survival model** was chosen, as it best fits the clinical data and matches the methods used in similar analyses. The partitioned survival model was used to model the experience of having advanced or unresectable HCC over time and compares treatment with STRIDE versus atezolizumab + bevacizumab, lenvatinib and sorafenib.

Modelling the impact of STRIDE on quality of life in advanced or unresectable HCC

Data from the HIMALAYA trial and the indirect treatment comparison were used to compare STRIDE, atezolizumab + bevacizumab, lenvatinib and sorafenib in a health economic model.^{29, 45} The economic analysis considers by how much STRIDE is likely to extend both survival (OS) and the amount of time patients can live without their tumour progressing (PFS). The economic analysis is modelled over a total of 40 years, far beyond the trial period. This is because the HIMALAYA results span four years, but patients can live longer and continue treatment.

Summary of information for patients for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

Quality of life and time spent alive is captured by **quality-adjusted life years (QALYs)**. Data on the quality of life of patients in the HIMALAYA were taken from a questionnaire called the EQ-5D-5L (**Section 3f**). In the economic model, the quality of life is captured using **utility values**. Utility values are generally a number between 0, which represents death, and 1, which represents perfect health. QALYs are a health outcome measure that considers both the length and the quality of life provided by a treatment. A year spent in perfect health (i.e. a utility score of 1) represents one QALY. In the model, each treatment was assigned a utility value, which reflected the impact adverse events associated with that particular treatment may have on patient quality of life.

STRIDE is expected to offer better quality of life benefits for patients with advanced or unresectable HCC compared to the lenvatinib and sorafenib, whilst showing similar results to atezolizumab + bevacizumab. The model showed this by modelling evaluating how helpful each treatment is in improving patients' overall well-being.

Furthermore, STRIDE is likely to help patients live longer compared to lenvatinib and sorafenib, and it is expected to have similar survival results to atezolizumab + bevacizumab.

Modelling the costs of treatments

Various different costs are included in the model for the different advanced or unresectable HCC treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of monitoring the patients during treatment
- The cost of side effects that happen during treatment
- The costs of end-of-life care

Uncertainty

There was some uncertainty about the estimated treatment effects within the model, which quality of life measures should be used, and whether sharing vials of the medicine should be included in the model. However, analyses varying these factors found that the overall conclusion remained unchanged.

Variations of other inputs in the model were also tested, the results of these tests are explained in **Document B, Section B.3.11**.

Cost effectiveness results

Based on the modelling inputs and assumptions from AstraZeneca, treatment with STRIDE was associated with similar health benefits (or '**quality-adjusted life years**' [QALYs]) at a reduced cost compared to atezolizumab + bevacizumab, the principle treatment used for advanced or unresectable HCC in the UK, based on AstraZeneca's calculations.

Benefits of STRIDE not captured in the economic analysis

Treatment with STRIDE may have many different positive impacts for people with advanced or unresectable HCC. The model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured. For example:

- While this evaluation highlights that STRIDE saves money by not needing endoscopy compared to atezolizumab + bevacizumab, it doesn't account for other benefits like reduced time to treatment initiation, or reduced strain on the NHS if STRIDE is recommended.
- The evaluation also doesn't consider the positive effects on carers and relatives due to better patient outcomes with STRIDE. It overlooks how these improved outcomes could boost the productivity of patients, carers, and relatives.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

STRIDE is an innovative treatment which would represent an important advancement in the treatment of advanced or unresectable HCC

STRIDE is an innovative treatment option that consists of two immune system-based therapies, durvalumab and tremelimumab. By bringing together these two therapies, the treatment leverages their unique strengths in enhancing the immune system's ability to fight cancer.³⁰

STRIDE is the first treatment for advanced or unresectable HCC that has strong evidence showing it is effective in patients without resulting in an increased risk of treatment-related bleeding. Therefore, STRIDE stands out as an effective treatment with manageable side effects, making it particularly beneficial for individuals who are not eligible for other treatments.

Advanced or unresectable HCC can greatly impact a patient's mental, emotional well-being, and quality of life. Unfortunately, current treatments often come with uncomfortable side effects or may not be suitable for all patients. STRIDE, however, has a manageable safety profile and serves as an alternative clinical option that can improve patients' quality of life compared to other treatments.

The treatment burden with STRIDE is lower compared to other options, as it requires less frequent treatment sessions. Additionally, unlike other treatments, not all patients need an endoscopy before starting STRIDE. This means patients will spend less time in hospital and experience fewer delays before beginning treatment, thereby improving their overall well-being.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues [here](#)

There are no equality issues that are anticipated for the use of STRIDE in adults with advanced or unresectable HCC.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Further information on advanced or unresectable HCC:

- National Health Service — Liver cancer: <https://www.nhs.uk/conditions/liver-cancer/>
- Macmillan cancer Support — Liver cancer: <https://www.macmillan.org.uk/cancer-information-and-support/liver-cancer>
- Summary of Product Characteristics (SmPC) for durvalumab for the treatment of adults with advanced or unresectable HCC who are ineligible for locoregional therapy and have had no prior systemic treatment: <https://www.medicines.org.uk/emc/product/9495/smpc#gref>
- Summary of Product Characteristics (SmPC) for tremelimumab for the treatment of adults with advanced or unresectable HCC who are ineligible for locoregional therapy and have had no prior systemic treatment: <https://www.medicines.org.uk/emc/product/14841/smpc#gref>
- ClinicalTrials.Gov information on HIMALAYA — NCT02519348: <https://clinicaltrials.gov/study/NCT02519348>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Summary of information for patients for durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]

Advanced	Advanced cancers are cancers that have spread or come back
Antibody	A protein made by plasma cells (a type of white blood cell) in response to an antigen (a substance that causes the body to make a specific immune response)
Antiviral	Medication that can help your immune system fight back by helping stop the virus multiplying in your body
Barcelona Clinic Liver Cancer (BCLC) Staging System	This is a way for doctors to describe the progression of liver cancer, from very early to terminal stages, helping them decide the best treatment options
Biopsy	A process of taking a tissue sample for medical examinations
Blood vessels	Tubes that carry blood through the body
Cell	Muscles and organs are made of small units called cells
Clinical trial	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease
Clinically meaningful	Makes a meaningful difference to someone with the disease, their carer or doctor.
Combination therapy	This is when you are given more than one medicine at the same time to treat your cancer
Cirrhosis	A condition where the liver becomes severely scarred

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Complete response	The disappearance of all signs of cancer in response to treatment. However, this does not always mean the cancer has been cured
Computerised tomography (CT) scan	A procedure that uses a computer and an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly
CTLA-4	A protein found on T cells (a type of immune cell) that helps keep the body's immune response in check
Cycle	Many cancer treatments are given in cycles. Each cycle is often divided into a period where you receive a treatment, followed by a period of rest from treatment to allow your body to recover from any side effects. The length of each cycle and the split between treatment and rest periods depend on the type of cancer you have, where it is in your body, if it has spread and where to
Diarrhoea	Having bowel movements that are soft, loose or watery more often than normal
Disease control rate (DCR)	The number of patients showing complete or partial improvement from the treatment
Duration of response (DoR)	The percentage of patients still responding to the treatment
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial

European Medicines Agency (EMA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union
Endoscopy	An endoscopy is a procedure where a doctor uses a thin, flexible tube with a light and camera on the end to look inside the digestive tract. This helps doctors see if there are any potential areas of bleeding, such as in the oesophagus, stomach, or intestines
EORTC QLQ-C30	This is a questionnaire designed to evaluate the overall quality of life of cancer patients participating in clinical trials, addressing a wide range of health and well-being aspects
EORTC QLQ-HCC18	This is a specialised questionnaire aimed at assessing the quality of life specifically for patients with liver cancer (hepatocellular carcinoma) involved in clinical trials
EQ-5D-5L	This is a standardised questionnaire that provides a general measure of health and well-being across various conditions by examining five key areas of daily functioning and health status
First-line	This is the first treatment given for your disease or illness.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial
Immune response	The way the body defends itself against substances it sees as harmful or foreign
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases

Incremental cost-effectiveness ratio	The incremental cost-effectiveness ratio (ICER), is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest
Indirect treatment comparison	An analysis that compares treatments that have not been compared directly in a head-to-head, randomised trial
Inflammation	The result of the immune response to injury of tissues including redness, swelling and loss of function
Intravenous (IV)	Some cancer drugs are diluted in a bag of fluid which is connected to a very thin tube and goes into one of your veins
Locoregional	Locoregional refers to treatments or effects that are focused on a specific area or region of the body, usually near the original site of the disease. In the context of cancer, it means treatments that target the tumour and surrounding tissues without affecting the entire body
Magnetic resonance imaging (MRI)	A scan that uses the body's natural magnetic properties to produce detailed images from any part of the body
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country
Marker	An indicator of a specific disease or process
Median	The median is the middle value when all patient results are sorted from lowest to highest

Medicines and Healthcare products Regulatory Agency (MRHA)	The regulatory body that evaluates, approves and supervises medicines throughout the UK
National Health Service (NHS)	This is the UK's government-funded healthcare service that everyone living in the UK can use without being asked to pay the full cost of the service
National Institute for Health and Care Excellence (NICE)	The body in England that decides whether to approve new medicines for funding on the NHS based on whether they can be demonstrated to be value for money
Objective response rate (ORR)	The number of patients showing complete or partial response from the treatment
Overall survival (OS)	The duration from the start of the trial until death of any cause
Partial response	A decrease in the size of the cancer, or in the extent of cancer in the body, in response to treatment
Partitioned survival model	A type of economic model used to follow a theoretical cohort through time as they move between a set of health states in a model
PD-L1	A protein that acts as a “brake” to keep the body's immune response under control
Positron emission tomography (PET)	A PET scan is a special test that allows doctors to see how different parts of your body are working. It involves a small amount of a safe, radioactive substance that highlights areas of your body on the scan, helping doctors to spot any unusual activity.
Phase 3 clinical trial	This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For

	example, it evaluates which group of patients has better survival rates or fewer side effects
Pneumonia	A severe inflammation of the lungs that can reduce the amount of oxygen that blood can be absorbed from air
Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	A tool that lets patients directly report any side effects of symptoms they experience during treatment, helping doctors understand how the treatment affects their daily lives
Progression-free survival (PFS)	The time from the start of the trial until the disease worsens or the patient dies
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living
Radioactive beads	Tiny particles that doctors use to treat certain types of cancer by deliver radiation directly to

	the tumour, helping to shrink it while causing less damage to health tissue
Side effect	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe
Stage	The stage of a cancer describes its size and whether it has spread from where it first started
Summary of Product Characteristics (SmPC)	A document describing the properties and the officially approved conditions of use of a medicine
Systemic	A type of cancer therapy that is aimed at the whole body or multiple organs, not just at a specific location
T cell	A type of white blood cell
Technology appraisal (TA)	Recommendations on the clinical and cost-effectiveness of medicines and treatments in the NHS
Terminal	Cancer that cannot be cured or controlled with treatment and leads to death
Tolerated	The ability of a patient to put up with the side effects of treatment
Time to progression (TTP)	The time from the start of the trial until the tumour progresses
Ultrasound	An ultrasound is a medical test that uses sound waves to create pictures of the inside of your body, helping doctors see organs and tissues.

Unresectable	Unresectable tumours are those that are not capable of being surgically removed
Upper respiratory tract infection	An infection that affects the sinuses and throat
Utility values	A measurement of how good or bad different health conditions are, from the perspective of those experiencing them

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B.1 Addendum

20th December 2024

B.1.1 *Description of survival curves in the submission*

- Company submission Document B, Figure 35: Base case overall survival (OS) parametric survival extrapolations (STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib)
 - The plot depicts the OS Kaplan Meier (KM) curves for STRIDE and sorafenib from the HIMALAYA trial, with the independently fit base case models extrapolated over the model time horizon. Also included on the plot are lenvatinib and atezolizumab + bevacizumab.
 - The atezolizumab + bevacizumab curve initially sits above the STRIDE curve, up to ~6.5 years, before falling below the STRIDE curve, as a result of applying the hazard ratio (HR) calculated in the indirect treatment comparison (ITC) presented in the Company submission to the sorafenib reference curve for atezolizumab + bevacizumab and using independently fit models for HIMALAYA. This is an appropriate approach given that the proportional hazards assumption holds within IMBRAVE150 between atezolizumab + bevacizumab and sorafenib, but does not hold within HIMALAYA for STRIDE and sorafenib.
 - The lenvatinib curve was generated by applying a HR of 1 to the sorafenib arm, reflecting the REFLECT study's conclusion that lenvatinib was statistically non-inferior to sorafenib in terms of OS.
- Company submission Document B, Figure 47: Base case progression-free survival (PFS) parametric survival extrapolations (STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib)
 - The plot depicts the PFS KM curves for STRIDE and sorafenib from the HIMALAYA trial, with the independently fit base case models extrapolated over the model time horizon. Also included on the plot are lenvatinib and atezolizumab + bevacizumab.
 - The atezolizumab + bevacizumab curve initially sits above the STRIDE curve, up to ~9 years, before falling below the STRIDE curve, as a result of applying the HR calculated in the ITC to the sorafenib reference curve for atezolizumab + bevacizumab, and using independently fit models for HIMALAYA. This is an appropriate approach given that the proportional hazards assumption holds within IMBRAVE150 between atezolizumab + bevacizumab and sorafenib, but does not hold within HIMALAYA for STRIDE and sorafenib.
 - Similarly, the lenvatinib curve initially sits above the STRIDE curve, up to ~3 years, before falling below the STRIDE curve, as a result of applying the HR calculated in the ITC to the sorafenib reference curve for lenvatinib, and using independently fit models for HIMALAYA. This is a pragmatic and conservative approach – although the proportional hazards assumption is violated in REFLECT between lenvatinib and sorafenib, time-varying analyses conducted for REFLECT suggested a positive treatment effect for lenvatinib at the beginning of the study follow-up that diminishes over time, meaning that the results of the NMA may overpredict survival for lenvatinib.

B.1.2 *Results updated with corrected half-cycle correction for tremelimumab*

Updates to model:

- Half-cycle correction made for tremelimumab, in line with the EAG's recommendations

B.1.2.1 Base-case results

B.1.2.1.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic and probabilistic cost-effectiveness results for STRIDE vs. atezolizumab + bevacizumab, sorafenib and lenvatinib are presented in Table 1 and Table 2, respectively. The fully incremental results for the deterministic and probabilistic analyses are presented in Table 3 and Table 4, respectively. In the deterministic base case, STRIDE dominated atezolizumab + bevacizumab, accumulating fewer costs and greater QALYs over a lifetime horizon. Relative to sorafenib and lenvatinib, STRIDE was associated with deterministic, pairwise ICERs of [REDACTED] and [REDACTED] per QALY, respectively; this also includes the application of a 1.2x severity modifier to the incremental QALYs for these two comparisons.

In the probabilistic analysis, the NHB results are similar to those in the deterministic analyses. Pairwise probabilistic ICERs for the comparison between STRIDE and sorafenib and STRIDE and lenvatinib were consistent with the deterministic ICERs. For the comparison of STRIDE and atezolizumab + bevacizumab, the incremental QALYs are close to zero for both the deterministic and probabilistic analysis, but for the probabilistic analysis the ICERs fall in the southwest (SW) quadrant of the cost-effectiveness plane, meaning that the results show cost saved per QALY forgone.

At a willingness-to-pay (WTP) threshold of £30,000/QALY gained, STRIDE represents a cost-effective use of NHS resources vs. the principal comparator, and SoC in NHS clinical practice, atezolizumab + bevacizumab, in both the deterministic and probabilistic analysis.

Table 1: 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	██████	██████	██████	-	-	-	-	-	-
Atezolizumab + bevacizumab	£244,087	3.02	2.42	██████	██████	██████	STRIDE is dominant	██████	██████
Sorafenib	£36,799	1.92	1.48	██████	██████	██████	██████	██████	██████
Lenvatinib	£48,445	1.92	1.48	██████	██████	██████	██████	██████	██████

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: Probabilistic 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	██████	██████	██████	-	-	-	-	-	-
Atezolizumab + bevacizumab	£243,759	3.08	2.46	██████	██████	██████	██████	██████	██████
Sorafenib	£36,825	1.92	1.48	██████	██████	██████	██████	██████	██████
Lenvatinib	£49,391	1.92	1.48	██████	██████	██████	██████	██████	██████

Footnotes: All results include the commercial access agreement in place for durvalumab. ^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; WPT: willingness to pay.

Table 3: Deterministic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER
Sorafenib	£36,799	1.92	1.48	-	-	-	-
Lenvatinib	£48,445	1.92	1.48	-	-	-	
STRIDE							
Atezolizumab + bevacizumab	£244,087	3.02	2.42	-	-	-	

Footnotes: All results include the commercial access agreement in place for durvalumab. ^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; WTP: willingness to pay.

Table 4: Probabilistic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER
Sorafenib	£36,913	1.93	1.49	-	-	-	-
Lenvatinib	£50,418	1.93	1.49	-	-	-	
STRIDE							
Atezolizumab + bevacizumab	£250,159	3.15	2.52				

Footnotes: All results include the commercial access agreement in place for durvalumab. ^aICER in the southwest (SW) quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; WTP: willingness to pay.

B.1.2.2 Exploring uncertainty

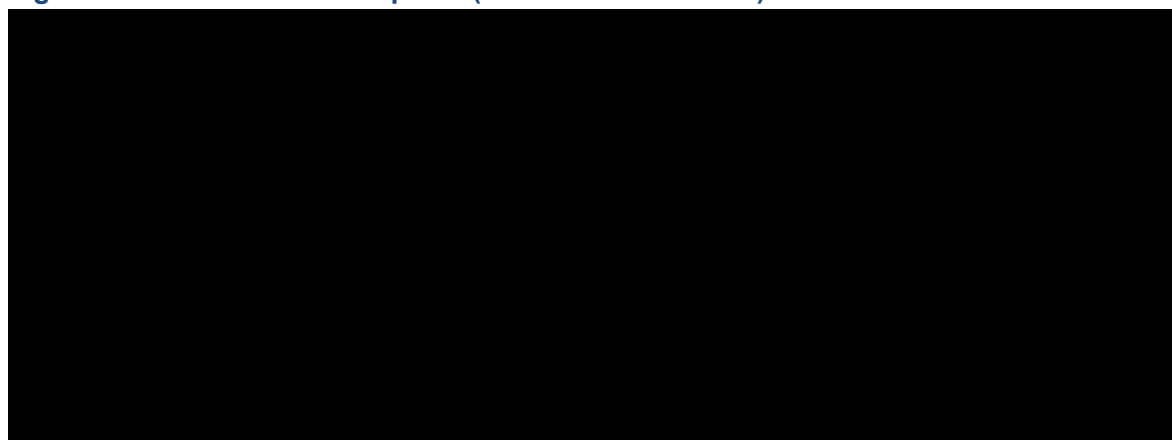
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections B.1.2.1 and B.1.2.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.1.2.4. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for, and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.1.2.2.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were run with 1,000 iterations, with estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Beta distributions were assumed for uncertain parameters bound by zero and one, including utilities, proportions, and probabilities. Log-normal distributions were assumed for hazard ratios. Gamma distributions were assumed for costs. Normal distributions were assumed for other uncertain parameters including resource use frequencies, with capping in place to ensure positivity for parameters which must be non-negative.

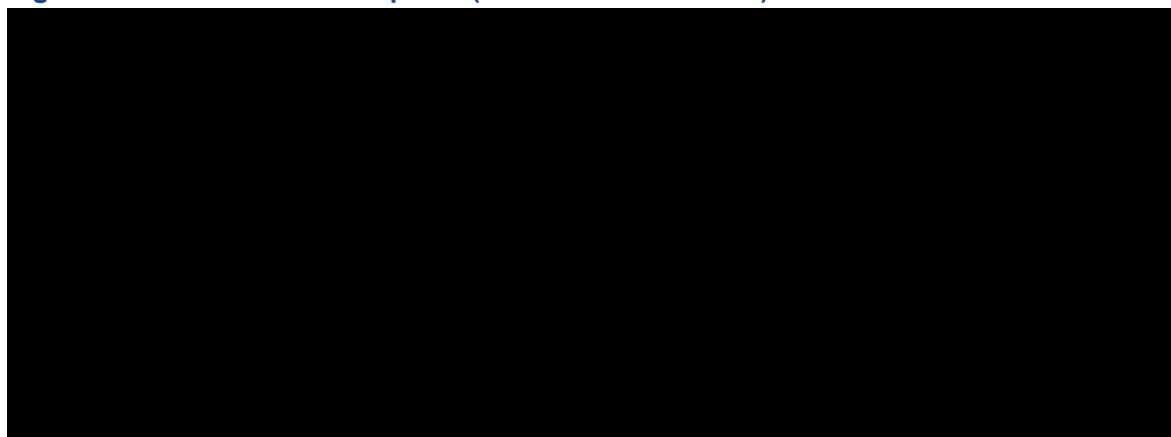
The probabilistic pairwise cost-effectiveness planes for STRIDE vs. relevant comparators are presented in Figure 1 to Figure 3. The cost-effectiveness acceptability curve is presented in Figure 4.

Figure 1: Cost-effectiveness plane (STRIDE vs sorafenib)



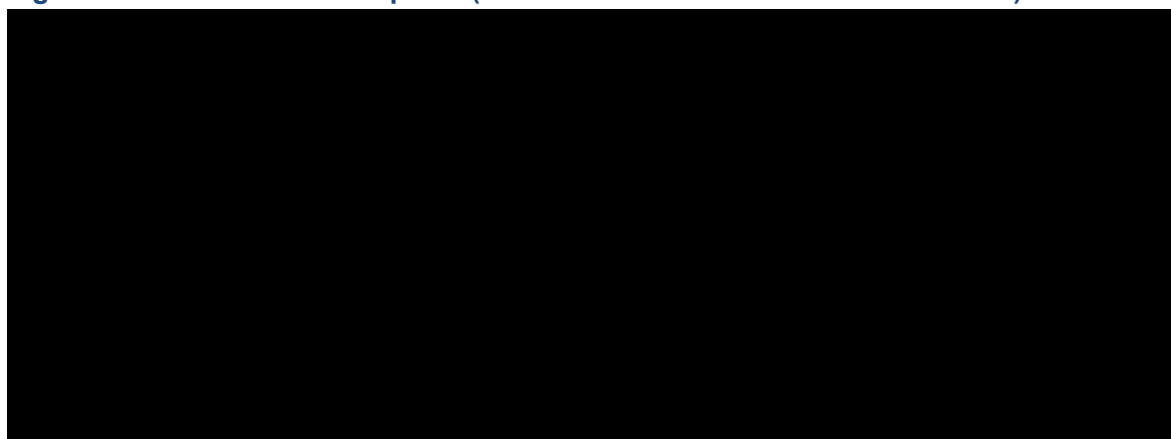
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 2: Cost-effectiveness plane (STRIDE vs lenvatinib)



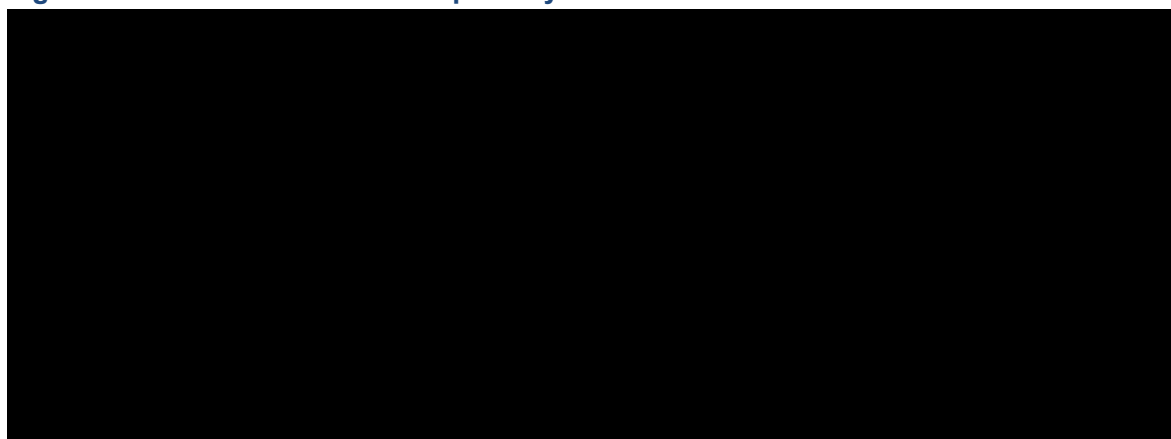
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 3: Cost-effectiveness plane (STRIDE vs atezolizumab + bevacizumab)



Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 4: Cost-effectiveness acceptability curve



Abbreviations: WTP: willingness to pay.

B.1.2.2.2 Cost comparison vs. atezolizumab + bevacizumab

The deterministic and probabilistic base case results show that incremental QALYs for the comparison between STRIDE and atezolizumab + bevacizumab fall either side of zero. This can

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be observed in Figure 3. This indicates, at a minimum, likely clinical equivalence between the two interventions, which is further supported by the results of the NMA presented in the Company submission, where no statistically significant difference was observed between STRIDE and atezolizumab + bevacizumab in terms of OS and PFS. To investigate this equivalence, a cost comparison was conducted where incremental QALYs were manually set equal for the two therapies. The results of this scenario analysis are presented in Table 5 and show that STRIDE is associated with cost-savings when compared to atezolizumab + bevacizumab.

Table 5: Cost comparison for STRIDE vs atezolizumab + bevacizumab (deterministic)

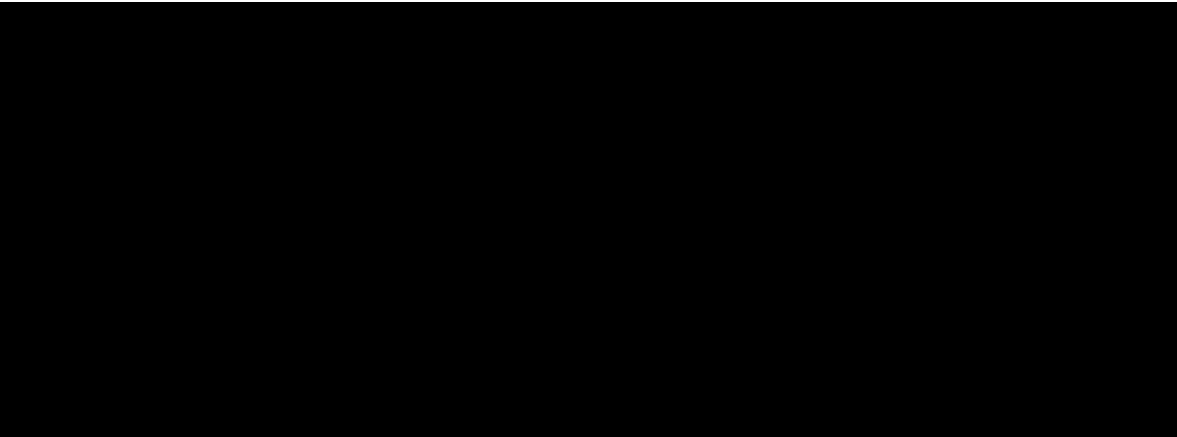
Scenario		STRIDE vs atezolizumab + bevacizumab		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Base case				Dominant
1	Cost-minimisation analysis, assuming equal efficacy		0.00	NA

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

B.1.2.2.3 Deterministic sensitivity analysis

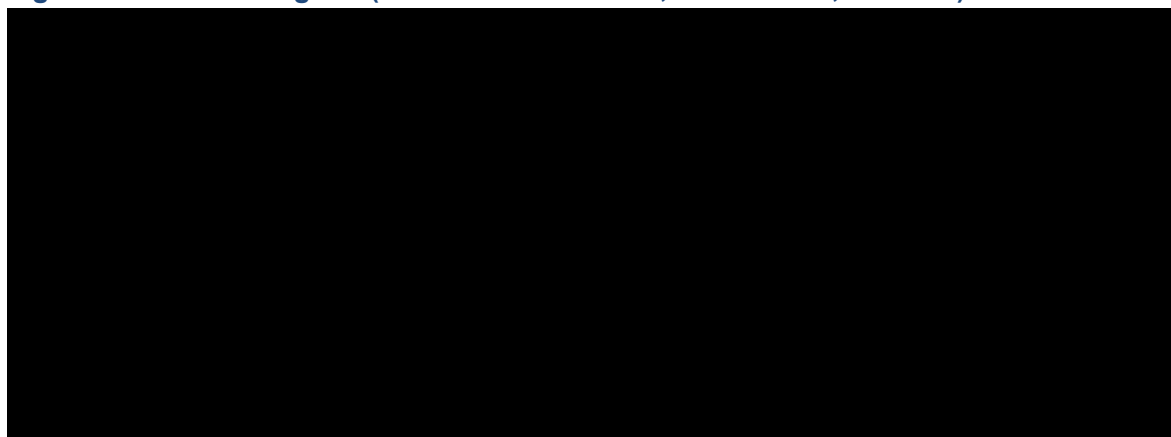
To assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted. The tornado diagrams for STRIDE vs. relevant comparators are presented in Figure 5, Figure 6 and Figure 7. The top 10 most influential parameters on the base case are presented in each case. In the comparison of STRIDE vs. sorafenib, the model was robust to variation in inputs. In the comparison of STRIDE vs. lenvatinib, results were most influenced by the PFS HR. Given PFS informs treatment duration for lenvatinib, and therefore drug costs, this likely explains the level of influence of this input. In the comparison of STRIDE vs. atezolizumab + bevacizumab, the PFS HR was again influential, and otherwise the model was robust to input variation.

Figure 5: Tornado diagram (STRIDE vs sorafenib; INHB at £30,000 WTP)



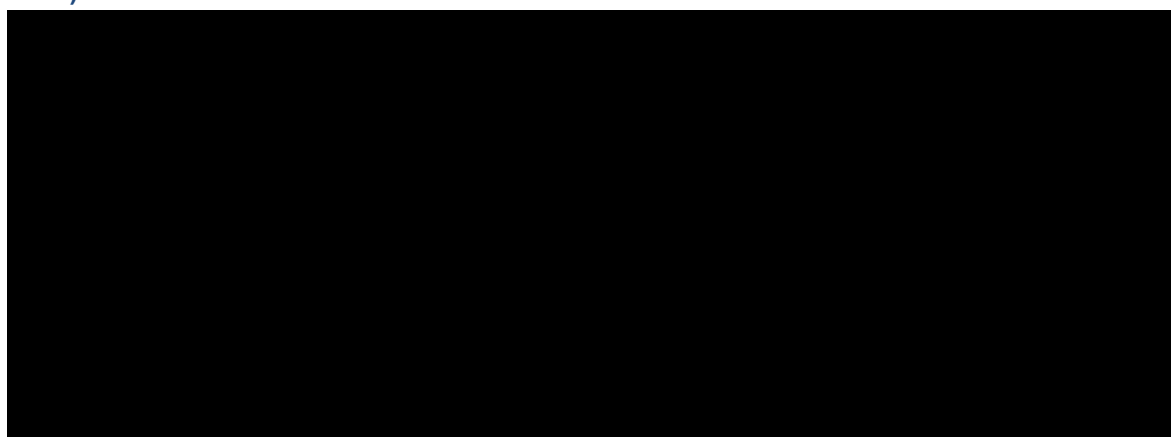
Abbreviations: DurvTrem: durvalumab with tremelimumab (otherwise referred to as STRIDE); IV: intravenous; INHB: incremental net health benefit; PD: progressed disease; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness-to-pay.

Figure 6: Tornado diagram (STRIDE vs lenvatinib; INHB at £30,000 WTP)



Abbreviations: DurvTrem: durvalumab with tremelimumab (otherwise referred to as STRIDE); IV: intravenous; INHB: incremental net health benefit; PD: progressed disease; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness-to-pay.

Figure 7: Tornado diagram (STRIDE vs atezolizumab + bevacizumab; INHB at £30,000 WTP)



Abbreviations: AtezoBev: atezolizumab + bevacizumab; DurvTrem: durvalumab with tremelimumab (otherwise referred to as STRIDE); IV: intravenous; INHB: incremental net health benefit; PD: progressed disease; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP: willingness-to-pay.

B.1.2.2.4 Scenario analysis

A number of scenario analyses were conducted to explore the impact of certain assumptions and alternative inputs on the results of the economic analysis. Each scenario analysis is described in turn below and full results of the scenario analysis are presented in Table 6. In the majority of scenarios, STRIDE remains dominant vs. atezolizumab + bevacizumab. In the two non-dominant scenarios, the ICER falls within the SW quadrant, where STRIDE remains cost-effective. The ICERs vs. sorafenib and lenvatinib remain relatively stable between scenarios, illustrating the robustness of the model to uncertainty.

Table 6: Scenario analysis results for STRIDE vs relevant comparators (deterministic)

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Base case										
1	Time horizon: 20 years									
2	Costs: Include vial sharing									
3	OS: Gen. gamma for Durva/Trem									
4	OS: Gen. gamma for Sora									
5	PFS: Gen.gamma for Durva/Trem									
6	PFS: Log-normal for Sora									
7	TTD: Gen.gamma for Durva/Trem									
8	TTD: Log-logistic for Sora									

Footnotes: ^aICER in the SW quadrant of the cost-effectiveness plane – cost saved per QALY forgone.

Abbreviations: ICER: incremental cost-effectiveness ratio; PFS: progression-free survival; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; SW: southwest; TTD: time to treatment discontinuation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

September 2024

File name	Version	Contains confidential information	Date
ID2725 durvalumab clarification questions to PM_27Sep24_[REDACTED]	1.0	Yes	27 September, 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searching (clinical effectiveness)

A1. Company submission (CS), Appendix C.2. 'UK public assessment report', the link provided for IMFINZI® (durvalumab) is for the EMA. The EAG have sourced the relevant EMA public assessment report, but please clarify whether there is also a Medicines and Healthcare products Regulatory Agency (MHRA) Public Assessment Report for Imfinzi® for the UK. If yes, please provide a (confidential) copy.

The current IMJUDO® MHRA Public Assessment report can be found via the link below:

<https://mhraproducts4853.blob.core.windows.net/docs/1bac9573d4fcc146a777788408a7cc3aadfd29f3>

There is no IMFINZI® MHRA Public Assessment report available. IMFINZI® was granted marketing authorisation in the EU before being grandfathered into a GB license from the EU license, following Brexit on 1st January 2021.

In addition to the EMA PARs provided in the CS Appendix, we are also providing via the link below to the variation related to the addition of HCC as an indication extension.

https://www.ema.europa.eu/en/documents/variation-report/imfinzi-h-c-4771-ii-0045-epar-assessment-report-variation_en.pdf

A2. CS, Appendix D.1.1, Bibliography Searches. Please provide a list of references and PDFs for the relevant systematic literature reviews (SLRs) and (network) meta-analyses identified during all 3 SLR iterations that were hand-searched to identify any additional, relevant studies for inclusion.

The bibliographies of all relevant SLRs and (network) meta-analyses identified during the SLR were searched, to identify any additional, relevant studies for inclusion. SLR and NMA articles themselves were not included in the review.

Hand-searched bibliography of SLRs and NMAs as part of the original 2020 SLR update is located in Table 12 in Appendix I.

Hand-searched bibliography of SLRs and NMAs as part of the 1st SLR update is located in Table 13 in Appendix I.

Hand-searched bibliography of SLRs and NMAs as part of the 2nd SLR update is located in Table 14 in Appendix I.

A3. CS, Document B, section B.2.9.1. Please provide a table of references for the '88 publications on 17 unique studies which were considered for inclusion in the NMA' (p63). For references not considered eligible for the NMA, please provide reasons for exclusion or clarify where these are located in Appendix D.

The company can confirm that there were 90 publications reporting on 18 unique studies from the original SLR and the two SLR updates, rather than 88 publications on 17 unique studies as originally reported; the company apologies for the typographical error here.

The references considered for inclusion within the NMA, grouped by study, are summarised in Table 15, alongside reasons for exclusion from the NMA if relevant. Studies were assessed for eligibility for the NMA as per Table 17, Section B.2.9.9 of the CS.

A4. CS, Appendix D. Please clarify which of the following numbers are correct in the first SLR update. The Medline and Embase results are 484 on the final line

of the CS, Appendix D, Table 3 when limited to English language, but 494 is reported in the PRISMA flow diagram (CS, Appendix D, Figure 2). Medline in Process via PubMed is 178 in the CS, Appendix D Table 4, but 162 in the PRISMA flow diagram (Figure 2). Cochrane library is 345 in the CS, Appendix D, Table 5, but 355 in the PRISMA flow diagram (Figure 2).

The numbers provided in the 3 database search strategy tables in Appendix D (one each from Embase.com, Cochrane library, and PubMed database platforms) were carried over from the final version of the SLR protocol (dated 26th October 2021). The PRISMA diagram values are correct. The updated database search strategy tables can be found in Table 16, Table 17 and Table 18 of Appendix I, matching the PRISMA diagram values provided in the CS.

Clinical trial

A5. CS, Appendix F. The most common hepatic adverse events are reported in Table 33 (p75).

- a) Please provide the extent to which each biomarker was elevated (mean/median/range) or changed due to each treatment in the HIMALAYA trial.

As per the HIMALAYA trial protocol, adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) classification version 4.03 published June 2010.¹ This approach was selected to facilitate the understanding of clinical impact of each biomarker change in a more comprehensive and standardised way than simply presenting mean, median and range values. The exact value that determines the classification of each chemistry parameter change into one grade or another can be found in the NCI CTCAE version 4.03.²

Clinically Important Changes in Clinical Chemistry Parameters classified as common hepatic AEs are shown in Table 1. Additional common hepatic AEs are summarised by grade in Table 19 In Appendix I. These tables complement the data provided in Table 33 of the CS Appendix.

Table 1 Clinically Important Changes in Clinical Chemistry Parameters (primary analysis; SAS) (DCO: 27th August 2021)

Clinical chemistry parameter	n/N# (%) of subjects					
	STRIDE (n=388)			Sorafenib (n=374)		
	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
ALT	212/ 377 (56.2)	71/ 377 (18.8)	67/ 377 (17.8)	185/ 352 (52.6)	41/ 352 (11.6)	43/ 352 (12.2)
Albumin	116/ 371 (31.3)	66/ 371 (17.8)	2/ 371 (0.5)	130/ 350 (37.1)	81/ 350 (23.1)	6/ 350 (1.7)
ALP	154/ 374 (41.2)	34/ 374 (9.1)	31/ 374 (8.3)	156/ 351 (44.4)	17/ 351 (4.8)	19/ 351 (5.4)
AST	238/ 377 (63.1)	87/ 377 (23.1)	101/ 377 (26.8)	191/ 350 (54.6)	48/ 350 (13.7)	74/ 350 (21.1)
Bilirubin	156/ 377 (41.4)	76/ 377 (20.2)	31/ 377 (8.2)	167/ 352 (47.4)	71/ 352 (20.2)	37/ 352 (10.5)

Abbreviations: AST: aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: alkaline phosphatase;

CTCAE: Common Terminology Criteria for Adverse Events

Source: EMA assessment report,³ HIMALAYA CSR, Jan 2022⁴

Liver biochemistry test results over time in subjects with elevated ALT or aspartate aminotransferase (AST) ($\geq 3 \times \text{ULN}$), and elevated total bilirubin ($\geq 2 \text{ULN}$) were included as well in Table 14.2.7.1.3 of the Clinical Study Report.⁴

b) Please specify the criteria used.

Hepatic AEs in the Safety Analysis set in the HIMALAYA trial were defined as worsening of CTCAE grades derived from laboratory assessment between the start of treatment and up to and including 90 days following the date of last dose of study treatment or until the initiation of the first subsequent therapy (whichever occurred first).³

A6. Priority question. CS, Document B, Figure 19. In Figure 19, the company presented data on serious adverse events that are treatment-related and not treatment-related. Please provide a definition, and a list of adverse events considered not treatment-related, along with their numerical input and analysis results.

Causality of AEs was collected in the HIMALAYA trial. AEs were considered as possibly related to any study treatment as assessed by the investigator. Treatment-related AEs were reported as possibly related with durvalumab, tremelimumab or sorafenib. A guide to interpreting the causality question was included in the HIMALAYA Clinical Study Protocol.⁴

The factors to consider when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug include: time course and exposure to suspect drug, consistency with known drug profile, de-challenge experience, no alternative cause, rechallenge experience, laboratory test, overdose of the drug or known mechanism. Missing responses were counted as related.³

For serious adverse events (SAEs), investigators were also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment-emergent (ie, SAEs that occur prior to the administration of study drug[s]) and treatment emergent SAEs.

There were no treatment-related SAEs by Preferred Term reported by $\geq 5\%$ patients.³ The most common SAEs that were not treatment-related are related to the underlying disease progression, such as [REDACTED] and [REDACTED].⁴

Table 20 in Appendix I summarises common not treatment-related SAEs from the HIMALAYA trial.

A7. Priority question. CS, Document B, Table 28. In Table 28, the company provided data summarising the treatment-related adverse events (TRAEs) for the HIMALAYA trial. The table includes 2 categories, ‘TRAEs of any cause’ and ‘TRAEs’. However, the details differentiating these categories are not reported. Please provide the criteria used to evaluate these adverse events. Please also provide the definition and list of adverse events included in the ‘TRAEs of any cause’ group but not in the ‘TRAEs’ group.

An AE was considered as an “AE on treatment” or “treatment-emergent AE” if it started after dosing or prior to dosing and it worsens following exposure to the treatment.¹

Investigators were required to provide an assessment of causality of the AEs. Therefore, treatment-related AEs (TRAEs) were defined as AEs with a reasonable possibility of causal relationship with any study treatment, as assessed by the investigator. Treatment-related AEs were reported as possibly related with durvalumab, tremelimumab or sorafenib. A guide to interpreting the causality question was included in the HIMALAYA Clinical Study Protocol.⁴

A new version of Document B, Table 28 is provided in Table 2 in response to this question. The AE categories are in alignment with the pivotal HIMALAYA publication (Abou Alfa G.K et al 2022)⁵.

Table 2 Summary of TRAEs experienced by patients in HIMALAYA (primary analysis; SAS) (DCO: 27th August 2021)

AEs	STRIDE (n=388)	Sorafenib (n=374)
Treatment-emergent AEs of any cause, n (%)		
Any	378 (97.4)	357 (95.5)
Any serious	157 (40.5)	111 (29.7)
Any grade 3 or 4	196 (50.5)	196 (52.4)
Leading to discontinuation	53 (13.7)	63 (16.8)
Leading to dose delay	134 (34.5)	178 (47.6)
Immune-mediated requiring high-dose steroids	78 (20.1)	7 (1.9)
Any grade 3 or 4 immune-mediated	49 (12.6)	9 (2.4)
Immune-mediated leading to death	6 (1.5)	0
Any grade 3 or 4 hepatic SMQ	54 (13.9)	39 (10.4)
Treatment-related AEs, n (%)		
Any	294 (75.8)	317 (84.8)
Any serious	68 (17.5)	35 (9.4)
Grade 3 or 4	100 (25.8)	138 (36.9)
Leading to discontinuation	32 (8.2)	41 (11.0)
Leading to dose delay	83 (21.4)	144 (38.5)
Leading to death	9 (2.3) ^a	3 (0.8) ^b
Grade 3 or 4 immune-mediated	49 (12.6)	9 (2.4)
Any immune-mediated leading to death	6 (1.5) ^c	0
Grade 3 or 4 hepatic SMQ	23 (5.9)	17 (4.5)

Footnotes: ^aTRAEs leading to death in the STRIDE arm included myasthenia gravis, nervous system disorder, myocarditis, acute respiratory distress syndrome, pneumonitis, hepatic failure, hepatitis (all n=1 each), and immune-mediated hepatitis (n=2); ^bTRAEs leading to death in the sorafenib arm included cerebral hematoma, hepatic failure, and haematuria (all n=1 each); ^cTRAEs leading to death in the STRIDE arm included pneumonitis, hepatitis, myocarditis, myasthenia gravis (all n=1 each), and immune-mediated hepatitis (n=2).

Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set; SMQ: standardised MedDRA queries; TRAE: treatment-related adverse event; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Abou-Alfa, G. et al. 2022b.⁶ (Table 3, pg 9).

A8. CS, Document B, section B.2.10. Please clarify whether there were any immune-related adverse events of the HIMALAYA trial that led to chronic conditions or remained unresolved.

Immuno-oncology therapies are associated with Immune-Mediated AEs (imAEs), which typically resolve following initiation of appropriate medical treatment or withdrawal of IO therapy. Immune-mediated AEs were reported at a higher

frequency in the tremelimumab-containing treatment arms, but there was no evidence that the incidence or outcome of imAEs differed meaningfully between IO regimens. In all categories, imAEs were reported at a low frequency overall. The frequency of imAEs that led to discontinuation of study treatment was also low.⁷

Immune-mediated AEs were identified as an important risk for tremelimumab at the time of initial EU Risk Management Plan approval and require careful monitoring, early recognition, timely intervention and appropriate medical intervention.

Characterisation of the risk in terms of frequency and severity and event outcome (resolved, not resolved, fatal or discontinuation of study treatment) of the most common imAEs are included in Table II-15-21 of the EU Risk Management Plan (RMP) of tremelimumab.⁷

AstraZeneca, as marketing authorisation holder are continuing to undertake the required pharmacovigilance activities and interventions detailed part of Routine Risk Minimisation Measures of the RMP of tremelimumab.

A9. Please specify if any other biomarkers, such as Glutamate Dehydrogenase (GLDH), Cytokeratin 18 (K18), MicroRNAs (miRNA), etc. have been used to evaluate liver toxicity.

All AEs in HIMALAYA were coded using MedDRA version 23.1 and graded according to the NCI CTCAE (version 4.03).⁸ Glutamate dehydrogenase (GDH), Cytokeratin 18 (K18) and MicroRNAs (miRNA) were not evaluated.

As per the HIMALAYA trial protocol, suggested laboratory tests to monitor liver status include AST, ALT, total bilirubin, direct bilirubin, albumin, alkaline phosphatase, gamma-glutamyl transferase, and international normalized ratio.¹

A10. Priority question. Please provide the recurrence rate of patients who have received STRIDE. If recurrence has been analysed, please provide the percentages of recurrence rates over different time frames and the follow-up results.

For this question AstraZeneca assumes that the terminology “recurrence rate” in the context of unresectable or advanced diseases refers to progression free survival (PFS). PFS data is included in section B.2.6.2.1 of the CS.

A11. CS, Document B, Table 9. Table 9 categorises 'Ethnic group' into 'Hispanic or Latino' and 'Not Hispanic or Latino'. Please provide details of the ethnic groups that comprise the 'Not Hispanic or Latino' category, including the mean/median/range/percentages. Please provide subgroup analysis results for each 'non-Hispanic or Latino' subgroup that has been added.

The data presented in Table 9 of the CS pertains to the distribution of race and ethnic group characteristics. The population who were "not Hispanic or Latino" may include individuals of different races, further data analysis has not been conducted as the characteristics by race are available in Table 9.

Upon analysis, it is evident that the distribution of Hispanic or Latino individuals remains relatively consistent across the two treatment arms (5.3% in the STRIDE arm and 5.4% in the sorafenib arm). Similarly, the distribution of non-Hispanic or Latino individuals follows a comparable pattern (94.7% in the STRIDE arm and 93.1% in the sorafenib arm). Race and ethnicity were not stratification factors and not part of the pre-specified subgroup analysis.

A12. CS, Document B, Figure 13. Please clarify the rationale for excluding Japan from the Asia category and considering it as part of the 'Rest of the World'. Please provide results of the subgroup analysis in Figure 13, considering Japan as part of the Asia region and analysing the 'Rest of the World' separately.

In areas characterized by a high prevalence of HCC (such as Asia and Africa), the primary risk factors are chronic HBV infection and exposure to aflatoxin B1. Conversely, in regions with lower HCC frequency, the main risk factors include HCV infection, excessive alcohol consumption, and conditions like diabetes, obesity, or metabolic syndrome. Notably, in Japan and Egypt, the predominant risk factor is HCV infection.⁹ In the analysis of the overall survival subgroup, the company compared Asia excluding Japan with the rest of the world, which includes Japan.

A13. CS, Document B, Figure 13. Please provide

1. The rationale for inclusion

Figure 13 from the CS submission shows the OS subgroup analysis in HIMALAYA (STRIDE vs sorafenib) from the updated analysis I (DCO: 23rd January 2023), which

provides more mature data compared to the primary subgroup analysis (DCO: 27th August 2021), which is presented in Appendix E, Figure 11 of the CS.

2. The company's interpretation of some of the subgroup analysis hazard ratios itemised in Figure 13.

With reference to:

1. Sex female
2. Age at randomisation
3. Programmed death ligand 1 (PD-L1) expression (both positive and negative)
4. Hepatitis C virus (HCV) as the aetiology of liver disease
5. Yes macrovascular invasion (MVI)
6. No extrahepatic spread (EHS)
7. Alpha-fetoprotein (AFP) at baseline <400 ng/mL
8. Barcelona Clinical Liver Cancer (BCLC) score B

Prior to initiating discussion on HRs from the HIMALAYA OS subgroup analysis, it is important to note that this subgroup analysis was not powered for formal comparisons; no multiplicity adjustments were made. This applies for both the primary subgroup analysis as well as the updated analysis I (DCO: 23rd January 2023), from the perspective of subgroup data.

1. Sex female: Upper CI crosses 1. The confidence interval range (HR 1.02 [0.68-1.56]) is large. Not powered for formal analysis.
2. Age at randomisation: Upper CI crosses 1 however HR is still <1 for patients aged <65. Age was not a stratification factor. Not powered for formal analysis.
3. Programmed death ligand 1 (PD-L1) expression (both positive and negative): The predictive value of PD-L1 status for the efficacy of PD-L1 and PD-1 inhibitors or combination therapies has not been clearly shown in the case of HCC. There is a notable spacial and cellular heterogeneity of PD-L1 expression in HCC samples, which could limit predictive capabilities. PD-L1 status is also known to change over time, therefore a simple biopsy specimen is insufficient for determining long term treatment.¹⁰ In the case of STRIDE,

based on the subgroup analysis there is no indication to suggest PD-L1 status may have an impact on OS. PD-L1 was not a stratification factor. Not powered for formal analysis.

4. Hepatitis C virus (HCV) as the aetiology of liver disease: As confirmed by post-hoc multivariate analysis, there was an imbalance observed across treatment arms in the HCV subgroup which was not present in other aetiology subgroups which may have contributed to the HRs observed. Extrahepatic spread (EHS) was more frequent in the STRIDE arm than in the durvalumab and sorafenib arms, and albumin-bilirubin (ALBI) score 2 was more frequent for STRIDE and durvalumab than for sorafenib. A stratified Cox proportional hazards model accounting for the imbalances in EHS and ALBI of the HCV subgroup was applied to all subgroups and resulted in an adjusted OS HR that favoured STRIDE versus sorafenib in the HCV subgroup (HR, 0.89 [0.63-1.25]).¹¹ Not powered for formal analysis.
5. Yes macrovascular invasion (MVI): Upper CI crosses 1 however HR is still <1, not powered for formal analysis.
6. No extrahepatic spread (EHS): Upper CI crosses 1 however HR is still <1. EHS was not a stratification factor. Not powered for formal analysis.
7. Alpha-fetoprotein (AFP) at baseline <400 ng/mL Upper CI crosses 1 however HR is still <1, not powered for formal analysis.
8. Barcelona Clinical Liver Cancer (BCLC) score B: Upper CI crosses 1 however HR is still <1. BCLC was not a stratification factor. Not powered for formal analysis. Very small number of patients leading to a very wide range.

A14. Priority question. CS, Appendix D, section D.3. Please provide the methods for the risk of bias tool used in section D.3 (p68).

The risk of bias tool used was the Cochrane Risk of Bias 2 tool.¹²

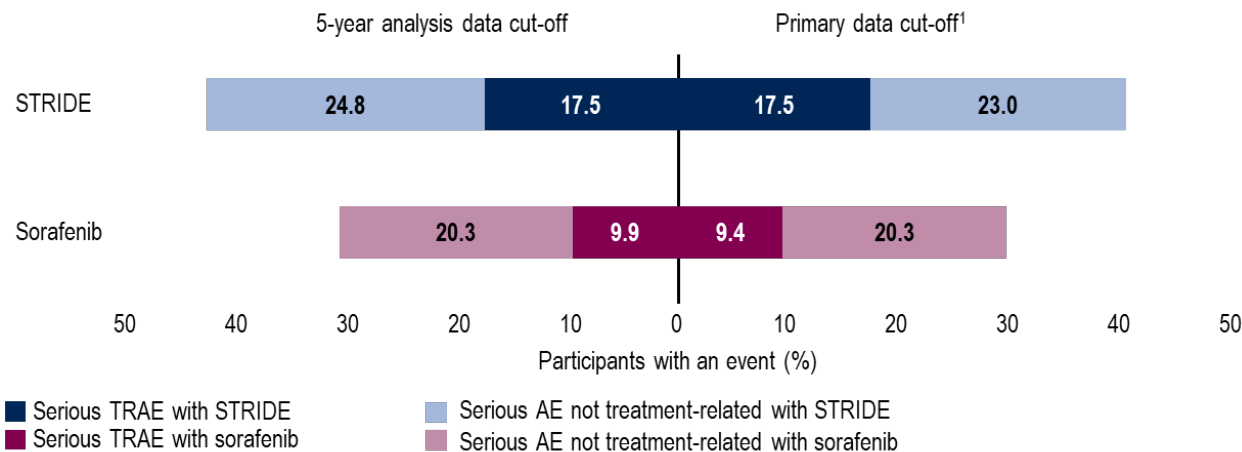
A15. Priority question. CS, Document B, section B.2.10. The EAG understands that the long-term safety of STRIDE is of major importance in this submission. Please provide in tabulated form all safety and adverse event data for the data cut-off dates of January 23, 2023, and March 1, 2024.

Please include immune-related adverse events and autoimmune diseases that might be associated with STRIDE and could be recurrent and/or delayed after several years.

The HIMALAYA trial data represents the longest follow-up for an immunotherapy treatment in advanced or unresectable HCC, reducing the level of uncertainty when compared with other IO treatments in this setting. This not only pertains to efficacy over time but also to long-term safety.

AE data were collected at the primary analysis (3-year) and updated exploratory OS analyses I (4-year) and II (5-year) in the HIMALAYA study. Section B.2.10 of the CS provides updated data on the duration of treatment exposure, treatment delays, and AEs leading to discontinuation from the updated analysis I. For completeness, Appendix F of the CS includes data on these endpoints from the primary analysis in Table 29, Table 30 and Table 31, respectively. Additionally, data on serious AEs reported in the HIMALAYA study at updated analysis I (4-year) are presented in Table 32 of the CS Appendix. Table 33 and Table 34 also outline most common hepatic AEs and treatment-related hepatic AEs from the primary analysis. In addition, Figure 1 below summarises serious TRAEs and AEs from updated analysis II (1st March 2024), which are aligned with AE findings from the updated analysis I and primary analysis, further supporting the long-term safety of the STRIDE regimen.

Figure 1 Serious TRAEs and AEs that were not treatment-related experienced by patients in HIMALAYA with STRIDE vs. sorafenib (primary analysis and updated analysis II; SAS) (primary DCO: 27th August 2021; updated II DCO: 1st March 2024)



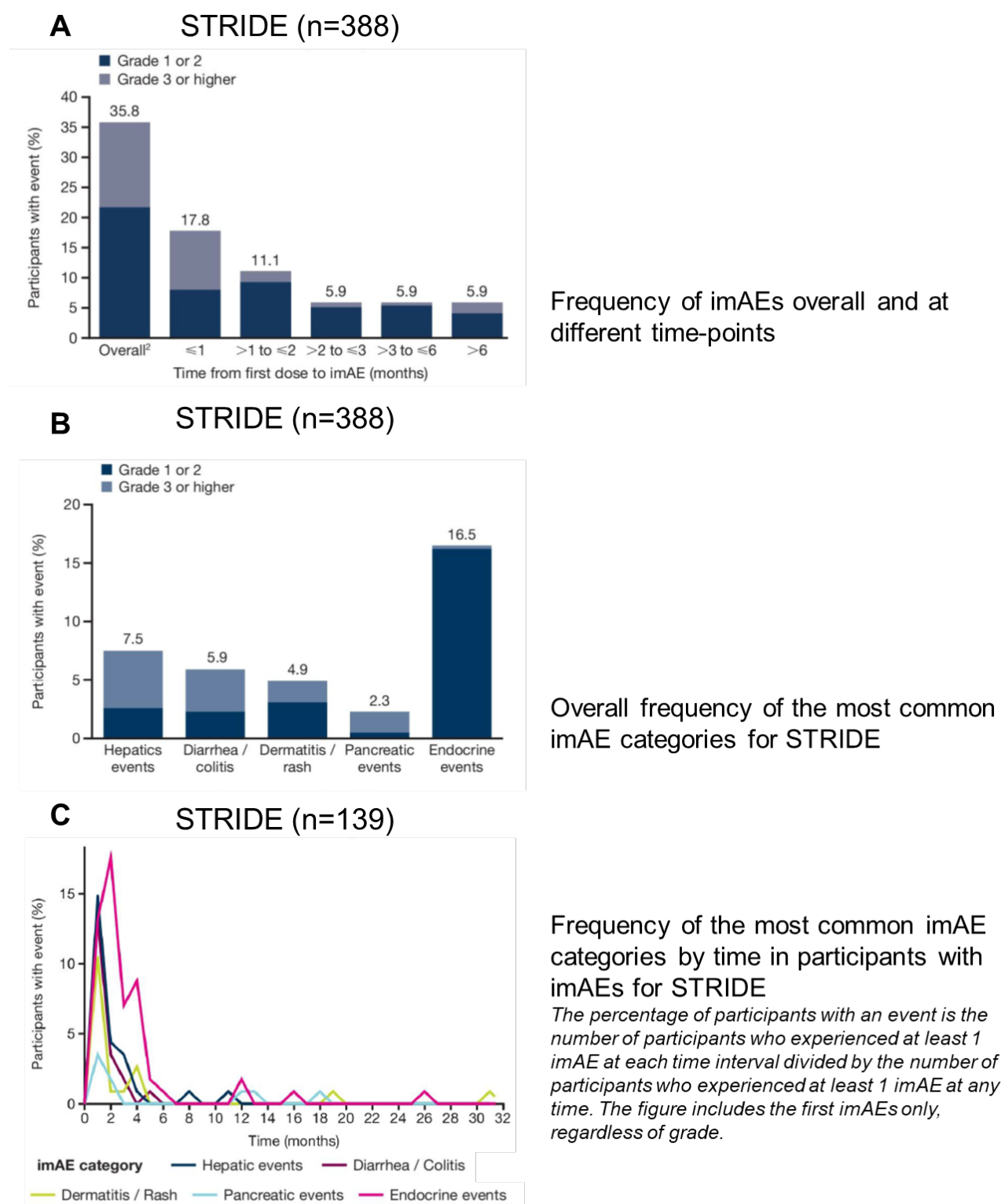
Source: Rimassa L et al. 2024¹³

imAEs

As previously mentioned in question A8, characterisation of the risk in terms of frequency and severity and event of the most common imAEs are included in Table II-15-21 of the EU RMP of tremelimumab.⁷

Although imAEs with STRIDE could occur at any time, most were observed within the first three months after treatment initiation (Figure 2). Therefore, the median follow-up of the DCOs submitted in the CS is considered sufficient to support the long-term safety of STRIDE. Further findings on the temporal patterns of imAEs with STRIDE are presented in Figure 2 in terms of imAE frequencies, highlighting the manageable safety profile of STRIDE which is differentiated from other currently available uHCC therapies.

Figure 2 Temporal patterns of imAEs with STRIDE in the phase 3 HIMALAYA study (primary analysis; SAS) (DCO: 27th August 2021)



Source: Lau G 2023¹⁴

A16. Priority question. CS, Document B, section B.2.3.2. Please provide information on the baseline characteristics, safety, and efficacy outcomes of participants in the phase II study (Study D4190C00022 / NCT02519348).

The Phase I/II study NCT02519348 evaluated tremelimumab and durvalumab as monotherapies and in combination for patients with HCC, including STRIDE regimen.¹⁵ The study population included patients with HCC who had progressed on, were intolerant to, or refused sorafenib.

For the purpose of this question, only data from the STRIDE (T300 + D) arm is included as the other arms included (durvalumab monotherapy, tremelimumab monotherapy or T75 +D) are not part of the decision problem and the CS.

Table 3 Phase I/II NCTT02519348 study baseline characteristics in the STRIDE arm

Characteristic	STRIDE (n=75)
Median age, years (range)	66.0 (26-86)
Sex, male, No. (%)	65 (86.7)
Race and ethnicity, No. (%)	
White	27 (36.0)
Black	4 (5.3)
Asian	44 (58.7)
Hispanic or Latino	4 (5.3)
Others	0
ECOG PS, No. (%)	
0	46 (61.3)
1	29 (38.7)
Child-Pugh score, No. (%)	
A/5	51 (68.0)
A/6	23 (30.7)
B/7	1 (1.3)
BCLC score, No. (%)	
A	1 (1.3)
B	13 (17.3)
C	58 (77.3)
Unknown or missing ^a	3 (4.0)
Extent of disease, No. (%)	
Macrovascular invasion	16 (21.3)
Extrahepatic disease	53 (70.7)
AFP, ≥ 400 ng/mL, No. (%)	35 (46.7)
Viral status, No. (%)	
HBV infection	27 (36.0)
HCV infection	21 (28.0)
Uninfected	27 (36.0)

PD-L1 status, No. (%)	
TC/IC ^b ≥ 1%	27 (36.0)
TC/IC, 1%	38 (50.7)
Missing	10 (13.3)
Prior sorafenib therapy, No. (%)	
Progressed	43 (57.3)
Intolerant	12 (16.0)
Refused	20 (26.7)
Previous treatment modalities, No. (%)	
Systemic therapy	55 (73.3)
Radiation	22 (29.3)
Cancer-related surgery	34 (45.3)

Source: Kelley et al. 2021¹⁵

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; IC, immune cell; PD-L1, programmed cell death ligand-1; T300 1 D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; TC, tumour cell. a At the start of the study, the Protocol required the use of modified TNM staging together with the fibrosis score. The study was amended to include BCLC at a later date. Thus, BCLC scores are missing for some patients. b Defined as PD-L1 staining of any intensity in TC membranes and/or tumour-associated ICs in the tumour area.

The primary endpoint was safety. AEs were monitored and graded by investigators using the NCI CTCAE, v4.03. Treatment-related AEs (TRAEs) summarised in Table 4 were determined based on investigator assessment of relationship to treatment, and imAEs were also assessed. The median (range) duration of exposure was 3.7 (0.8- 27.1) months for the STRIDE arm.

Table 4 Common TRAEs in NCTT02519348 (≥ 5% in Any Group)

AE	STRIDE (n=74) No. (%)	
	All Grades	Grade ≥3
Patients with any TRAE	61 (82.4)	28 (37.8)
Pruritus	24 (32.4)	-
Rash	24 (32.4)	2 (2.7)
AST increased	12 (16.2)	9 (12.2)
ALT increased	11 (14.9)	3 (4.1)
Amylase increased	11 (14.9)	5 (6.8)
Lipase increased	9 (12.2)	5 (6.8)
Fatigue	8 (10.8)	-
Diarrhoea	7 (9.5)	1 (1.4)
Alkaline phosphatase increased	6 (8.1)	3 (4.1)
Hyperthyroidism	6 (8.1)	-
Hypothyroidism	6 (8.1)	-
Bilirubin increased	4 (5.4)	1 (1.4)
Abdominal pain	2 (2.7)	-
Rash maculopapular	2 (2.7)	1 (1.4)

Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase

Secondary end points included objective response rate (ORR) by RECIST v1.1 and OS.

The confirmed ORR by BICR was highest for STRIDE (24.0%; [95% CI, 14.9-35.3]). Confirmed complete responses were achieved by one patient receiving STRIDE. Median time to response was shortest with STRIDE (1.86 months). The median DoR was not reached with STRIDE. The median PFS (95% CI) was 2.17 (1.91-5.42) months with STRIDE. The median (95% CI) OS was highest with STRIDE at 18.73 (10.78-27.27) months. No differences in efficacy from the overall population were observed for any viral subgroup.

A17. Priority question: The company stated that in the HIMALAYA trial protocol that they have measured and included [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] However, the data and outcomes have not been reported in the company's submission. Please provide responses to the following questions:

1. What number of participants were involved, and for each individual, how long after follow-up and after progressed disease were the decisions made regarding:
 - a) No rechallenge
 - b) Rechallenge being undertaken

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Thirty patients in the STRIDE arm were retreated with 1 additional dose of tremelimumab 300 mg in combination with durvalumab.⁴

For all patients who were treated through progression or retreated with STRIDE, the investigator determined the following criteria were met:⁵

- Progression had not occurred after confirmed response (defined as complete or partial response per RECIST 1.1) in tumour lesions (regardless of the appearance of new lesions); ie, the response and progression events both occurred in tumours during the same treatment period.
- There were no significant, unacceptable, or irreversible toxicities indicating continuing treatment would not further benefit the patient.
- There were no clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO or ECOG performance status to greater than 1.
- There was no rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumour compression, or spinal cord compression) that required urgent alternative medical intervention.

All eligibility criteria were met, with the exception of (1) must not have received prior systemic therapy for HCC, (2) at least 1 measurable lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter with computerize tomography or magnetic resonance imaging, or (3) known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.⁵

As has been discussed, patient progression was one of the main criteria for receiving tremelimumab rechallenge. Among the subjects in the rechallenge group, the time from the report of RECIST 1.1 progression to the second dose of tremelimumab ranged from [REDACTED], with a time interval from randomization to tremelimumab rechallenge of [REDACTED].

The details of each individual patient can be observed in the swimmer plots included in Figure 5 in Appendix I.

2. Was time-to-event data analysis conducted for the duration from start to ceasing rechallenge?

Time to event data analysis was not conducted. Please note that tremelimumab rechallenge is not part of the MHRA regulatory approval for the STRIDE regimen.

Swimmer plots included in Figure 5 in Appendix I provide a visual representation of the events experienced by each of the 30 patients who received rechallenge from the randomization until DCO, including: RECIST 1.1 progression, discontinuation of durvalumab, second dose of tremelimumab, and death.

3. What are the results of the [REDACTED] [REDACTED]?

Similarly to our response to question A17/2, exploratory analyses of progression-free survival from rechallenge and progression-free survival from post-discontinuation therapy were not conducted. Please note that tremelimumab rechallenge is not part of the MHRA regulatory approval for the STRIDE regimen.

The only data available to the company are derived from the individual patient data included in the swimmer plots in Figure 5 in Appendix I, where the following was observed:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Figure 5 in Appendix I shows swimmer plot for the 30 subjects rechallenged with tremelimumab in the STRIDE arm of the HIMALAYA trial. The median OS was [REDACTED], and the OS rates were [REDACTED] at

■ months, ■ at ■ months, ■ at ■ months, and ■ at ■ months.⁴ While the median OS for rechallenged patients is long, given the small sample size and resulting wide CIs for the median and landmarks, confirmatory inference cannot be drawn about the impact of rechallenge in the study. Overall, the results of the rechallenge group were consistent with those of the overall FAS; however, the study was not powered for this comparison and no multiplicity adjustments were made.

A18. Priority question. CS, Document B, Figure 24. In Figure 24 (p98), the company presented the observed raw and smoothed hazards from the HIMALAYA trial.

a) Please clarify how the raw hazard was generated.

The raw hazards were generated using the pehaz function in R. These represent the piecewise exponential hazard function. Time is split into equal segments, and the function calculates the hazard as the total number of events divided by the total follow up time in that segments. This is an approximation for the observed hazard.

b) Please explain the purpose of undertaking this analysis in the context of the cost-effectiveness model that was developed.

The hazards for each treatment arm within the HIMALAYA trial period were assessed through visual inspection of the observed raw and smoothed hazard plots. Assessment of the hazard plots can indicate whether standard parametric survival models such as proportional hazards and accelerated failure time (AFT) models are suitable, or whether models with greater flexibility to capture changes in the direction of the hazard, such as spline-based models, should be explored.

A19. Priority question. CS, Appendix O, Figure 20. Figure 20 (p129) is entitled “*observed vs modelled hazard rate*” and depicts hazard plots of parametric models of survival in STRIDE arm of HIMALAYA. Figure 20 also includes a dotted line.

a) Please clarify what the dotted line represents.

Figure 20 is titled “Smoothed hazard plots for OS for STRIDE” and shows the observed OS smoothed hazard of the STRIDE arm from HIMALAYA (represented by the dotted black line) compared with the hazards of the standard survival models extrapolated out to 20 years (represented by the solid colourful lines).

b) Please clarify how the dotted line plot was derived and how it relates to decisions made in developing the economic model.

The raw hazard was generated using the pehaz function in R as described in response to Question A18a. The smoothed hazard was generated using the muhaz function in R.

The within-trial period hazard (i.e., the dotted line) was visually compared to the hazards predicted by each parametric model (i.e., the solid colourful lines) to assess how well the modelled hazard fit the observed hazard.

c) Please explain why Figure 20 (Appendix O, p129) “dotted line plot” is so dissimilar to the hazard plot shown in the main text (CS, Document B, Figure 24, p98), as illustrated in Figure 1 below.

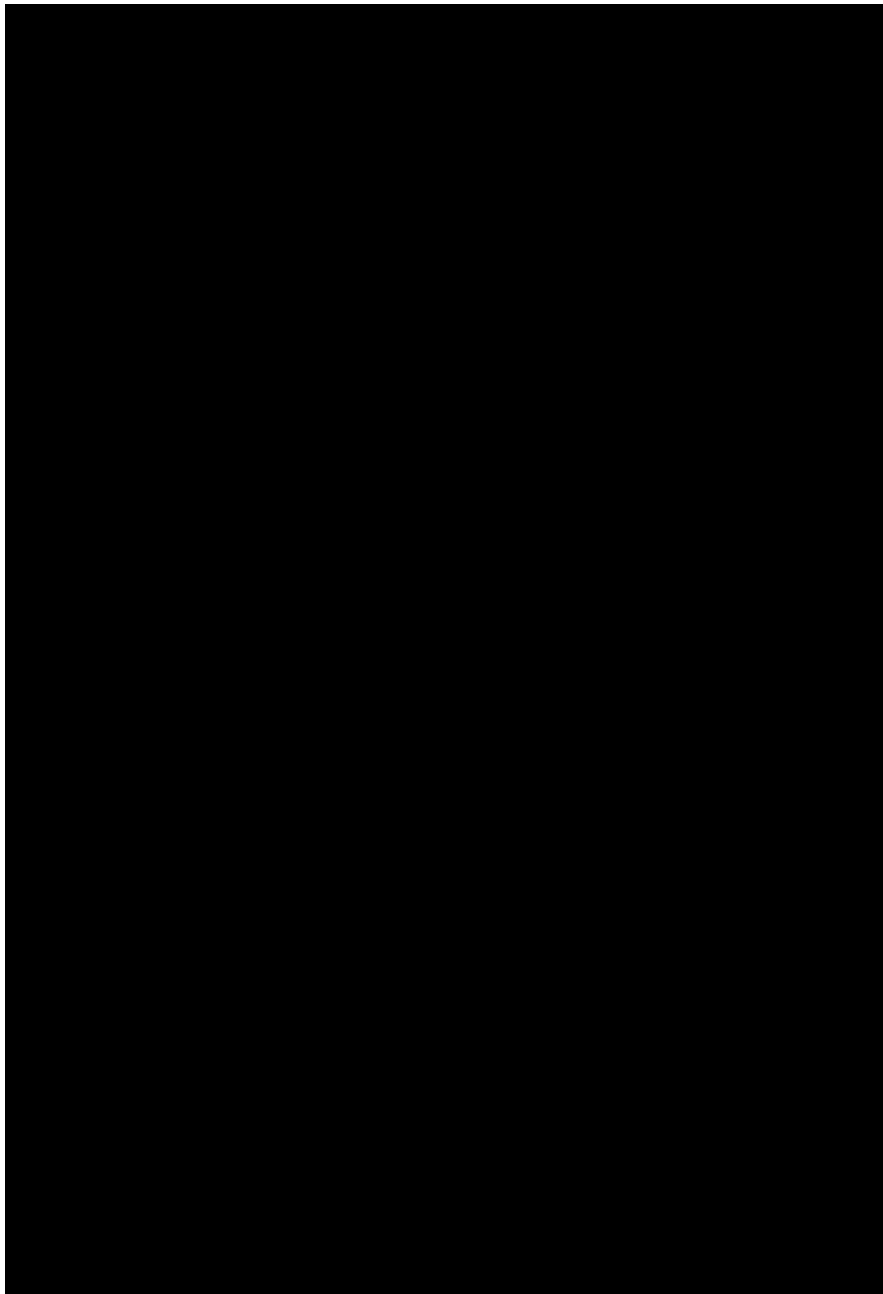
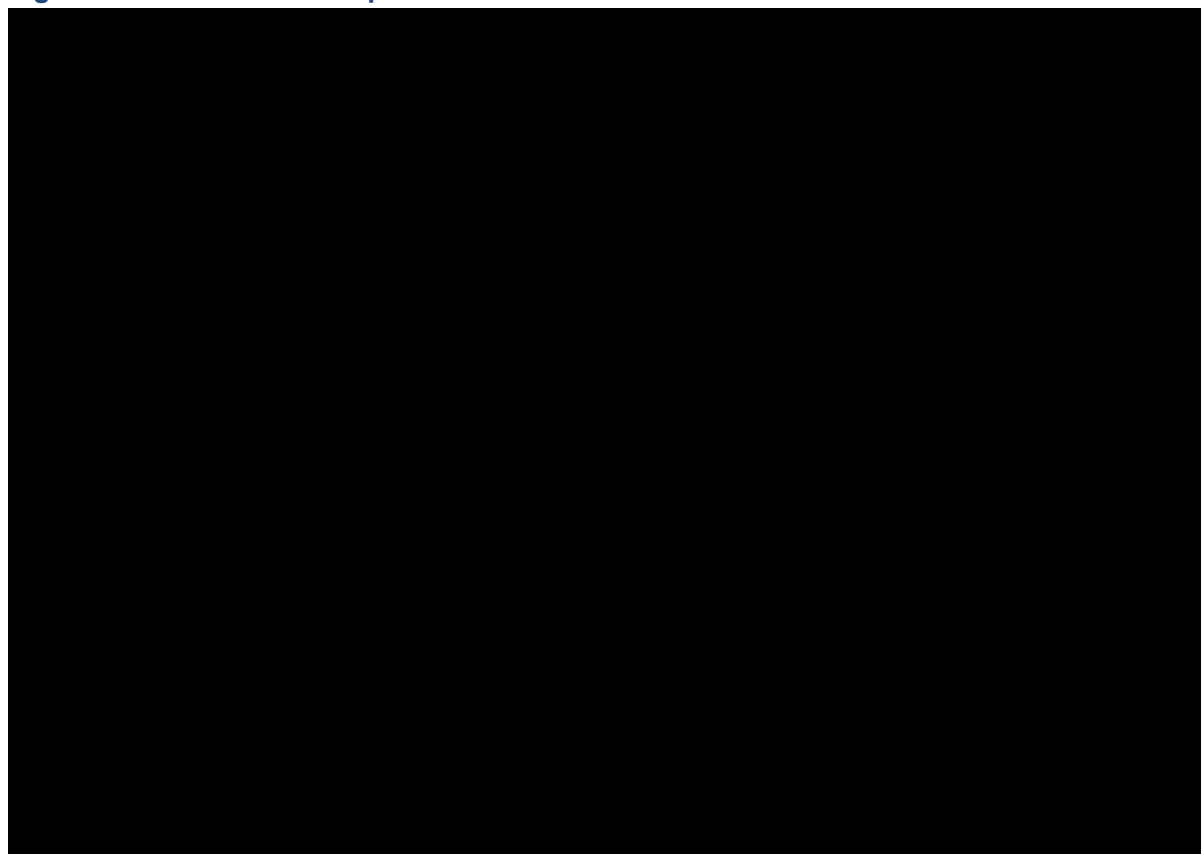


Figure 1: Excerpt from Figure 20 (Appendix O, p129) overlaid with Figure 24 (CS Document B, page 98)

Figure 20 in the Appendix shows the smoothed hazards plots for OS for STRIDE and a comparison to the standard parametric models. The plots included in the appendix were erroneously based on the 4-year data (DCO: 23rd January 2023), whereas the hazard shown in the main text Document B figure 24 were based on the latest 5-year OS data cut (DCO: 1st March 2024). The plot for the parametric fits based on the latest 5-year data cut has been provided in Figure 3 below.

Figure 3 Smoothed hazard plots for standard models for OS for STRIDE



A20. Priority question. CS, Document B, section B.3.3.3.3. In section B.3.3.3.3, it states that, *‘As described above, independent fitting of spline-based models was considered the most appropriate approach to capturing the varying hazards observed in the STRIDE arm of HIMALAYA. As such, the goodness of fit assessment of spline-based models is discussed in the sections that follow, with all information related to fitting of standard models for the STRIDE arm presented in Appendix N for completeness. Scenario analyses are conducted with the most appropriate standard model.’ (p98)*

The EAG notes because proportional hazards assumption was not supported for HIMALAYA analysis the company decided to model each arm separately. However, based on AIC and BIC scores, the best fitting of standard models for both arms of HIMALAYA (lognormal, loglogistic, and generalised gamma) all support an accelerated failure time (AFT) analysis.

- a. Please clarify the reasons why splines designed to accommodate varying hazard was selected to be most appropriate approach.**

Plots of the observed raw and smoothed hazards were assessed to judge the complexity of observed trial hazards and determine whether parametric models with greater flexibility should be considered alongside standard parametric models.

For OS, Figure 24 in Document B shows that for sorafenib, the observed smoothed hazards [REDACTED]. For the STRIDE arm, the observed smoothed hazards [REDACTED]

[REDACTED].

For PFS, Figure 36 in Document B shows that for sorafenib, the observed smoothed hazards [REDACTED]. There is [REDACTED]

[REDACTED]. For the STRIDE arm, the observed smoothed [REDACTED].

To capture the changes observed in the OS and PFS hazards, independent spline models were considered the most appropriate parametric extrapolations for both arms, as they offer flexibility to capture the changing hazards observed.

b. Please clarify why an AFT approach was not explored.

Standard AFT models (e.g., lognormal and loglogistic) were explored and presented in Appendix O (incorrectly referenced as Appendix N in Document B).

Spline-based AFT models (the spline normal and odds families) were also explored and presented in Document B Section B.3.3.3, and the spline normal 1 knot was selected in the Company base case to extrapolate STRIDE OS.

c. If spline-based models are favoured by the company, then the EAG suggest that an AFT approach should be explored using methods described by Crowther Royston and Clements in Biostatistics (2023) 24, 3, pp. 811–831 (<https://doi.org/10.1093/biostatistics/kxac009>) since these accommodate the use of splines.

The fitting of spline models to patient level data in the HIMALAYA trial was performed using the flexsurvspline function in the R package, flexsurv. This included the fitting of Royston Parmar restricted cubic spline models on the “hazard”, “odds”

and “normal” scale, with specifications of 1 to 3 knots. This yielded a total of 9 fitted models per arm, providing an extensive range of extrapolations for the economic model.

When no knots are specified, the “hazard”, “odds” and “normal” spline models are equivalent to the standard distributions of Weibull, log-logistic and log-normal, respectively. Beyond the last knot, the splines behave in a similar manner to their related standard distribution, i.e., a spline normal behaves like a log-normal distribution. The spline “normal” models fitted to HIMALAYA would therefore produce long-term extrapolations that are consistent with the hazard profile predicted by an accelerated failure time model, such as the log-normal distribution. The spline normal 1 knot was selected in the Company base case to extrapolate STRIDE OS. Spline based normal and odds models for 1-3 knots are also explored and presented for OS and PFS in the CS in Document B Section B.3.3.3 (OS) and B.3.3.4 (PFS).

The method proposed by the EAG is available through the rstpm2 package in R.¹⁶ As stated in the help files of this package, the rstpm2 function will yield different spline estimates to flexsurv due to the use of a different natural spline basis. If however, the knot placement is the same across packages, as expected, the authors state that “predictions and coefficients are expected to be very similar”.¹⁶

A21. Priority question. CS, Document B, section B.3.3.3.3. Please clarify the following statements.

‘The observed hazard of the STRIDE arm from HIMALAYA was compared with the hazards of spline-based survival models in Figure 27, Figure 28 and Figure 29 below.

’ (p102)

- a. Please clarify the sentence: *’ as the EAG note that the models only do so over years 0 to 3. In contrast, from 3 to 6 years in Figure 27 (CS, Document B, p102), the hazard predicted by spline models departs considerably from “observed hazard”. The latter suggests that in extrapolation beyond 6*

years, the hazard is likely to increase and the spline models are likely to underestimate hazard.

Considering the plot of the raw and smoothed observed trial hazards for STRIDE (CS Document B Figure 24), the [REDACTED]

[REDACTED] this observation is based on a very small group of patients, and caution should be taken to avoid overinterpreting this trend. The number at risk have been provided in Table 5 for reference.

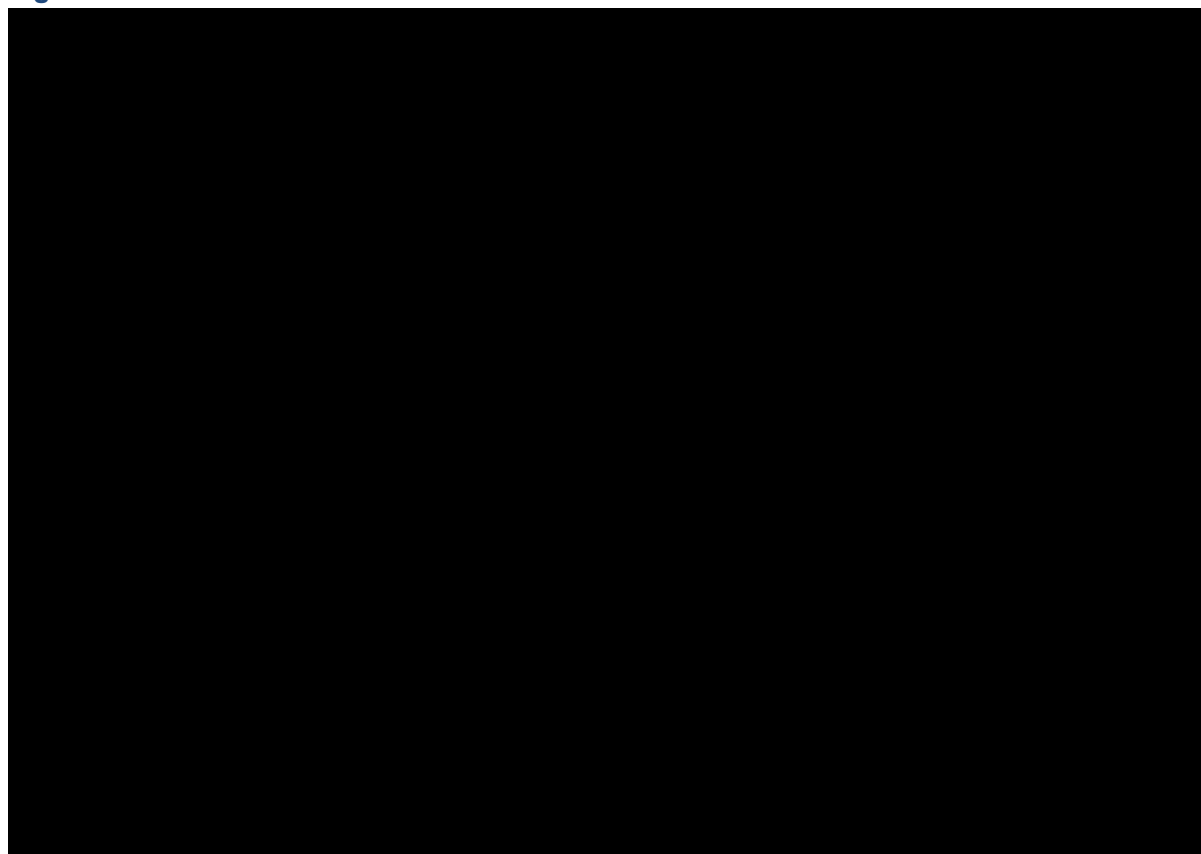
Table 5 Number at risk in STRIDE arm for OS post-60 months

Month	60	[REDACTED]	[REDACTED]	66	[REDACTED]	[REDACTED]	72	[REDACTED]
Number at risk (STRIDE)	46	[REDACTED]	[REDACTED]	20	[REDACTED]	[REDACTED]	2	[REDACTED]

The observed smoothed hazard for STRIDE OS is shown to [REDACTED]. The trends observed at the tail of the hazard distribution are often highly uncertain and unstable due to small numbers at risk. There is also evidence that the hazard trend at the end of the curve may differ depending on the function and kernel density used (muhaz package in R was utilised).^{17,18} Therefore, trends at the tail may not be reliable to inform the long-term hazards. As noted by Palmer et al, turning points observed at the tail of the survival curve should be assessed for validity.¹⁸ There is no clear biological rationale for the hazard to increase suddenly at the tail, and the OS Kaplan-Meier curves (Company submission Document B, Figure 4) show no dramatic decline in survival or changes in the direction of the curve.

The x-axis used in Figure 27, 28 and 29 in the CS Document B covers 20 years (240 months) in order to assess the extrapolated hazards. This x-axis scale means the [REDACTED] appears more extreme than it is. Figure 4 shows the observed hazard for OS over the trial period and demonstrates that the [REDACTED]

Figure 4: Observed raw and smoothed hazards from the HIMALAYA trial



Abbreviations: ITT: intention-to-treat; OS: overall survival; sora: sorafenib; TREME 300 + DURVA: tremelimumab (300mg) + durvalumab (otherwise referred to as STRIDE).

b. In view of the change of observed hazard seen in years 0 to 3 versus years 3 to 6, please clarify whether the company has explored piecewise models.

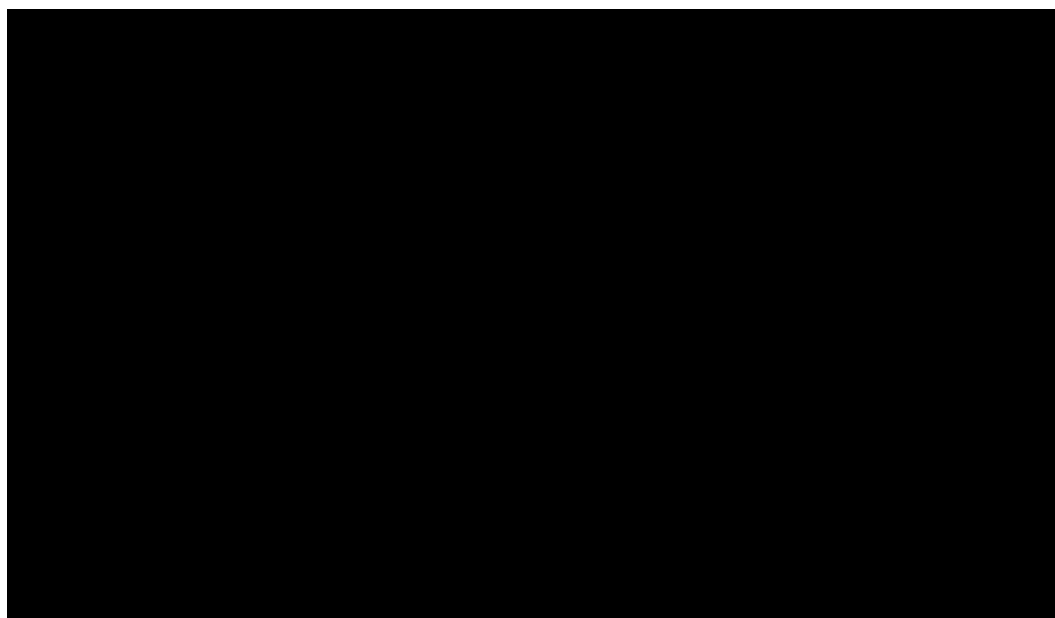
As noted in response to section a, the trends observed at the tail of the hazard distribution are often highly uncertain and unstable due to small numbers at risk. As noted by Palmer et al, turning points observed at the tail of the survival curve should be assessed for validity.¹⁸ There is no clear biological rationale for the [REDACTED], and the OS Kaplan-Meier curves (Company submission Document B, Figure 4) show no dramatic decline in survival or changes in the direction of the curve.

The restricted cubic spline models (Royston and Parmar)¹⁹ explored by the Company permit estimation of a continuous function and allow more complex shapes to be modelled. A cubic spline is a piecewise cubic polynomial, where the number of “pieces” is dictated by the number of knots used, ensuring that notable changes in the trial hazard are captured. The Company believe that the spline-based models

sufficiently capture the observed trial hazard from year 0 to 5, and benefit from not being overly influenced by the trend in the hazard observed at the end of the follow-up period which is based on a small number of patients as described in response to Question A21a. These models provide a robust fit to the KM probabilities and were explored following guidelines from the NICE DSU TSD 21.²⁰

‘Piecewise models’ as described in NICE DSU TSD 21²⁰ were not explored, and there are some noteworthy drawbacks of piecewise models which are described in the NICE DSU TSD 21.²⁰ Splitting data into sections according to time means that sample sizes are reduced, especially in the later segments of the curve, where patient numbers at risk may be very small and the number of observed events may be low, leading to large standard errors and uncertainty when fitting survival models. This is particularly important as it is the model fitted to the latest section of the curve that is used for extrapolation. The modeller also has to decide at which points the new models are fitted, which could introduce bias.

- c. The observed hazard in Figure 27 (CS Document B, p102) contrast with that shown in Figure 20 (CS, Appendix O, p129) (please see below). Please clarify how each of these were derived and explain why they differ.**



The response to this question is consistent with A19c) as it is referring to the same endpoint (OS) for the same treatment (STRIDE). Figure 20 in the CS Appendix

shows the smoothed OS hazards plots for STRIDE and a comparison to the standard parametric models. The plots included in the appendix were erroneously based on the 4-year data (DCO: 23rd January 2023), whereas the hazard shown alongside the extrapolated hazards in the main text, Document B figure 27, were based on the latest 5-year OS data cut (DCO: 1st March 2024).

A22. Priority question. CS, Document B, section B.2.8 to B.2.9.9; Appendix D.

The EAG understands that results from the NMA have been used in the company's economic model. To assess the transitivity in the NMA, the EAG requests the following information:

a) For each outcome, please list all hazard ratios available for each included treatment itemising:

1) The maximum follow-up to which the hazard ratios refer.

Table 22 in the CS Appendix details the median follow-up time across the trials. The maximum follow-up is provided in Table 6. If the maximum is not reported, this was estimated by visual inspection of the Kaplan Meier curve.

Table 6 Maximum follow-up reported in trials

Study	Treatment arm	Maximum follow-up (months)	
		OS	PFS (INV)
HIMALAYA ⁴	STRIDE		
	Sorafenib		
IMbrave150 ²¹	Atezolizumab + bevacizumab	28.6	14.5* (KM curve only available for PFS [BICR])
	Sorafenib	27.9	14.5* (KM curve only available for PFS [BICR])
REFLECT ²²	Lenvatinib	40*	35*
	Sorafenib	40*	39*

Abbreviations: BICR: blinded independent central review; HR: hazard ratio; INV: investigator-assessed; KM: Kaplan Meier; OS: overall survival; PFS: progression free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab; *approximated from KM curve

2) Whether the hazard ratio is adjusted or unadjusted.

Hazard ratios were adjusted. The covariates used for adjustment are detailed in response to A22)a)3).

3) If adjusted, please itemise the covariates used for adjusted hazard ratios.

Table 7 Covariates used for adjusted hazard ratios

HIMALAYA	• Macrovascular invasion (yes or no) • Aetiology of liver disease (hepatitis B or C virus [but not both] or other/nonviral) • ECOG performance status (0 or 1)
IMbrave150	• Geographic region (Asia excluding Japan vs. the rest of the world) • Macrovascular invasion or extrahepatic spread of disease (presence vs. absence) • Baseline alpha-fetoprotein level (<400 vs. ≥400 ng per milliliter)
REFLECT	• Region (Asia-Pacific [defined as China, Hong Kong, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand] or western [defined as Belgium, UK, Spain, Germany, Italy, Poland, France, USA, Canada, Israel, and Russia]) • Macroscopic portal vein invasion, extrahepatic spread, or both (yes or no) • Eastern Cooperative Oncology Group performance status (0 or 1) • Bodyweight (<60 kg or ≥60 kg)

b) Please explain how the confidence intervals associated with the NMA outputs have been utilised in the cost-effectiveness analysis.

The confidence intervals were used to reflect uncertainty in the analysis and were included in both the PSA and in one-way deterministic sensitivity analysis for comparisons with lenvatinib and atezolizumab plus bevacizumab.

A23. CS, Document B, Figures 4 and 35 and Table 35. Table 35 has no landmark values for 6 years as seen in Figure 4 (p49).

a) Please confirm that the latest overall survival data cut was employed for the presentation in Figure 35 (p113).

The Company confirms the latest presented overall survival data is from the updated analysis II (DCO: 1st March 2024), which was an exploratory analysis of OS at 60 months of median follow-up (5 years). While survival data beyond that up to 6 years may be available, a 6-year OS exploratory analysis has not been conducted.

b) Please supply all landmark values for 6 years.

Since a 6-year OS exploratory analysis has not been conducted, 6-year landmark values are not available.

Section B: Clarification on cost-effectiveness data

Literature searching (cost-effectiveness)

B1. CS, Appendix G.2.2, Table 36. In the second paragraph and heading for Table 36, the dates '13th June' and '13th June 2023' are given. However, date limits in lines 46 and 48 of Table 36 indicate a different search date and year '20211020-20240605' (i.e. 5th June 2024). Furthermore, the exact database segments in the footnote of Table 36 say '2024 June 12'. Please clarify the search date and date limits used for the MEDLINE and Embase update search.

The company can confirm that the date the databases were searched on was the 13th June 2024. The differences in the dates are explained below:

- The search string contains a different date as this reflects when the protocol was written
- The date in the heading of the table is a typographical error and should read 13th June 2024.
- The footnote contains the date 2024 June 12, as it is typical for databases to only search to the end of the day prior to the search date, to ensure only full days are captured.

B2. CS, Appendix G.2.3, Bibliography Searches. Please provide a list of references and PDFs for the relevant SLRs and (network) meta-analyses identified during the SLR that were hand-searched to identify any additional, relevant studies for inclusion.

Table 21 in Appendix I outlines relevant SLR and NMA references that were hand-searched as part of the economic SLR 2024 update, associated PDFs are included in the reference pack.

A list of SLR and NMA references that were hand-searched as part of the 2020 and 2021 economic SLRs is unavailable.

Treatment pathway

B3. Priority question. CS, Document B, Figure 2 and Table 55. Figure 2 (p28) provides the treatment pathway for patients with advanced or unresectable HCC who are ineligible for locoregional therapy in the UK. Additionally, Table 55 (p142) lists subsequent treatments received by patients in the STRIDE and atezolizumab + bevacizumab arms in the first line. Please clarify why treatments such as best supportive care (BSC), cabozantinib, and regorafenib are not included in Figure 2.

In Document B, Figure 2 is intended to represent the first-line treatment choices for patients with advanced or unresectable HCC who are ineligible for locoregional therapy, as outlined by the British Society of Gastroenterology and NICE guidance. Table 55 is the subsequent treatments received after disease progression based on the first-line therapy received.

Model Structure

B4. Priority question. CS, Document B, section B.3.2.2. In the model structure, the company uses 3 primary health states: progression-free, progressed disease, and death. However, for some patients unable to continue treatment (STRIDE), there appears to be 2 additional health states: pre-progression (off treatment) and progressed (off treatment) (CS Model, Sheets: Engine). Please clarify the following:

- a) The EAG assumes that pre-progression (on treatment) and pre-progression (off treatment) correspond to the progression-free health state, while progressed (on treatment) and progressed (off treatment) correspond to the progressed disease health state. Additionally, it appears that patients in progressed (off treatment) are only receiving first-line treatments in durvalumab and tremelimumab and sorafenib. Please clarify whether this interpretation is correct.**

The Company confirm that the model is a 3-state model consisting of progression-free, progressed disease, and death. Pre-progression (off treatment) and progressed (off treatment) do not represent additional health states as stated in the EAG's question.

The EAG's assumption that "pre-progression (on treatment) and pre-progression (off treatment) correspond to the progression-free health state, while progressed (on treatment) and progressed (off treatment) correspond to the progressed disease health state" is correct. However, patients in progressed (off treatment) are not receiving the first-line treatments durvalumab and tremelimumab and sorafenib.

Subsequent treatments are modelled in the progressed disease health state as a weighted one-off cost applied upon entering the state. This is consistent with the modelling approaches used in previous NICE technology appraisals in advanced HCC.^{23,24}

b) What is the main outcome or next health state for patients undergoing subsequent treatment? Is it death? Additionally, what proportion of patients received third-line treatments?

A proportion of patients progressing from the progression-free to the progressed disease health state receive a subsequent treatment, which is a one-off cost applied upon entering the progressed disease health state. From this point, patients can either stay in the progressed disease health state or move to the death state.

Only second-line subsequent treatments are modelled, as only a small proportion of patients receive active therapy beyond first-line treatment for advanced or unresectable HCC. Very few patients receive third-line treatment as a result of the poor disease prognosis, worsening of liver function and reduced patient fitness impacting the potential benefits from further lines of active therapy. This is consistent with the modelling approaches used in previous technology appraisals in advanced HCC.²³

c) It appears that people who received subsequent treatment or in the pre-progression (off-treatment) or progressed (off-treatment) health states have different characteristics to those who progressed (on-treatment) and pre-progression (on-treatment) health states, particularly regarding outcomes and resource use. Please provide further justification why separate health states were not used.

The model is a 3-state model consisting of progression-free, progressed disease, and death. This model structure was deemed the most appropriate based on the clinical data available. It also aligns with the structure adopted in previous NICE evaluations in advanced or unresectable HCC.²³⁻²⁵

It is unclear where the assertion that patients on-treatment in the pre-progression health state have different outcomes and resource use from those off-treatment in the pre-progression health state originated from, given that no evidence has been provided to support this. Similarly, it is unclear where the assertion that patients on-treatment in the post-progression health state have different outcomes and resource use from those off-treatment in the post-progression health state originated from. The data are not available to model these groups independently. As all treatments have treat-to-progress protocols, a significant majority of patients receive the initial therapies until the point of transitioning into the progressed disease health state.

Non-treatment related costs and resource use differ depending on the health state the patient is in, but not by on/off treatment status. Utility values were derived from the HIMALAYA trial and do not differ by health state but is dependent upon first-line treatment received, but not by on/off treatment status. Subsequent treatment costs were applied as a weighted one-off cost upon entering the progressed disease health state, and there were no utility values explicitly ascribed to the subsequent treatments received.

Separate health states for on- and off- treatment in the progression-free and progressed disease, respectively, were not considered necessary, particularly given the data requirements for this technology appraisal, as well as the highly mature HIMALAYA data.

B5. CS, Document B, Table 32. Table 32 (p91), states that the model structure for TA551 is a Markov model with 4 health states: non-progressive advanced disease, PD, BSC, and death. However, in the Committee Papers for TA551, on page 125, it is indicated that a model

structure with 3 health states progression-free, progressed, and dead were used. Please clarify which model structure was applied in TA551.

The Company recognise that there is an error in this table, and TA551 did indeed use a 3-state partitioned survival model. Thank you for identifying.

B6. Priority question. CS, Document B, section B.3.9.2, Table 67. The company used a 40-year time horizon in their NICE submission. However, the EAG noted that in the recent CADTH report titled "CADTH Reimbursement Review Tremelimumab (Imjudo) in Combination With Durvalumab (Imfinzi)," published in January 2024, the time horizon used was 15 years.

a) Please clarify the discrepancy between the time horizon in the NICE submission and the one provided in the CADTH report.

The NICE decision problem and CADTH decision problem are distinctly different. The approaches to modelling reflect the different requirements by each HTA body. The 40-year time horizon was selected as it captures the relevant consequences of first-line HCC treatment in terms of costs and QALYs, and is the timepoint at which <0.01% of patients had died. At 15 years, 6% of patients remained alive in the model submitted to NICE. A scenario was provided in the NICE submission whereby a 20-year time horizon was explored. The time horizon in the company base case is consistent with the NICE reference case and final scope for this appraisal (lifetime time horizon).²⁶

b) Please also explain what factors or new insights, observed in such a short time, led to the decision to extend the time horizon from 15 years to 40 years.

As explained in the response to part a), the 40-year time horizon was selected as it captures the relevant consequences of first-line HCC treatment in terms of costs and QALYs and is consistent with the NICE reference case and final scope for this appraisal.²⁶

B7. CS, Document B, section B.3.2.2. The company stated "*Patients in the 'Progressed disease' health state can either remain alive with progressed disease or die, but the model does not allow for patients to improve their health state.*" (p89). Based on this, it appears that patients in the progression-

free survival health state have a better health condition than those in a progressed disease health state. However, in Figure 23 (p90), the company showed that the proportion of patients in the "Progressed disease (PD)" health state is assumed to be the difference between the OS and PFS health states. Please provide further clarification on this. Specifically, please explain how this aligns with the health conditions and utility values of patients in the PD health state compared to those in the PFS health state.

The EAG understanding is correct.

NICE DSU TSD 19 describes that a partitioned survival model (PSM) with three health states requires two survival curves to estimate state membership:

1. PFS: describes time from model entry to exiting the progression-free state via progression or death (a composite outcome);
2. OS: time from model entry to death.

The first survival curve (PFS) directly provides the proportion of patients remaining in the first health state – progression-free – over time. State membership for the dead state is simply 1 minus the OS curve at each time point. For the progressed health state, state membership is derived as the difference between the OS and the PFS curve at each time point, as this provides the proportion of patients who are alive but not progression-free.

The benefits of this approach is that the model structure directly leverages key time-to-event endpoints in the HIMALAYA study, namely OS and PFS. This reflects the natural disease course and the primary objectives of treatment for patients with advanced or unresectable HCC in the form of delaying progression.

Utility values were derived using a mixed model for repeated measures (MMRM) analysis of all the post-baseline scores for each visit from the HIMALAYA trial to estimate the statistical relationship between utilities and randomised treatment. Deriving utility values from the primary trial informing the efficacy and in the population of interest in the model is aligned with the NICE reference case.²⁶ In the model, utilities were assigned based on treatment received, and it was assumed that atezolizumab + bevacizumab would have the same utility value as STRIDE, and

lenvatinib would have the same utility value as sorafenib. This approach was adopted as it was considered to be the most robust way of capturing the impact of AEs due to TKIs on patients, as evidenced in IMbrave150 and HIMALAYA, and a systematic review and meta-analysis of systemic therapies for advanced HCC which shows that patients treated with TKIs are almost twice as likely as those treated with immune checkpoint inhibitors to experience an AE that is Grade 3 or higher (69% vs. 35%).^{27,28} Utility values were also age-adjusted using the age- and sex-matched general population utility values reported in Hernández-Alava et al.

An alternative utility approach has been provided in response to Question B12. This demonstrates consistent results to the Company base case.

B8. Priority question. CS, Document B, section B.3.2.2. The company stated *“In line with clinical practice, within the progression-free and progressed health states, patients may either be on or off treatment.”* (p89). However, the CS Model 'Model Structure' worksheet indicates that *“Time to Treatment Discontinuation (TTD) data is used to separate the progression-free and progressed health states.”* It appears that TTD might be used to distinguish between on-treatment and off-treatment status within both progression-free and progressed health states. Please clarify these 2 statements and provide more details on the role of TTD.

The statement that “within the progression-free and progressed health states, patients may either be on or off treatment” is correct. Time on treatment is modelled using TTD data, as this is the most accurate approach to model this parameter. Time on treatment is independent of progression status. This approach was used when individual patient data were available for TTD (i.e., for sorafenib and STRIDE from HIMALAYA). When TTD data were not available (i.e., for atezolizumab plus bevacizumab and lenvatinib), an assumption was made that TTD is equivalent to PFS.

Utility values

B9. Priority question. CS, Document B, section B.3.4.5 and Table 55. It is unclear to the EAG what utility values were applied to people who

received subsequent treatments following progressed disease. For example, following primary treatment with durvalumab plus tremelimumab, [REDACTED]% people who progressed received BSC, [REDACTED]% received lenvatinib and [REDACTED]% received sorafenib. Please confirm if subsequent treatment related utility values were applied to these people who progressed following treatment with durvalumab plus tremelimumab, and also for the other comparators who received subsequent treatments.

As described in the response to B4 c), there were no utility values explicitly assigned to the subsequent treatments received. Treatment-specific utility values were applied as outlined in the CS Document B Section B.3.4.5. Data on the utility values in second line advanced or unresectable HCC by treatment received from the HIMALAYA trial are unavailable, and it was considered inappropriate to apply a weighted utility value from an external source based on the treatments received in the model.

B10. Priority question. CS, Document B, sections B.2.6.3.2 and B.3.4.5. Table 50 (p139) provides a summary of utility values for the cost-effectiveness analysis. Given the company's model, the EAG expected different utility values for the 2 health states: progression-free and progressed disease. According to the company, "Post-hoc analyses of the HIMALAYA EQ-5D data were conducted to determine treatment-specific health state utility values based on the EQ-5D data from HIMALAYA." (p58). Please clarify the following points.

- a) Please provide a rationale, in terms of both internal and external validity, for using the same utility value for both health states.**

The utility values in Document B Sections B.2.6.3.2 were post-hoc analysis and exploratory in nature.

As described in response to Question B7, utility values were derived using a MMRM analysis of all the post-baseline scores for each visit from the HIMALAYA trial to estimate the statistical relationship between utilities and randomised treatment and were then assigned based on treatment received in the model. This approach was

adopted as captures the totality of the quality of life data by treatment arm and was considered to be the most robust way of capturing the impact of AEs due to TKIs on patients, as evidenced in IMbrave150 and HIMALAYA, and a systematic review and meta-analysis of systemic therapies for advanced HCC.^{27,28} Utility values were also age-adjusted using the age- and sex-matched general population utility values reported in Hernández-Alava et al.²⁹

Overall survival has been established as an unquestionable, unbiased primary endpoint in oncology and in all randomized studies testing systemic first- and second-line therapies in advanced HCC, and weak surrogacy exists between OS and PFS in advanced or unresectable HCC, particularly for IO-IO therapies.³⁰⁻³³ Given that PFS is a less clinically relevant endpoint, the Company believes that applying the same utility value in both health states is appropriate.

b) Please provide more details on the post-hoc analyses of the HIMALAYA EQ-5D-5L data, particularly regarding the timing of data collection, the relationship between the data and the disease stage, and the time interval to death.

[REDACTED]

A time-to-death utility approach has been provided in response to Question B12.

B11. CS, Document B, section B.3.4.5. The company states that *"In the model, utilities were treatment-dependent."* (p138). This viewpoint suggests that different utility values were assigned for the same health state between comparators, such as 0.812 for STRIDE and 0.779 for sorafenib. Please provide more details on what is meant by "treatment-dependent" utility values. Specifically, what factors led to the different values between comparators for the same health state.

Utility values were derived using a MMRM analysis of all the post-baseline scores for each visit to estimate the statistical relationship between utilities and treatment. The results of this analysis suggested a statistically different utility by randomised treatment arm, as shown in Table 8. This approach was considered an accurate way of capturing the AEs associated with TKIs vs. the IO regimens in the model.

Table 8 Point estimate from MMRM utility model

Parameter	Treatment
(Intercept)	████████████████████
TREME 300 + DURVA	████████████████████

B12. Priority question. CS, Document B, section B.3.9.2. Table 67 outlines the assumptions used in the company’s economic analysis. The EAG notes the company’s rationale about HRQoL is treatment dependent. Please provide further information to support this approach. The company stated, “*this approach was selected as it was considered to be the most robust way of capturing the impact of adverse events due to TKIs on patients.*” (p159). Please provide a model that allows other approaches to be used.

As noted by the EAG, treatment dependent utilities were used in order to capture the impact of AEs due to TKIs on patients.

The EAG has requested a model that allows other approaches to be used. The Company considered NICE TA666 (atezolizumab with bevacizumab in advanced or unresectable HCC) which used a time to death approach for utilities.²³ The Company has performed a similar analysis using the HIMALAYA data and implemented it in the cost-effectiveness model. The methodology and results are detailed here.

UK utility values were derived from the EQ-5D-5L profiles in HIMALAYA using the UK value set by Hernandez et al. as per the original CS.²⁹ The statistical relationship between EQ-5D utility and time to death was assessed using regression analysis. To account for the repeated measurements in the study, a MMRM method was used to model EQ-5D utilities.³⁴ This method accounts for the autocorrelation in utility score within each patient and is appropriate when handling data that are missing at

random. Notably, a random intercept model assuming independent within-subject errors was fitted to account for the subject variability.

The analysis set comprised all patients in the full analysis set with an observed death prior to the Updated analysis I DCO date (August 2021), as well as observations from patients who were censored for death, recorded > 30 weeks from their date of censoring. The EQ-5D time-to-death analysis uses the August 2021 DCO, whilst the OS data used in the model uses the latest 5-year OS DCO (March 2024). This is a limitation in the analysis as the censoring/deaths driving the utility analysis have a different DCO (August 2021 DCO) versus the survival data in the CS (March 2024). This cannot be addressed because EQ-5D data were not collected beyond August 2021.

Observations were categorized according to the proximity to a patient's death, using the following categories: ≤ 5 weeks, $>5\text{--}\leq 15$ weeks, $>15\text{--}\leq 30$ weeks and >30 weeks from death date. These cut-offs were selected as they align with what was used in TA666.

Observations from patients who were censored for death, that were recorded >30 weeks from date of censoring, were included in the > 30 week category only. Although these patients hadn't experienced a death event whilst on the trial, we know death will occur at some point in the future, thereby verifying these as observations > 30 weeks from death. Observations from censored patients that were recorded < 30 weeks from their date of censoring were not included. As the death date for these patients is unknown, we are unable to classify these observations under any of the bounded time intervals.

Table 9 provides a summary of the marginal means from the time-to-death utility analysis.

Table 9: Summary of marginal mean utility values for time-to-death analysis

Treatment	≤ 5 weeks before death	5-15 weeks before death	15-30 weeks before death	>30 weeks before death
Utility values				

The deterministic pairwise cost-effectiveness results using these values are provided in Table 10.

Table 10: Deterministic base-case results (pairwise analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)
STRIDE				-	-	-	-
Atezolizumab + bevacizumab	£244,087	3.02	2.43				STRIDE is dominant
Sorafenib	£36,799	1.92	1.53				
Lenvatinib	£48,445	1.92	1.53				

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.

The results are highly consistent with the Company base case submission.

B13. CS, Document B, section B.3.11.3. Please clarify if the treatment-dependent utility values have been included in the deterministic one-way sensitivity analysis. If not included, please explain the rationale for excluding these inputs from the analysis.

Utilities were included in the probabilistic analysis but were not included in the one-way deterministic sensitivity analysis because the utility for STRIDE is correlated with the value for sorafenib as the STRIDE value is calculated from the MMRM model outputs (i.e., model intercept is [REDACTED] which is the utility for sorafenib, and the coefficient associated with treatment is [REDACTED], meaning that the STRIDE utility value was calculated to be [REDACTED]).

Resource use and costs

B14. Priority question. CS, Document B, section B.3.5.2. Tables 57 and 58 present resource use information by treatment. Table 57 shows the proportion of patients receiving each healthcare resource use item by treatment and health state, and Table 58 presents the frequency per week. The company stated that these values were calculated based on resource use estimates from previous technology appraisals (TA666 and TA551) and were adjusted following a validation exercise with clinicians. The EAG reviewed TA666 ([TA666 Committee Papers](#), Table 50, p125) to compare the data on the frequency per weekly cycle and the monthly proportion (%) of patients receiving resource use related to atezolizumab + bevacizumab. Based on the comparison between the Table 57 and

TA666, it can be observed that the monthly proportion (%) of patients receiving resource use in TA666 is approximately similar to the respective weekly values in Table 57. Please confirm that the company's new weekly proportions for atezolizumab + bevacizumab are correct (please see Tables 1 and 2 below). Please explain the reasoning behind using the same (or nearly the same) value for both the monthly and weekly cycles.

Table 1: Weekly and monthly proportion of people receiving resource use

Resource use	Weekly proportion (%) of patients having atezolizumab + bevacizumab (CS, Table 57)		Monthly proportion (%) of patients having atezolizumab + bevacizumab (TA666, Committee Papers, Table 50)	
	Progression-free	Progressed	Progression-free	Progressed
Oncologist			92	56
Hepatologist			3	22
Gastroenterologist			0	12
AFP test			100	51
Endoscopy			12	7
CT scan: abdominal			90	26
Hospitalisation			8	23
GP			19	32

Table 2: Frequency per weekly cycle for resource use

Resource use	Frequency per weekly cycle for atezolizumab + bevacizumab (CS, Table 58)		Frequency per weekly cycle for atezolizumab + bevacizumab (TA666, Committee Papers, Table 50)	
	Progression-free	Progressed	Progression-free	Progressed
Oncologist			0.27	0.24
Hepatologist			0.08	0.15
Gastroenterologist			0.04	0.14
AFP test			0.23	0.19
Endoscopy			0.08	0.04
CT scan: abdominal			0.14	0.09
Hospitalisation			0.17	0.18
GP			0.11	0.14

The CS used previous submissions as a starting point for what healthcare resource use items are relevant for advanced HCC and validated the proportions and frequency with UK clinicians to reflect current clinical practice in the UK.²³ The values used in the model are averaged across clinician responses. These values may differ

from TA666 as the research used in TA666 was conducted prior to an immunotherapy regimen being recommended in advanced HCC, and clinicians have since gathered more experience in treating patients with the atezolizumab plus bevacizumab regimen now.

Proportions of patients receiving each resource used across TAs are very consistent, with the exception of hepatology in progressed disease, which clinicians had said was not so widely used. As a proportion is a relative value, it is inconsequential whether the proportions are referring to a month or week duration.

Once you multiply the frequency by proportion in both appraisals there are similar figures across appraisals (Table 11), with the only noticeable difference being GP visits and endoscopy in the progressed disease state.

Table 11 Multiplied frequency by proportion

	Weekly frequency weighted by proportion receiving (atezolizumab + bevacizumab in CS)		Weekly frequency weighted by proportion receiving (atezolizumab + bevacizumab in TA666) ²³	
	Progression-free	Progressed	Progression-free	Progressed
Oncologist			0.25	0.13
Hepatologist			0.00	0.03
Gastroenterologist			0.00	0.02
AFP test			0.23	0.10
Endoscopy			0.01	0.00
CT scan: abdominal			0.13	0.02
Hospitalisation			0.01	0.04
GP			0.02	0.04

B15. Priority question. CS, Document B, sections B.3.5.1 and B.3.5.2. Table 55 indicates that the majority of patients receiving different treatments after discontinuing first-line treatments are placed on BSC as their subsequent treatment. The EAG assumes that the resource use data by treatment and health state provided in Table 57 (p146) are related to BSC and apply to all patients in the progression-free and progressed disease health states, regardless of prior first-line treatments.

a) Please clarify the role and features of BSC in this context.

Palliative/best supportive care is offered to patients with end-stage liver disease to alleviate symptom burden and is employed when no active treatment options are

deemed to bring benefit.³⁵ There is a holistic focus on management of pain, nutrition and psychological support. End-stage liver disease has further implications from the perspective of pharmacokinetics/metabolising medications such as analgesics and anti-anxiety treatments leading to use with caution, with non-pharmacological approaches often preferred. These patients are still monitored (costs included) – resource use items reflected in Table 57.

- b) The EAG considers that patients having BSC, as well as those receiving other subsequent treatments, may require medications to improve quality of life and manage symptoms, such as opioids, ondansetron, and metoclopramide. It is unclear how these supportive care medications are incorporated into the subsequent treatments or management of adverse reactions. Please provide clarification on how these supportive care measures are addressed in the model.**

Monitoring, healthcare professional and hospitalisation costs are included for patients in the progressed disease health states, which make up the majority of the costs for BSC. Opioids, ondansetron, and metoclopramide are all low-cost drugs and are not anticipated to result in a notable additional cost to this health state. These costs were not included in recent technology appraisals in advanced HCC.^{23,24}

The costs of AEs is believed to be adequately captured using the NHS reference costs, and this aligned with previous appraisals in advanced HCC.^{23,24}

B16. Priority question. CS, Document B, section B.3.5.1. It appears that many patients received further active therapies after ceasing the use of STRIDE (with named subsequent treatments). Although the company submission documents the duration of some administered treatments, it is unclear when these treatments started and finished (e.g., Table 56, p143). This information is important for assessing the validity of costings used in the economic model.

- a) Please state the maximum time reached post randomisation when all active treatments ceased in each arm of HIMALAYA. By active treatments we mean all administrations oral or IV of any drugs.**

Time to treatment discontinuation data for the randomised treatments in HIMALAYA was provided in the Company submission Document B section B.3.3.5. Time to treatment discontinuation for any treatment received post-randomised treatment was not available from the trial.

It should be noted that the treatments included in Table 56, p143 in the Company Submission do not necessarily reflect the treatments received in the HIMALAYA trial. The cost of subsequent therapies received in the model is applied as a weighted one-off cost upon entering the progressed disease health state. This calculation accounts for the average treatment duration for each treatment. This approach was used in previous appraisals in advanced HCC (TA666).²³

Please document by named drug used in HIMALAYA post STRIDE administration:

- b) The time since the patients' randomisation that administration of each of the drug started.**

The information is not available at this time.

- c) The time since the patient's randomisation that the administration of the drug ceased.**

The information is not available at this time.

Please provide the same data for the sorafenib arm of HIMALAYA.

The information is not available at this time.

Section C: Textual clarification and additional points

C1. Please provide PDFs of the following 'data on file' references, cited in CS, Document B, or clarify where they are saved in the reference pack.

- a) 122. AstraZeneca. HIMALAYA Study Protocol D419CC00002 (Long Term Follow Up 1 [LTFU1]), 2023. [Cited in many places. We have the 2019 protocol in the reference pack, but not this 2023 version]

Reference 122 is a duplicate of reference 89: AstraZeneca. Data on File: HIMALAYA CSR (Jan 2022), 2022. Both documents refer to the CSR for the updated analysis I. There is only one version of the HIMALAYA trial protocol which is the 2019 version noted above.

The associated pdf has been shared as part of the original reference pack in the sub-folder “Data on file” under the name “AZ HIMALAYA Clinical Study Report Jan_2022”.

- b) 124. AstraZeneca Data on File. Advisory Board Meeting for HIMALAYA Trial of Imfinzi plus Tremelimumab for 1st-line Unresectable Liver Cancer. Meeting Report - Draft. 2022. [Cited in 2 places (B.2.12. Interpretation of clinical effectiveness and safety evidence, B.3.2.3 Intervention technology and comparators)]

This reference has been added erroneously and is not required in support of the statements made. Please interpret the statements excluding this source.

Appendix I

Clarification question A2.

Table 12 Hand-searched bibliography of SLRs and NMAs as part of the original 2020 clinical SLR update

Reference	Title
Bakouny 2019	Second-line Treatments of Advanced Hepatocellular Carcinoma
Facciorusso 2020	Efficacy of regorafenib in hepatocellular carcinoma patients: A systematic review and meta-analysis
Voutsadakis 2019	PD-1 inhibitors monotherapy in hepatocellular carcinoma: Meta-analysis and systematic review
Cucchetti 2017	Efficacy and Safety of Systemic Therapies for Advanced Hepatocellular Carcinoma: A Network Meta-Analysis of Phase III Trials
Finn 2018	Therapies for advanced stage hepatocellular carcinoma with macrovascular invasion or metastatic disease: A systematic review and meta-analysis
Spallanzani 2018	Lenvatinib as a therapy for unresectable hepatocellular carcinoma
Park 2019	Relative Efficacy of Systemic Treatments for Patients with Advanced Hepatocellular Carcinoma According to Viral Status: A Systematic Review and Network Meta-Analysis
Cabibbo 2019	Outcomes of hepatocellular carcinoma patients treated with sorafenib: A meta-analysis of Phase III trials
Guo 2019	Evaluation of Targeted Agents for Advanced and Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis
McNamara 2018	Sorafenib as first-line therapy in patients with advanced Child-Pugh B hepatocellular carcinoma—a meta-analysis
Barone 2019	Systematic review: Renin-angiotensin system inhibitors in chemoprevention of hepatocellular carcinoma

Table 13 Hand-searched bibliography of SLRs and NMAs as part of the 1st clinical SLR update (2021)

Reference	Title
Aitcheson 2021	Recent Advances in Systemic Therapies for Advanced Hepatocellular Carcinoma
Ding 2020	First-line targeted therapies of advanced hepatocellular carcinoma: A Bayesian network analysis of randomized controlled trials
Han 2021	Selection of first-line systemic therapies for advanced hepatocellular carcinoma: A network meta-analysis of randomized controlled trials
Park 2021	Comparison of Efficacy of Systemic Therapies in Advanced Hepatocellular Carcinoma: Updated Systematic Review and Frequentist Network Meta-Analysis of Randomized Controlled Trials
Pollock 2021	A systematic literature review and network meta-analysis of first-line treatments for unresectable hepatocellular carcinoma based on data from randomized controlled trials
Sonbol 2020	Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma
Facciorusso 2021	Lenvatinib versus sorafenib as first-line therapy of advanced hepatocellular carcinoma: a systematic review and meta-analysis
Gordon 2020	Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline
Haber 2021	Evidence-Based Management of Hepatocellular Carcinoma: Systematic Review and Meta-analysis of Randomized Controlled Trials (2002-2020)

Oranratnachai 2021	Efficacy of First Line Systemic Chemotherapy and Multikinase Inhibitors in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis
Pan 2021	Comparative safety and efficacy of molecular-targeted drugs, immune checkpoint inhibitors, hepatic arterial infusion chemotherapy and their combinations in advanced hepatocellular carcinoma: findings from advances in landmark trials
Vogel 2021	Comparative efficacy of atezolizumab plus bevacizumab and other treatment options for patients with unresectable hepatocellular carcinoma: A network meta-analysis
Xie 2021	Transarterial chemoembolization plus sorafenib versus sorafenib for intermediate-advanced hepatocellular carcinoma: A meta-analysis comparing clinical outcomes
Zhang 2021	Frequent fragility of randomized controlled trials for HCC treatment
Ziogas 2021	The Role of Immunotherapy in Hepatocellular Carcinoma: A systematic Review and Pooled Analysis of 2,402 patients

Table 14 Hand-searched bibliography of SLRs and NMAs as part of the 2nd clinical SLR update (2024)

Reference	Title
Altayar 2022	Technical Review on Systemic Therapies for Hepatocellular Carcinoma
An 2022	Ranking of transarterial and targeted therapies for advanced hepatocellular carcinoma in the era of immuno-oncology: A network meta-analysis of randomized sorafenib-controlled trials
Balcar 2024	A meta-analysis and real-world cohort study on the sex-related differences in efficacy and safety of immunotherapy for hepatocellular carcinoma
Brown 2022	Trends of Clinical Outcomes of Patients with Advanced Hepatocellular Carcinoma Treated with First-Line Sorafenib in Randomized Controlled Trials
Cao 2024	Hepatic arterial infusion chemotherapy with anti-angiogenesis agents and immune checkpoint inhibitors for unresectable hepatocellular carcinoma and meta-analysis
Changez 2023	Efficacy of Atezolizumab Plus Bevacizumab Versus Lenvatinib in Patients with Unresectable Hepatocellular Carcinoma: a Meta-analysis
Chen 2024	New First-line Immunotherapy-based Therapies for Unresectable Hepatocellular Carcinoma: A Living Network Meta-analysis
Ciliberto 2023	First-line systemic treatment for hepatocellular carcinoma: A systematic review and network meta-analysis
Fong 2023	First-Line Systemic Therapies for Advanced Hepatocellular Carcinoma: A Systematic Review and Patient-Level Network Meta-Analysis
Fulgenzi 2022	Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma: A network metanalysis of phase III trials
Fulgenzi 2023	Efficacy and safety of frontline systemic therapy for advanced HCC: A network meta-analysis of landmark phase III trials
Griffiths 2022	Toxicity Profiles of Systemic Therapies for Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-analysis
Hu 2023	Comparison of the effects of lenvatinib and sorafenib on survival in patients with advanced hepatocellular carcinoma: A systematic review and meta-analysis
Hua 2024	Efficacy and safety comparison between Lenvatinib and Sorafenib in hepatocellular carcinoma treatment: a systematic review and meta-analysis of real-world study
Jacome 2021	Efficacy and Safety Associated With Immune Checkpoint Inhibitors in Unresectable Hepatocellular Carcinoma: A Meta-analysis
Kudo 2022	Objective Response Predicts Survival in Advanced Hepatocellular Carcinoma Treated with Systemic Therapies
Kulkarni 2023	Effectiveness and safety of atezolizumab-bevacizumab in patients with unresectable hepatocellular carcinoma: a systematic review and meta-analysis

Li 2023	Efficacy and safety of transarterial chemoembolization plus lenvatinib in the treatment of advanced hepatocellular carcinoma: A meta-analysis
Li 2024	The long-term efficacy and safety of apatinib are inferior to sorafenib in the first-line treatment of advanced hepatocellular carcinoma: A systematic review and meta-analysis
Liu 2023	Treatment modalities to manage hepatocellular carcinoma patients with portal vein thrombosis: a systematic review and meta-analysis
Liu 2023b	Identification of the most effective subgroup of advanced hepatocellular carcinoma from immune checkpoint blocker treatment: a meta-analysis
Liu 2022	Immunotherapy or targeted therapy as the first-line strategies for unresectable hepatocellular carcinoma: A network meta-analysis and cost-effectiveness analysis
Liu 2021	First-Line Systemic Treatment Strategies for Unresectable Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials
Long 2023	Comparative efficacy and safety of molecular targeted agents combined with transarterial chemoembolization in the treatment of unresectable hepatocellular carcinoma: a network meta-analysis
Luo 2022	Efficacy and safety of lenvatinib versus sorafenib in first-line treatment of advanced hepatocellular carcinoma: A meta-analysis
Pan 2023	Safety and Efficacy of TACE + Lenvatinib in Treating Advanced Hepatocellular Carcinoma: A Systematic Review and Meta- analysis
Pei 2024	Transarterial Chemoembolization Combined with Lenvatinib for Hepatocellular Carcinoma: A Systematic Review and Meta-analysis of Randomized Controlled Trials
Peng 2023	Sorafenib Plus Hepatic Arterial Infusion Chemotherapy in Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-analysis
Sun 2022	First-line treatments for advanced hepatocellular carcinoma: a network meta-analysis and cost-effectiveness analysis in China and the United States
Tan 2023	Survival Trends in Sorafenib for Advanced Hepatocellular Carcinoma: a Reconstructed Individual Patient Data Meta-Analysis of Randomized Trials
Vogel 2023	Atezolizumab in Combination with Bevacizumab for the Management of Patients with Hepatocellular Carcinoma in the First-Line Setting: Systematic Literature Review and Meta-Analysis
Xie 2023	Immune Checkpoint Inhibitors for Child-Pugh Class B Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis
Yang 2022	Efficacy and safety of combined targeted therapy and immunotherapy versus targeted monotherapy in unresectable hepatocellular carcinoma: a systematic review and meta-analysis
Yu 2023	Lenvatinib plus Immune Checkpoint Inhibitors versus Lenvatinib monotherapy as treatment for advanced hepatocellular carcinoma: a meta-analysis
Yuanren 2023	The treatment of transarterial chemoembolization/hepatic arterial infusion chemotherapy combined with lenvatinib and PD-1 inhibitor is effective against hepatocellular carcinoma with portal vein tumor thrombus: A systematic review
Zeng 2023	Comparison of the efficacy and safety of selective internal radiotherapy and sorafenib alone or combined for hepatocellular carcinoma: a systematic review and Bayesian network meta-analysis
Zhang 2023	Dual immune checkpoint inhibitors or combined with anti-VEGF agents in advanced, unresectable hepatocellular carcinoma
Zhang 2024	Approved immune checkpoint inhibitors in hepatocellular carcinoma: a large-scale meta-analysis and systematic review
Zeng 2022	Survival Outcomes and Safety of Programmed Cell Death/Programmed Cell Death Ligand 1 Inhibitors for Unresectable Hepatocellular Carcinoma: Result From Phase III Trials

Clarification question A3.

Table 15: Records considered for inclusion within the NMA

#	Study Name	Reference	Reason for exclusion from the NMA (if relevant)
Records included in original SLR			
1	Sorafenib AP	Cheng, A.L., Kang, Y.K., Chen, Z., Tsao, C.J., Qin, S., Kim, J.S., Luo, R., Feng, J., Ye, S., Yang, T.S. and Xu, J., 2009. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. <i>The lancet oncology</i> , 10(1), pp.25-34.	The study does not include at least 2 interventions of interest to the NMA
2	IMBrave150	Finn, R.S., Qin, S., Ikeda, M., Galle, P.R., Ducreux, M., Kim, T.Y., Kudo, M., Breder, V., Merle, P., Kaseb, A.O. and Li, D., 2020. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. <i>New England Journal of Medicine</i> , 382(20), pp.1894-1905.	Included
3	HIMALAYA	Data on File	Included
4	NR	Ji, Y.X., Zhang, Z.F., Lan, K.T., Nie, K.K., Geng, C.X., Liu, S.C., Zhang, L., Zhuan, X.J., Zou, X., Sun, L. and Zhang, Z.C., 2014. Sorafenib in liver function impaired advanced hepatocellular carcinoma. <i>Chinese Medical Sciences Journal</i> , 29(1), pp.7-14.	The study does not include at least 2 interventions of interest to the NMA
5	REFLECT	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. <i>Lancet</i> . 2018;391(10126):1163-1173	Included
6	SHARP	Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. <i>N Engl J Med</i> . 2008;359(4):378-390.	The study does not include at least 2 interventions of interest to the NMA
7	CheckMate 459	Yau, T., Park, J.W., Finn, R.S., Cheng, A.L., Mathurin, P., Edeline, J., Kudo, M., Han, K.H., Harding, J.J., Merle, P. and Rosmorduc, O., 2019. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). <i>Annals of Oncology</i> , 30, pp.v874-v875.	The study does not include at least 2 interventions of interest to the NMA
8	CA209-459	Bristol-Myers Squibb. NCT02576509: an investigational immuno-therapy study of nivolumab compared to sorafenib as a first treatment in patients with advanced hepatocellular carcinoma. https://clinicaltrials.gov/ct2/show/NCT02576509 . Accessed October 5, 2020	The study does not include at least 2 interventions of interest to the NMA
Records included in 1st SLR update			
9	CheckMate 459	NCT. An Investigational Immuno-therapy Study of Nivolumab Compared to Sorafenib as a First Treatment in Patients With Advanced Hepatocellular Carcinoma. https://clinicaltrials.gov/study/NCT02576509	The study does not include at least 2

10		Yau, T. Park, J.W. Finn, R.S. Cheng, A.-L. Mathurin, P. Edeline, J. Kudo, M. Han, K.-H. Harding, J.J. Merle, P. Rosmorduc, O. Wyrwicz, L. Schott, E. Choo, S.P. Kelley, R.K. Begic, D. Chen, G. Neely, J. Anderson, J. Sangro, B.. 2022. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial.. The Lancet Oncology 23(1):77-90.	interventions of interest to the NMA
11	IMbrave150	Andrew X Zhu, Richard Finn, Michel Ducreux, Youyou Hu, Nicolas Sommer, Wendy Verret, Laura M Kulik and Peter R. Galle. 2021. imBRAVE150: Exploratory Efficacy and Safety of Atezolizumab (Atezo) + Bevacizumab (Bev) Vs Sorafenib (Sor) in Patients with Hepatocellular Carcinoma (HCC) with Non-Viral Etiology in a Global Phase III Study. AASLD :646A.	The data were not relevant for informing the primary NMA analyses that used data from the full trial population.
12		C Hsu, M Ducreux, A.X. Zhu, S. Qin, M. Ikeda, T. Kim, P.R. Galle, R. Finn, E. Chen, H. Shao, S.F. Stanzel, D. Zhu, A. Cheng. 2020. Hepatic events and viral kinetics in patients (PTS) with hepatitis b/c virus (HBV/HCV)-related, unresectable hepatocellular carcinoma (HCC) treated with atezolizumab (ATEZO) + bevacizumab (BEV) or sorafenib (SOR) in imbrave150. Hepatology 72(1 Suppl):779A-780A.	
13		D Li, H Toh, P Merle, K Tsuchiya, S Hernandez, H Shao, S Mulla, B Ding, M Kudo. 2020. Atezolizumab + bevacizumab vs sorafenib for unresectable hepatocellular carcinoma: Results from older adults enrolled in IMbrave150. Annals of Oncology 31(S3):S234.	
14		Ducreux M, Zhu A, Qin S, Ikeda M, Kim T-Y, Lim HY, Kudo M, Breder V, Merle P, Kaseb A, Li D, Verret W, Xu Z, Hernandez S, Liu J, Shao H, Huang C, Cheng A-LII, Finn R, Galle P. 2020. Atezolizumab + bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma: safety results from the Phase III IMbrave150 study. Journal of Hepatology 73():S121.	
15		M. Kudo, R.S. Finn, P.R. Galle, A. Zhu, M.P. Ducreux, A. Cheng, W. Verret, V.E. Gaillard, A. Nicholas, R. Lencioni. 2021. IMbrave150: Exploratory efficacy and safety results in patients with hepatocellular carcinoma without macrovascular invasion (MVI) or extrahepatic spread (EHS) treated with atezolizumab (atezo) + bevacizumab (bev) or sorafenib (sor). Annals of Oncology 32(S5):S818.	
16		Richard S. Finn, Shukui Qin, Masafumi Ikeda, Peter R. Galle, Michel Ducreux, Tae-You Kim, Masatoshi Kudo, Ho Yeong Lim, Valeriy Vladimirovich Breder, Philippe Merle, Ahmed Omar Kaseb, Daneng Li, Yin-Hsun Feng, Wendy Verret, Derek-Zhen Xu, Sairy Hernandez, Beiying Ding, Andrew X. Zhu, and Ann-Lii Cheng. 2020. Complete responses (CR) in patients receiving atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in IMbrave150: A phase III clinical trial for unresectable hepatocellular carcinoma (HCC).. Journal of Clinical Oncology 38(15 Supplement):4596-4596.	
17		Richard S. Finn, Shukui Qin, Masafumi Ikeda, Peter R. Galle, Michel Ducreux, Tae-You Kim, Masatoshi Kudo, Ho Yeong Lim, Valeriy Breder, Philippe Merle, Ahmed Kaseb, Daneng Li, Yin-Hsun Feng, Wendy Verret, Alan Nicholas, Lindong Li, Ning Ma, Andrew X. Zhu, and Ann-Lii Cheng. 2021. IMbrave150: Updated efficacy and safety by risk status in patients (pts) receiving atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment for unresectable hepatocellular carcinoma (HCC). Cancer Research 81(13 Supplement): .	

18		Finn Richard S. 2021. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo)+ bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). Journal of Clinical Oncology 39(3_suppl):267.	
19		Riad Salem, Daneng Li, Nicolas Sommer, Sairy Hernandez, Wendy Verret, Beiying Ding, Riccardo Lencioni. 2021. Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: Results from the IMbrave150 trial. Cancer Medicine 10(16):5437-5447.	
20	IMbrave150 (China)	Qin S, Ren Z, Feng YH, Yau T, Wang B, Zhao H, Bai Y, Gu S, Li L, Hernandez S, Xu DZ, Mulla S, Wang Y, Shao H, Cheng AL.. 2021. Atezolizumab plus Bevacizumab versus Sorafenib in the Chinese Subpopulation with Unresectable Hepatocellular Carcinoma: Phase 3 Randomized, Open-Label IMbrave150 Study. Liver Cancer 10(4):296-308.	The data were not relevant for informing the primary NMA analyses that used data from the full trial population.
Records deprioritised at 2nd SLR update			
21	Alliance	Abou-Alfa GK, Geyer SM, Nixon AB, et al. CALGB 80802 (Alliance): impact of Sorafenib with and without Doxorubicin on Hepatitis C Infection in Patients with Advanced Hepatocellular Carcinoma. Cancer research communications 2024;4:682-690.	The study does not include at least 2 interventions of interest to the NMA
22	CARES-310	Chan SL, Kaseb AO, Shi W, et al. Patient-reported outcomes (PROs) <65 or ≥ 65 years old (yo) from CARES-310 camrelizumab + rivoceranib vs sorafenib as first-line treatment for patients with unresectable hepatocellular carcinoma (uHCC). Journal of clinical oncology 2024;42.	The study does not include at least 2 interventions of interest to the NMA
23		Qin S, Chan LS, Gu S, et al. LBA35 Camrelizumab (C) plus rivoceranib (R) vs. sorafenib (S) as first-line therapy for unresectable hepatocellular carcinoma (uHCC): a randomized, phase III trial. Annals of oncology 2022;33:S1401-S1402.	
24		Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet (london, england) 2023;402:1133-1146.	
25		Vogel A, Cheng AL, Shi W, et al. Impact of baseline liver function on survival outcomes in patients with unresectable hepatocellular carcinoma (uHCC) treated with camrelizumab + rivoceranib vs sorafenib: a post hoc analysis of study CARES-310. Journal of clinical oncology 2024;42.	
26		Nct. A Study to Evaluate SHR-1210 in Combination With Apatinib as First-Line Therapy in Patients With Advanced HCC. https://clinicaltrials.gov/study/NCT03764293 2024.	
27	CheckMate 459	Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. The lancet. Oncology 2022;23:77-90.	The study does not include at least 2 interventions of interest to the NMA

28	COSMIC-312	Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. <i>The lancet. Oncology</i> 2022;23:995-1008.	The study does not include at least 2 interventions of interest to the NMA
29		Yau T, Kaseb A, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): final results of a randomised phase 3 study. <i>The lancet. Gastroenterology & hepatology</i> 2024;9:310-322.	
30	FOHAIC-1	Lyu N, Wang X, Li JB, et al. Arterial Chemotherapy of Oxaliplatin Plus Fluorouracil Versus Sorafenib in Advanced Hepatocellular Carcinoma: A Biomolecular Exploratory, Randomized, Phase III Trial (FOHAIC-1). <i>Journal of Clinical Oncology</i> 2022;40:468-480.	The study does not include at least 2 interventions of interest to the NMA
31	HIMALAYA	Chan SL, Kudo M, Sangro B, et al. 67O Outcomes in the Asian subgroup of the phase III HIMALAYA study of tremelimumab (T) plus durvalumab (D) in unresectable hepatocellular carcinoma (uHCC). <i>Annals of oncology</i> 2022;33:S1456.	The data were not relevant for informing the primary NMA analyses that used data from the full trial population.
32		De Toni EN, Sangro B, Chan SL, et al. Adverse Event Profiles and Time to Onset and Resolution with Tremelimumab (T) plus Durvalumab (D) in Patients with Unresectable Hepatocellular Carcinoma (uHCC) in the Phase 3 HIMALAYA Trial. <i>Oncology research and treatment</i> 2023;46:239-240.	
33		Qin L, Miranda M, Shephard C, et al. The impact of treatment and treatment status on health state utility in patients with unresectable hepatocellular carcinoma: an EQ-5D analysis from Himalaya. <i>Journal of hepatology</i> 2022;77:S110.	
34		Vogel A, Chan S, Furuse J, et al. O-5 Outcomes by baseline liver function in patients with unresectable hepatocellular carcinoma treated with tremelimumab and durvalumab in the phase 3 HIMALAYA study. <i>Annals of oncology</i> 2022;33:S380-S381.	
35		Vogel A, Chan SL, Furuse J, et al. OUTCOMES BY BASELINE LIVER FUNCTION IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA TREATED WITH TREMELIMUMAB AND DURVALUMAB IN THE PHASE 3 HIMALAYA STUDY. <i>Hepatology (Baltimore, Md.)</i> 2022;76:S1418-S1419.	
36		Lau G, Cheng A-L, Sangro B, et al. Outcomes by occurrence of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC): American Society of Clinical Oncology, 2023.	
37		Chan LS, Kudo M, Sangro B, et al. 714P Impact of viral aetiology in the phase III HIMALAYA study of tremelimumab (T) plus durvalumab (D) in unresectable hepatocellular carcinoma (uHCC). <i>Annals of Oncology</i> 2022;33:S869-S870.	
38	IMbrave150	Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. <i>Journal of hepatology</i> 2022;76:862-873.	The data were not relevant for informing the primary NMA analyses that used
39		Galle PR, Salem R, Finn RS, et al. IMbrave150: exploratory efficacy and safety results of atezolizumab + bevacizumab vs sorafenib in patients (pts) with unresectable hepatocellular carcinoma (HCC) who had prior locoregional therapy (LRT). <i>Oncology research and treatment</i> 2022;45:78.	

40		Hsu C, Ducreux M, Zhu AX, et al. Hepatic Events and Viral Kinetics in Hepatocellular Carcinoma Patients Treated with Atezolizumab plus Bevacizumab. <i>Liver cancer</i> 2023;12:44-56.	data from the full trial population.
41		Kaseb AO, Guan Y, Gok Yavuz B, et al. Serum IGF-1 Scores and Clinical Outcomes in the Phase III IMbrave150 Study of Atezolizumab Plus Bevacizumab versus Sorafenib in Patients with Unresectable Hepatocellular Carcinoma. <i>Journal of Hepatocellular Carcinoma</i> 2022;9:1065-1079.	
42		Kudo M, Finn RS, Cheng AL, et al. Albumin-Bilirubin Grade Analyses of Atezolizumab plus Bevacizumab versus Sorafenib in Patients with Unresectable Hepatocellular Carcinoma: a Post Hoc Analysis of the Phase III IMbrave150 Study. <i>Liver cancer</i> 2023;12:479-493.	
43		Kudo M, Finn RS, Galle PR, et al. IMbrave150: efficacy and Safety of Atezolizumab plus Bevacizumab versus Sorafenib in Patients with Barcelona Clinic Liver Cancer Stage B Unresectable Hepatocellular Carcinoma: an Exploratory Analysis of the Phase III Study. <i>Liver cancer</i> 2023;12:238-250.	
44		Kudo M, Tsuchiya K, Shao YY, et al. IMbrave150: exploratory analysis to examine the association between bevacizumab (bev) ever being skipped and bev never being skipped in patients with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab (atezo) + bev in a global phase 3 study. <i>Journal of clinical oncology</i> 2023;41:538.	
45		Kudo M, Yamashita T, Finn RS, et al. IMbrave150: exploratory analyses for investigating associations between overall survival (OS) and depth of response (DpR) or duration of response (DoR) in patients (pts) with unresectable hepatocellular carcinoma (HCC). <i>Annals of oncology</i> 2023;34:S1534-S1535.	
46		Li D, Toh HC, Merle P, et al. Atezolizumab plus Bevacizumab versus Sorafenib for Unresectable Hepatocellular Carcinoma: Results from Older Adults Enrolled in the IMbrave150 Randomized Clinical Trial. <i>Liver Cancer</i> 2022;11:558-571.	
47		Lim M, Muquith M, Miramontes B, et al. Surrogate and modified endpoints for immunotherapy in advanced hepatocellular carcinoma. <i>Hepatology</i> 2023;78:1755-1762.	
48		Toh HC, Galle PR, Zhu AX, et al. IMbrave150: exploratory efficacy and safety in patients with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab beyond radiological progression until loss of clinical benefit in a global phase III study. <i>Journal of clinical oncology</i> 2022;40.	
49		Ying-Chun Shen T-HL, Li-Chung Lu,, Alan Nicholas SH, Peter R. Galle,, Michel Ducreux RFaA-LC. Clinicopathological Characteristics and Outcome of Hepatocellular Carcinoma Patients who Achieved Durable Partial Response or Stable Disease Status in Imbrave150 Study, 2022, WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, 2022.	
50		Nct. An Investigational Immuno-therapy Study of Nivolumab Compared to Sorafenib as a First Treatment in Patients With Advanced Hepatocellular Carcinoma. https://clinicaltrials.gov/study/NCT02576509 2024.	
51	LAUNCH	Peng Z, Fan W, Zhu B, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment of advanced hepatocellular carcinoma: a phase 3, multicenter, randomized controlled trial. <i>Journal of clinical oncology</i> 2022;40.	The study does not include at least 2 interventions of interest to the NMA.
52		Peng Z, Fan W, Zhu B, et al. Lenvatinib Combined With Transarterial Chemoembolization as First-Line Treatment for Advanced Hepatocellular Carcinoma: a Phase III, Randomized Clinical Trial (LAUNCH). <i>Journal of clinical oncology</i> 2023;41:117-127.	

53	LEAP-002	Finn RS, Kudo M, Merle P, et al. LBA34 Primary results from the phase III LEAP-002 study: lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). <i>Annals of oncology</i> 2022;33:S1401.	The study does not include at least 2 interventions of interest to the NMA.
54		Finn RS, Kudo M, Merle P, et al. Lenvatinib plus pembrolizumab versus lenvatinib alone as first-line therapy for advanced hepatocellular carcinoma: longer-term efficacy and safety results from the phase 3 LEAP-002 study. <i>Journal of clinical oncology</i> 2024;42.	
55		Llovet JM, Kudo M, Merle P, et al. Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): a randomised, double-blind, phase 3 trial. <i>The lancet. Oncology</i> 2023;24:1399-1410.	
56		Llovet JM, Kudo M, Merle P, et al. Health-related quality of life (HRQoL) impact of lenvatinib (len) plus pembrolizumab (pembro) versus len plus placebo (pbo) as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC): phase 3 LEAP-002 study. <i>Journal of clinical oncology</i> 2023;41:506.	
57		Finn RS, Kudo M, Merle P, et al. LBA34 Primary results from the phase III LEAP-002 study: Lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). <i>Annals of Oncology</i> 2022;33:S1401.	
58		Qin S, Chan LS, Gu S, et al. LBA35 Camrelizumab (C) plus rivoceranib (R) vs. sorafenib (S) as first-line therapy for unresectable hepatocellular carcinoma (uHCC): A randomized, phase III trial. <i>Annals of Oncology</i> 2022;33:S1401-S1402.	
59		Nct. Safety and Efficacy of Lenvatinib (E7080/MK-7902) in Combination With Pembrolizumab (MK-3475) Versus Lenvatinib as First-line Therapy in Participants With Advanced Hepatocellular Carcinoma (MK-7902-002/E7080-G000-311/LEAP-002). https://clinicaltrials.gov/study/NCT03713593 2024.	
60		Nct. Sorafenib Tosylate With or Without Doxorubicin Hydrochloride in Treating Patients With Locally Advanced or Metastatic Liver Cancer. https://clinicaltrials.gov/study/NCT01015833?titles=Sorafenib%20Tosylate%20With%20or%20Without%20Doxorubicin%20Hydrochloride%20in%20Treating%20Patients%20With%20Locally%20Advanced%20or%20Metastatic%20Liver%20Cancer&rank=1 2024.	
61	NRG/RTOG 1112	Dawson LA, Winter K, Knox J, et al. NRG/RTOG 1112: randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937). <i>International journal of radiation oncology biology physics</i> 2022;114:1057.	The study does not include at least 2 interventions of interest to the NMA.
62		Dawson LA, Winter KA, Knox JJ, et al. NRG/RTOG 1112: randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC). <i>Journal of clinical oncology</i> 2023;41:489.	
63	ORIENT-32	Ren Z, Xu J, Bai Y, et al. ORIENT-32: updated characterization of response to sintilimab plus bevacizumab biosimilar (IBI305) vs sorafenib for unresectable hepatocellular carcinoma. <i>Journal of clinical oncology</i> 2023;41:570.	The study does not include at least 2 interventions of interest to the NMA.
64		Ren Z, Xu J, Bai Y, et al. Report of adverse events of special interest (AESIs) for sintilimab plus a bevacizumab biosimilar (IBI305) in unresectable hepatocellular carcinoma. <i>Journal of clinical oncology</i> 2023;41:530.	

65	PHOCUS	Abou-Alfa GK, Galle PR, Chao Y, et al. PHOCUS: a Phase 3, Randomized, Open-Label Study of Sequential Treatment with Pexa-Vec (JX-594) and Sorafenib in Patients with Advanced Hepatocellular Carcinoma. Liver cancer 2023.	The study does not include at least 2 interventions of interest to the NMA.
66	RATIONALE-301	Finn RS, Qin S, Kudo M, et al. Tislelizumab versus sorafenib in first-line treatment of unresectable hepatocellular carcinoma: impact on health-related quality of life in RATIONALE-301 population. Journal of clinical oncology 2023;41:495.	The study does not include at least 2 interventions of interest to the NMA.
67		Kudo M, Vogel A, Meyer T, et al. Impact of baseline liver function on overall survival (OS) and safety in patients (pts) with unresectable hepatocellular carcinoma (HCC) treated with first-line (1L) tislelizumab (TIS): results from the RATIONALE-301 study. Journal of hepatology 2023;78:S574.	
68		Meyer T, Finn RS, Kudo M, et al. Association of tumor response with survival in patients with unresectable hepatocellular carcinoma treated with first-line tislelizumab versus sorafenib: results from the RATIONALE-301 study. Journal of hepatology 2023;78:S580-S581.	
69		Qin S, Guo Y, Meng Z, et al. LBA2 Tislelizumab (TIS) versus sorafenib (SOR) in first-line (1L) treatment of unresectable hepatocellular carcinoma (HCC): the RATIONALE-301 Chinese subpopulation analysis. Annals of oncology 2022;33:S1454-S1455.	
70		Qin S, Kudo M, Meyer T, et al. Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Phase 3 Randomized Clinical Trial. JAMA Oncology 2023;9:1651-1659.	
71		Qin S, Kudo M, Meyer T, et al. LBA36 Final analysis of RATIONALE-301: randomized, phase III study of tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma. Annals of oncology 2022;33:S1402-S1403.	
72		Vogel A, Kudo M, Qin S, et al. Randomized, phase 3 study of tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma (HCC): RATIONALE-301 age ≥65 years subgroup. Annals of oncology 2023;34:S167-S168.	
73	REFLECT	Jones A, Degregorio P, Sung MW, et al. Characterization and Management of Adverse Reactions in Patients With Unresectable Hepatocellular Carcinoma Treated With Lenvatinib. Journal of the Advanced Practitioner in Oncology 2023;14:598-607.	The data were not relevant for informing the primary NMA analyses that used data from the full trial population.
74		Kudo M, Finn RS, Qin S, et al. Overall survival and objective response in advanced unresectable hepatocellular carcinoma: a subanalysis of the REFLECT study. Journal of hepatology 2023;78:133-141.	
75		Kudo M, Qin S, Piscaglia F, et al. Characterization of tumor responses in patients (pts) with unresectable hepatocellular carcinoma (uHCC) treated with lenvatinib in REFLECT. Journal of clinical oncology 2022;40.	
76		Okusaka T, Kudo M, Ikeda K, et al. Impact of bodyweight-based starting doses on the safety and efficacy of lenvatinib in primarily Japanese patients with hepatocellular carcinoma. Hepatology Research 2022;52:784-793.	
Records included at 2 nd SLR update			

77	HIMALAYA	Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. Journal of clinical oncology 2022;40.	This study was included. However, the most up-to-date data on file data were used to inform the NMA.
78		Chan SL, Sangro B, Kelley RK, et al. Four-year overall survival (OS) update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC). Annals of oncology 2023;34:S1530-S1531.	The data were not relevant for informing the primary NMA analyses that used data from the full trial population.
79		Kang YK, Galle PR, Van Dao T, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Annals of Oncology. 2024.	
80		Sangro B, Chan S, Kelley R, et al. Four-year overall survival update from the phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Annals of oncology 2023;34:S168.	
81		Sangro B, Chan SL, Kelley K, et al. Four-year overall survival update from the phase 3 HIMALAYA study of tremelimumab (T) plus durvalumab (D) in unresectable hepatocellular carcinoma (uHCC). Oncology research and treatment 2024;47:69-70.	
82		Sangro B, Galle PR, Kelley RK, et al. Patient-reported outcomes from the phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Journal of clinical oncology 2022;40.	
83		Vogel A, Chan SL, Furuse J, et al. 79P Outcomes by baseline liver function in patients with unresectable hepatocellular carcinoma treated with tremelimumab and durvalumab in the phase III HIMALAYA study. Annals of oncology 2022;33:S1463-S1464.	
84		Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM evidence 2022;1:EVIDoa2100070.	
85		Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA: American Society of Clinical Oncology, 2022.	
86		Sangro B, Galle PR, Kelley RK, et al. Patient-reported outcomes from the phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma: American Society of Clinical Oncology, 2022.	
87		Lau G, Cheng A-L, Sangro B, et al. Outcomes by occurrence of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC): American Society of Clinical Oncology, 2023.	
88		Nct. Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA). https://clinicaltrials.gov/study/NCT03298451 2024.	

89	IMbrave150	Nct. A Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma. https://ClinicalTrials.gov/show/NCT03434379 2024.	Included
90	REFLECT	Nct. A Multicenter, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-line Treatment of Participants With Unresectable Hepatocellular Carcinoma. https://ClinicalTrials.gov/show/NCT01761266 2024.	Included

Clarification question A4.

Table 16: MEDLINE and Embase (via Embase.com) search strategy used in the first SLR update. Search date: 26th October 2021

No.	Query	Results
1	'liver cell carcinoma'/exp	181254
2	'liver cancer'/exp	281371
3	((hepato* OR hepatic OR liver) NEAR/3 (carcinoma* OR cancer* OR neoplasm* OR tumour* OR tumor* OR malign*)):ab,ti	233035
4	hepatocarcinoma*:ab,ti OR hepatoma*:ab,ti	40220
5	'liver tumor'/mj	36039
6	#1 OR #2 OR #3 OR #4 OR #5	370076
7	'sorafenib'/syn OR 'bay 43 9006' OR 'bay 43-9006' OR 'bay 439006' OR 'bay43 9006' OR bay439006 OR nexavar	33775
8	'lenvatinib'/syn OR lenvima	3909
9	'atezolizumab'/syn OR 'mpdl 3280a' OR mpdl3280a OR 'rg 7446' OR rg7446 OR tecentriq OR tecntriq	9390
10	'bevacizumab'/syn OR abevmy OR 'abp 215' OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR 'ask b1202' OR askb1202 OR avastin OR aybintio OR 'bat 1706' OR bat1706 OR 'bcd 021' OR bcd021 OR bevax OR 'bevz 92' OR bevz92 OR 'bi 695502' OR bi695502 OR boyounuo OR bryxta OR byvasda OR 'cbt 124' OR cbt124 OR 'chs 5217' OR chs5217 OR cizumab OR 'ct p16' OR ctp16 OR equidacent OR 'fkb 238' OR fkb238 OR 'gb 222' OR gb222 OR 'hd 204' OR hd204 OR 'hlx 04' OR hlx04 OR 'ibi 305' OR ibi305 OR 'jyv028' OR jyv028 OR krabeva OR kyomarc OR lextemy OR 'ly 01008' OR ly01008 OR 'mb 02' OR mb02 OR 'milv0' OR milv0 OR mvasi OR 'myl 14020' OR 'myl 1402o' OR myl14020 OR myl1402o OR 'nsc 704865' OR nsc704865 OR onbevzi OR 'ons 1045' OR 'ons 5010' OR ons1045 OR ons5010 OR oyavas OR 'pf 06439535' OR 'pf 6439535' OR pf06439535 OR pf6439535 OR pusintin OR 'ql 1101' OR ql1101 OR 'r 435' OR r435 OR 'rg 435' OR rg435 OR 'rhumab vegf' OR 'ro 4876646' OR ro4876646 OR 'rph 001' OR rph001 OR 'sb 8' OR sb8 OR 'sct 510' OR sct510 OR 'stc 103' OR stc103 OR 'tab 008' OR tab008 OR 'tot 102' OR tot102 OR 'trs 003' OR trs003 OR 'tx 16' OR tx16 OR versavo OR zirabev OR 'zrc 113' OR zrc113	66434
11	'nivolumab'/syn OR 'bms 936558' OR bms936558 OR 'cmab 819' OR cmab819 OR 'mdx 1106' OR mdx1106 OR 'ono 4538' OR ono4538 OR opdivo	26593
12	'durvalumab'/syn OR imfinzi OR 'medi 4736' OR medi4736	6284

13	'ticilimumab'/syn OR 'cp 675 206' OR 'cp 675, 206' OR 'cp 675206' OR 'cp675 206' OR 'cp675, 206' OR cp675206 OR tremelimumab	3084
14	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	120960
15	'clinical trial'/exp	1659062
16	'randomized controlled trial'/de	684473
17	'controlled clinical trial'/de	435407
18	'multicenter study'/de	304296
19	'phase 1 clinical trial'/de	60906
20	'phase 2 clinical trial'/de	91982
21	'phase 3 clinical trial'/de	56929
22	'phase 4 clinical trial'/de	4546
23	'randomization'/exp	92481
24	'single blind procedure'/de	44415
25	'double blind procedure'/de	189858
26	'crossover procedure'/de	68603
27	'placebo'/de	380722
28	'randomi?ed controlled trial?':ti,ab,kw	277458
29	rct:ti,ab,kw OR random* OR sham:ti,ab,kw OR placebo*:ti,ab,kw	2157809
30	(random* NEAR/2 allocat*):ti,ab,kw	48186
31	(allocated NEAR/2 random*) OR (random* NEAR/1 assign*) OR random*	1961393
32	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	333015
33	'prospective study'/de OR 'control group'/de	830002
34	((control* OR equivalence OR superiority OR 'non inferiority' OR noninferiority OR pragmatic OR practical OR quasiexperimental OR 'quasi experimental' OR experimental OR phase) NEAR/3 (study OR studies OR trial* OR group*)):ab,ti	1936115
35	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	4579379
36	'case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de OR editorial:it OR letter:it OR note:it	5474355
37	#35 NOT #36	4350914
38	#6 AND #14 AND #37	6819
39	#38 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)	157
40	#38 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [conference abstract]/lim)	4188
41	#39 OR #40	4251
42	#38 NOT #41	2568
43	#38 NOT #41 AND [31-8-2020]/sd	504

44	#43 AND [english]/lim	494

Database(s): MEDLINE and Embase (via Embase.com) 31st August 2020 to 26th October 2021.

Table 17: MEDLINE-In-Process (via PubMed) search used in the first SLR update. Search date: 26th October 2021

#	Query	Results
1	carcinoma, hepatocellular[MeSH Terms]	92,721
2	(hepato* OR hepatic OR liver) AND (carcinoma* OR cancer* OR neoplasm* OR tumour* OR tumor* OR malign*)	448,435
3	hepatocarcinoma*[TIAB] OR hepatoma*[TIAB] OR "Liver tumo*" [TIAB]	48,326
4	#1 OR #2 OR #3	452,957
5	sorafenib OR "bay 43 9006" OR "bay 43-9006" OR "bay 439006" OR "bay43 9006" OR bay439006 OR nexavar	10,135
6	lenvatinib OR lenvima	1,221
7	atezolizumab OR "mpdl 3280a" OR mpdl3280a OR "rg 7446" OR rg7446 OR tecentriq OR tecntriq	1,932
8	bevacizumab OR abevmy OR "abp 215" OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR "ask b1202" OR askb1202 OR avastin OR aybintio OR "bat 1706" OR bat1706 OR "bcd 021" OR bcd021 OR bevax OR "bevz 92" OR bevz92 OR "bi 695502" OR bi695502 OR boyounuo OR bryxta OR byvasda OR "cbt 124" OR cbt124 OR "chs 5217" OR chs5217 OR cizumab OR "ct p16" OR ctp16 OR equidacent OR "fkb 238" OR fkb238 OR "gb 222" OR gb222 OR "hd 204" OR hd204 OR "hlx 04" OR hlx04 OR "ibi 305" OR ibi305 OR "jyv028" OR jy028 OR krabeva OR kyomarc OR lextemy OR "ly 01008" OR ly01008 OR "mb 02" OR mb02 OR "milv0" OR mil60 OR mvasi OR "myl 14020" OR "myl 1402o" OR myl14020 OR myl1402o OR "nsc 704865" OR nsc704865 OR onbevzi OR "ons 1045" OR "ons 5010" OR ons1045 OR ons5010 OR oyavas OR "pf 06439535" OR "pf 6439535" OR pf06439535 OR pf6439535 OR pusintin OR "ql 1101" OR ql1101 OR "r 435" OR r435 OR "rg 435" OR rg435 OR "rhumab vegf" OR "ro 4876646" OR ro4876646 OR "rph 001" OR rph001 OR "sb 8" OR sb8 OR "sct 510" OR sct510 OR "stc 103" OR stc103 OR "tab 008" OR tab008 OR "tot 102" OR tot102 OR "trs 003" OR trs003 OR "tx 16" OR tx16 OR versavo OR zirabev OR "zrc 113" OR zrc113	44,358
9	nivolumab OR "bms 936558" OR bms936558 OR "cmab 819" OR cmab819 OR "mdx 1106" OR mdx1106 OR "ono 4538" OR ono4538 OR opdivo	7,216
10	durvalumab OR imfinzi OR "medi 4736" OR medi4736	947
11	ticilimumab OR "cp 675 206" OR "cp 675, 206" OR "cp 675206" OR "cp675 206" OR "cp675, 206" OR cp675206 OR tremelimumab	373
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	62,556
13	"clinical trial" OR clinical trial [pt]	1,016,085
14	"randomized controlled trial" OR randomized controlled trial [pt] OR "randomised controlled trial" OR "randomized controlled trials" OR "randomised controlled trials"	775,961
15	"controlled clinical trial" OR controlled clinical trial [pt]	641,701

16	"multicenter study" OR multicenter study [pt]	313,615
17	"phase 1 clinical trial" OR 'phase 1 clinical trial'[MeSH Major Topic]	2,050
18	"phase 2 clinical trial" OR 'phase 2 clinical trial'[MeSH Major Topic]	3,408
19	"phase 3 clinical trial" OR 'phase 3 clinical trial'[MeSH Major Topic]	3,867
20	"phase 4 clinical trial" OR 'phase 4 clinical trial'[MeSH Major Topic]	393
21	randomization OR "random allocation"[MeSH Terms]	1,313,844
22	"single blind procedure" OR "Single-Blind Method"[Mesh]	30,978
23	"double blind procedure" OR "double-blind procedure" OR Double-Blind Method[Mesh]	167,547
24	"crossover procedure" OR "Cross-Over Studies"[Mesh]	51,657
25	placebo OR "Placebos"[Mesh]	246,734
26	"rct"[tiab]	27,747
27	random* AND allocat*	165,213
28	(allocated AND random*) OR (random* AND assign*) OR random*	1,500,849
29	(double [tiab] OR single [tiab] OR doubly [tiab] OR singly [tiab] OR triple[tiab] OR treble[tiab]) AND (blind [tiab] OR blinded [tiab] OR blindly [tiab] OR mask [tiab] OR masked [tiab])	201,301
30	placebo [tiab]	228,263
31	(control* OR equivalence OR superiority OR "non inferiority" OR noninferiority OR pragmatic OR practical OR quasiexperimental OR "quasi experimental" OR experimental OR phase) AND (study OR studies OR trial* OR group*)	6,143,179
32	"prospective study" OR "Prospective Studies"[Mesh]	641,342
33	controlled [tiab] AND (study [tiab] OR design [tiab] OR trial [tiab])	519,221
34	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	7,173,889
35	#4 AND #12 AND #34	3586
36	#35 AND (inprocess[sb] OR pubstatusaheadofprint)	162

Database(s): MEDLINE-In-Process (via PubMed) 31st August 2020 to 26th October 2021.

Table 18: CDSR and CENTRAL (via Cochrane library) search strategy used in the first SLR update. Search date: 26th October 2021

ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	1856
#2	((hepato* OR hepatic OR liver) AND (carcinoma* OR cancer* OR neoplasm* OR tumour* OR tumor* OR malign*)):ti,ab,kw (Word variations have been searched)	20815
#3	(hepatocarcinoma* OR hepatoma* OR "Liver tumor" OR "Liver tumour"):ti,ab,kw (Word variations have been searched)	763

#4	MeSH descriptor: [Liver Neoplasms] explode all trees	3107
#5	#1 OR #2 OR #3 OR #4	20874
#6	sorafenib OR nexavar OR lenvatinib OR lenvima OR nivolumab OR opdivo OR atezolizumab OR tecentriq OR durvalumab OR imfinzi OR tremelimumab OR bevacizumab OR Avastin (Word variations have been searched)	12153
#7	MeSH descriptor: [Sorafenib] explode all trees	507
#8	MeSH descriptor: [Nivolumab] explode all trees	512
#9	MeSH descriptor: [Bevacizumab] explode all trees	2065
#10	#6 OR #7 OR #8 OR #9	12153
#11	#5 AND #10	2242
#12	#5 AND #10 with Cochrane Library publication date Between Aug 2020 and Oct 2021, in Cochrane Reviews, Trials	355

Database(s): CDSR and CENTRAL (via Cochrane library) 31st August 2020 to 26th October 2021.

Clarification question A5.

Table 19 Additional hepatic AEs by maximum reported CTCAE grade (primary analysis; SAS) (DCO: 27th August 2021)

	n/N# (%) of subjects									
Clinical chemistry parameter	STRIDE (n=388)					Sorafenib (n=374)				
	CTCAE Grade									
	Total	1	2	3	4	Total	1	2	3	4
ALT	100	1	1	1	1	100	1	1	1	1
AST	100	1	1	1	1	100	1	1	1	1
ALP	100	1	1	1	1	100	1	1	1	1
Gamma-GT	100	1	1	1	1	100	1	1	1	1
Prothrombin time	100	1	1	1	1	100	1	1	1	1
INR	100	1	1	1	1	100	1	1	1	1
Bilirubin	100	1	1	1	1	100	1	1	1	1
Albumin	100	1	1	1	1	100	1	1	1	1
Aspartate aminotransferase	100	1	1	1	1	100	1	1	1	1
Alanine aminotransferase	100	1	1	1	1	100	1	1	1	1
Alkaline phosphatase	100	1	1	1	1	100	1	1	1	1
Gamma-glutamyl transaminase	100	1	1	1	1	100	1	1	1	1
Prothrombin time (seconds)	100	1	1	1	1	100	1	1	1	1
International normalized ratio	100	1	1	1	1	100	1	1	1	1
Total bilirubin	100	1	1	1	1	100	1	1	1	1
Albumin	100	1	1	1	1	100	1	1	1	1

Source: HIMALAYA CSR, Jan 2022⁴

Clarification question A6.

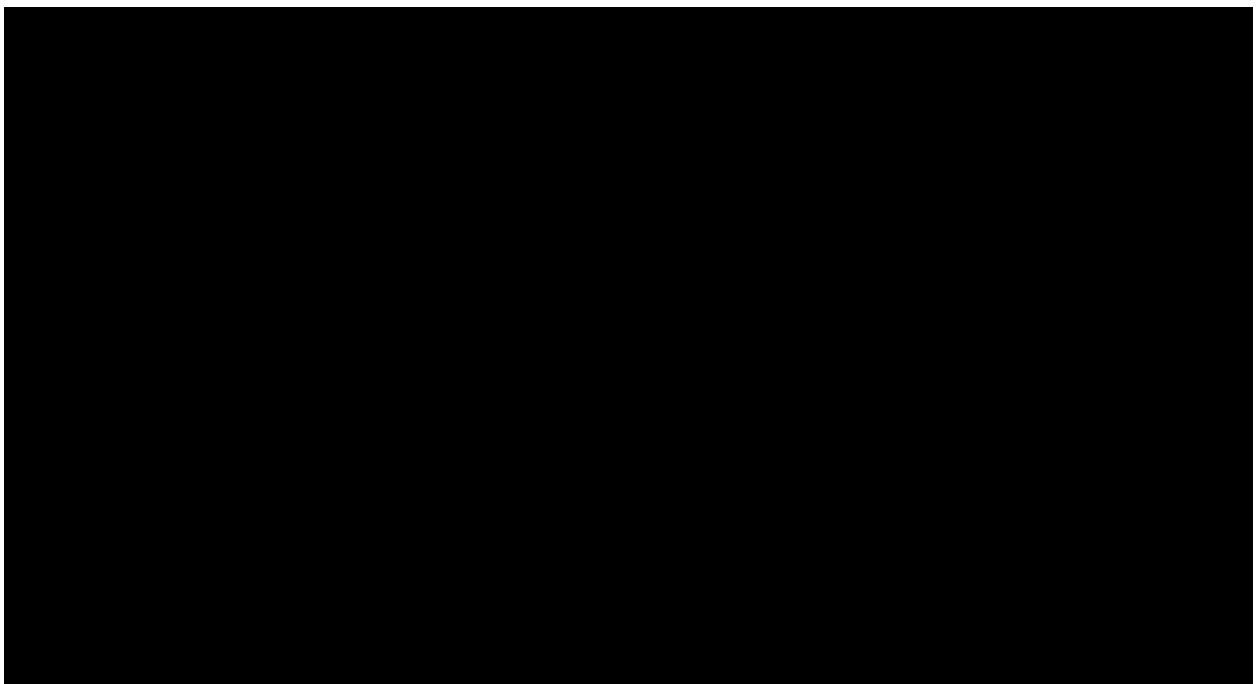
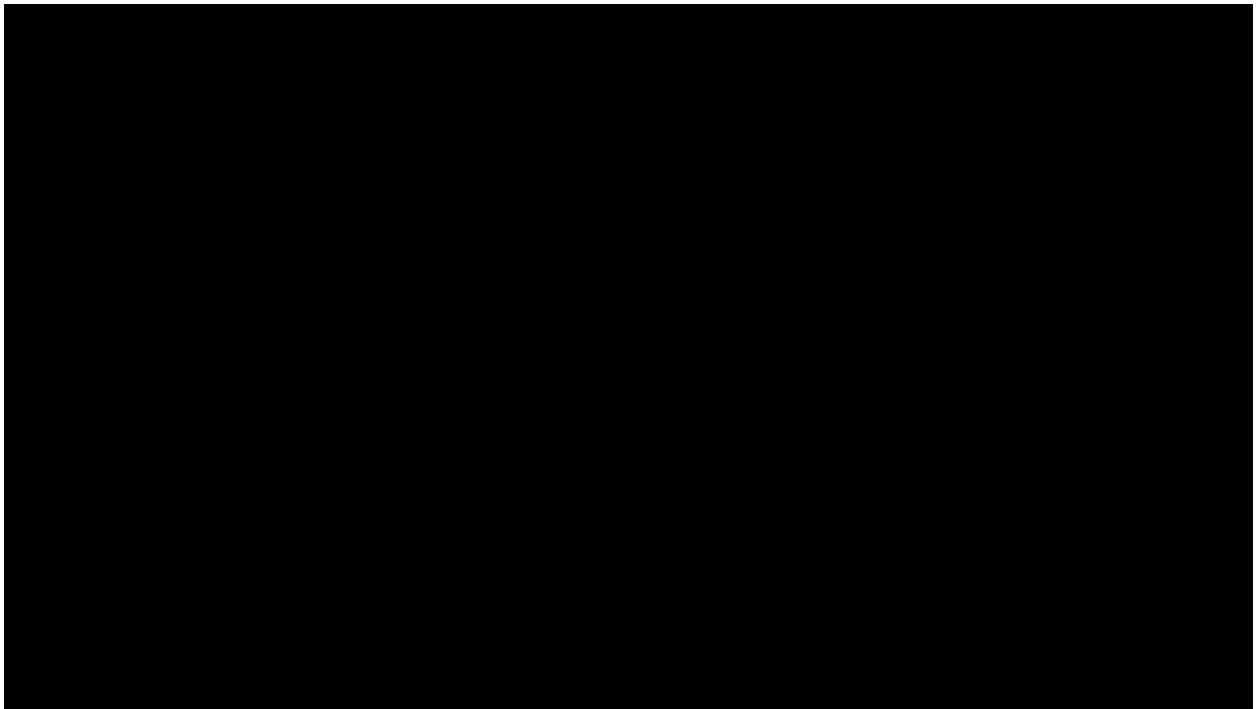
Table 20 Not treatment-related serious AEs observed, no reasonable possibility the AE is casually related to durvalumab/tremelimumab/sorafenib (primary analysis, SAS) (DCO: 27th August 2021) (>1% frequency)

[illegible]

Source: HIMALAYA CSR, Jan 2022⁴

Clarification question A17.

Figure 5 OS (Inv. RECIST 1.1) for subjects rechallenged with tremelimumab, Swimmer Plot (primary analysis; SAS) (DCO: 27th August 2021)



Clarification question B2.

Table 21 Hand-searched bibliography of SLRs and NMAs as part of the 2nd economic SLR update

Reference	Title
Attri 2023	A Systematic Literature Review of Patient-Reported Outcomes in Phase III Randomized Controlled Trials of Hepatocellular Carcinoma in a First-Line Setting", Value in Health, 26(6 Supplement), p.S35
Diez de Los Rios de la Serna 2023	A rapid review of patient-reported outcomes investigated in the context of advanced renal cell cancer or advanced hepatocellular cancer", European journal of oncology nursing: the official journal of European Oncology Nursing Society, 63, p.102241.
Hwang 2024	Home-based supportive care in advanced cancer: systematic review", BMJ Supportive and Palliative Care, 14(2), pp.132-148.
Pollock 2021	Effects of trial population selection on quality of life and healthcare decision-making: A systematic review and example in the treatment of hepatocellular carcinoma with radioembolization", ClinicoEconomics and Outcomes Research, 13, pp.835-841.
Rimmer 2024	Characteristics and Components of Self-Management Interventions for Improving Quality of Life in Cancer Survivors: A Systematic Review", Cancers, 16(1).
Sharma 2023	1010P A parametric network meta-analysis of first-line systemic therapies for advanced hepatocellular carcinoma related to overall survival", Annals of Oncology, 34(Supplement 2), pp.S616-S617
Si 2022	Hepatic arterial infusion chemotherapy versus transarterial chemoembolization for unresectable hepatocellular carcinoma: A systematic review with meta-analysis", Frontiers in Bioengineering & Biotechnology, 10, p.1010824
Xie 2023	Immune Checkpoint Inhibitors for Child-Pugh Class B Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis", JAMA Oncology, 9(10), pp.1423-1431
Zou 2023	Comparative analysis of disease modelling for health economic evaluations of systemic therapies in advanced hepatocellular carcinoma", PLoS ONE, 18(10), no pagination

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https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
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Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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2. Name of organisation	British Association for the Study of the Liver (BASL) / HCC-UK
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Association for the Study of the Liver is the National Association for specialists in liver disease (hepatology). BASL is composed of interested individuals from clinical medicine, clinical and basic research and allied professions. BASL is funded through membership fees and organising and hosting an annual meeting and educational events.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes – Astra Zeneca (company). BASL received £65,000 in sponsorship funding towards their Annual Conference, the HCC UK Annual Conference and other educational events between July 2023 and July 2024. Yes – Eisai (comparator). BASL received £4,000 in sponsorship funding towards their Annual HCC UK Conference between July 2023 and July 2024. Yes – Roche (comparator). BASL received £7,500 in sponsorship funding towards their Annual HCC UK Conference between July 2023 and July 2024. Yes – Sirtex (comparator). BASL received £2,000 in sponsorship funding towards their Annual HCC UK Conference between July 2023 and July 2024.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Systemic therapy for advanced hepatocellular carcinoma aims to improve symptoms, reduce tumour burden, delay progression and prolong life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. A radiological reduction in size of tumour by 30% is considered a partial response and deemed clinically significant however smaller reduction or stabilisation of tumour is also clinically relevant so disease control rate should be considered as an indicator of efficacy. 2. An improvement of median survival by around 3 months is considered valuable as is longer term improvement in survival at 4 years and beyond. 3. A delay in deterioration of quality of life
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are limitations to the application of current first line therapies and this combination provides an important alternative.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In patient with preserved liver function and good performance status, advanced HCC is managed with systemic therapy, The most effective approved therapy s the combination of atezolizumab and bevacizumab (AB). For those with contraindications to AB, sorafenib or lenvatinib may be offered but both are less effective than AB.
9a. Are any clinical guidelines used in the	1. British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults. Suddle A, Reeves H, Hubner R, Marshall A, Rowe I, Tiniakos D, Hubscher S, Callaway M, Sharma D, See TC,

treatment of the condition, and if so, which?	Hawkins M, Ford-Dunn S, Selemani S, Meyer T. Gut. 2024 Jul 11;73(8):1235-1268. doi: 10.1136/gutjnl-2023-331695. PMID: 38627031 2. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, Nault JC, Neumann U, Ricke J, Sangro B, Schirmacher P, Verslype C, Zech CJ, Arnold D, Martinelli E; ESMO Guidelines Committee. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv238-iv255. doi: 10.1093/annonc/mdy308. PMID: 30285213 3. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. J Hepatol. 2018 Jul;69(1):182-236. doi: 10.1016/j.jhep.2018.03.019. Epub 2018 Apr 5. Note that the ESMO and EASL guidelines are currently being updated and the BASL guidelines represent the most up to date version and most relevant to UK clinical practice.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The therapeutic algorithm for HCC is well established and recent UK (BASL) guidelines have defined recommendations for managing advanced disease.
9c. What impact would the technology have on the current pathway of care?	Currently, the combination of atezolizumab and bevacizumab is considered the standard first-line therapy for advanced HCC. This combination was shown to be superior to sorafenib which was the previous standard of care. The combination of tremelimumab and durvalumab has also be shown to be superior to sorafenib and therefore represents an alternative first line therapy in this patient population. Cross trial comparisons do not provide a robust method of comparing efficacy and both combinations are therefore considered reasonable options. In practice, clinicians may make choices based on side effect profile. For example, patients with hypertension, proteinuria or high risk of bleeding complications with bevacizumab would more likely be offered

	tremelimumab and durvalumab. Tremelimumab and durvalumab would be offered in preference to sorafenib or lenvatinib.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it will be used as an alternative to the standard of care with atezolizumab and bevacizumab, sorafenib or lenvatinib.
10a. How does healthcare resource use differ between the technology and current care?	- Both combinations; tremelimumab plus durvalumab and atezolizumab plus bevacizumab are delivered as three weekly outpatient infusions. - Atezolizumab plus bevacizumab treated patients require endoscopies before treatment and are at risk of vascular and bleeding complications which requires additional medical resource. Bevacizumab may also increase need for medication to control hypertension. - Both combinations carry a risk of autoimmune complications which require supportive therapy and may require in patient management
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment should be offered in secondary care, ideally in specialised multidisciplinary clinics specialising in the management of HCC. Centres should have experience of managing immunotherapy related toxicity.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional training should be required in centres that already treat patients with atezolizumab plus bevacizumab.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There are patients who have contraindications to atezolizumab plus bevacizumab and these patients will benefit from the availability of tremelimumab plus durvalumab.
11a. Do you expect the technology to increase	The four-year survival data for tremelimumab plus durvalumab shows a survival of 25% compared to 15% for sorafenib. Long term survival is a clinically important outcome and 4 year survival data is not currently available for atezolizumab and bevacizumab. (Ref doi: 10.1016/j.annonc.2024.02.005.)

length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	Both tremelimumab plus durvalumab and atezolizumab plus bevacizumab have been shown to delay deterioration in QOL measures compared to sorafenib but a direct comparison between the two combinations has not been performed. Similarly, cross trial comparisons of toxicity are not robust but the current data do not suggest major differences in tolerability.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The subgroup analysis of the Himalaya trial does not demonstrate a convincing benefit for any particular subgroup. The therapy would be applicable to those with preserved liver function, good performance status and no contraindications to immune checkpoint inhibitors who are not suitable for locoregional therapy.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The route and frequency of administration is the same as the current standard of care. There will be a reduced requirement for endoscopy, hypertensive medication and management of bleeding complications There may be an increased requirement for high dose steroids to manage autoimmune toxicity

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients should be ECOG PS 1 and Child Pugh A with advanced disease not suitable for locoregional therapy or progressed despite locoregional therapy. Patients should discontinue therapy in line with local guidelines relating to toxicity or loss of clinical benefit
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It will provide an alternative to the current best standard of care particularly for those that have an absolute or relative contraindication to atezolizumab and bevacizumab.
16a. Is the technology a 'step-change' in the management of the condition?	No
16b. Does the use of the technology address any particular unmet need of the patient population?	It will provide an alternative to the current best standard of care particularly for those that have an absolute or relative contraindication to atezolizumab and bevacizumab.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Compared with sorafenib, the combination of tremelimumab and durvalumab delays the deterioration in QOL (ref doi: 10.1200/JCO.23.01462.) 13% discontinue treatment due to toxicity and 34% have dose delay. 20% require high dose steroids to manage toxicity 17% get grade 3 or 4 diarrhoea

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The trial was not run in the UK but 34% of the trial population was from European countries and 41% non-viral aetiology of liver disease. The stage of patients treated is consistent with that treated systemic therapy in the UK. Subgroup analysis did not suggest any subgroup deriving more or less benefit. Therefore, the trial included patients representative of those treated in the UK

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are overall survival, response rate, toxicity and quality of life all of which were measured.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The recently published 4 year follow-up data for the Himalaya trial did not report and new adverse events compared to the primary publication.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA666]?	No
21. How do data on real-world experience	To my knowledge there is only one real world data publication. The study was done in Japan and included 120 patients receiving tremelimumab and durvalumab. 76% were receiving it as second line

compare with the trial data?	therapy and about one third did not meet the criteria of the Himalaya trial. Therefore this does not provide meaningful data to inform the process. Ref doi: 10.3892/ol.2024.14530

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Tremelimumab and durvalumab provides a survival benefit to patients with advanced HCC compared to sorafenib. • Long term survival is improved with 25% patients alive at 4 years. This is the best long term outcome thus reported for patients with advanced disease. • Patients with contraindications to bevacizumab may benefit from immunotherapy if tremelimumab and durvalumab is approved • Tremelimumab and durvalumab delays deterioration in QOL compared to sorafenib • High dose steroids will be required to control side effects in 20%

Thank you for your time.

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Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	British Liver Trust
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	The British Liver Trust is the UK's leading liver health charity, working to improve liver health for all and supporting all adults and children affected by liver disease or liver cancer. We are funded by voluntary donations, including community and event fundraising, individual donors, gifts in wills, corporate supporters and trust and foundation grants. We operate throughout the UK, reaching more than two million people each year. Our two website has over 1.6 million unique visitors annually, our online forum has over 38,000 members, our nurse-led Helpline handles over 400 enquiries a month, regular newsletter goes to circa 17,000 people with liver disease and liver cancer, we run around 250 support groups each year (currently virtual but moving to a mix of virtual and face to face post Covid); and connect with around 20,000 people via social media.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	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) Pfizer (bevacizumab) £25,153 Roche (atezolizumab, bevacizumab) 15,000

the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The British Liver Trust have collated information for this submission via a variety of different sources and channels; 1. Direct feedback and communication from patient and carers via our nurse-led specialist helpline 2. Feedback and comments via threads on our liver community forum (32K members) 3. Feedback from focus groups and support groups with liver cancer patients 4. Survey of patients living with HCC 5. Interview with a liver palliative clinical nurse specialist on her experiences of caring for patients with refractory ascites and indwelling drains 6. Input from Monica Walsh, our nominated patient expert who will be attending the committee meeting – you can read her story here: Monica's story: "I was unbelievably lucky because my liver disease was picked up so early" - Liver Cancer UK 7. Literature search and review of current guidelines

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Liver cancer is the fastest-rising cause of cancer related deaths. Around 6,200 people are diagnosed with liver cancer each year. Incidence of liver cancer has increased by 50% over the past decade and is expected to continue to rise. The most common form of liver cancer is hepatocellular carcinoma (HCC), making up around 80% of all liver cancers. Only around 20% of liver cancers are diagnosed early (stage 1 or 2). The biggest risk factor for HCC is pre-existing liver disease, with liver cirrhosis being present in 80-90% of people with HCC. Risk factors include Hep B, Hep C, ARLD, MASLD. There are strong links with deprivation (including: homelessness, heavy alcohol and drug use, obesity). Hepatocellular Carcinoma (HCC) is complex, varied and fluctuates, meaning that no one person's experience is the same as another. A diagnosis of hepatocellular carcinoma usually comes as a huge shock. Many patients with HCC (approx. 80%) also have underlying liver cirrhosis, which not only makes treatment difficult but also means that they may have other complications. Often the patient is diagnosed with cancer whilst at the same time being told that they have a liver condition with cirrhosis. They live with uncertainty, hopelessness and often stigma and isolation due to the image of liver cancer. The diagnostic process can be protracted. Patients and carers are fearful of the future, the prognosis is extremely poor with only around 13% living for 5 years. Patients often express frustration that they have been diagnosed too late for curative options. Patients and carers worry about whether there will be any treatment options, whether those options will be available in their area, how will family life/finances be impacted by the diagnosis and treatment. What will their quality of life be like and how long are they likely to live for. Primary liver cancer in adults has a poor outlook because it tends to be diagnosed late (only between 10% and 20% of people are diagnosed at a point when surgery can help). For people where surgery is not an option, the prognosis is particularly poor, and it is rare for people to live more than three years. The lack of other chemotherapeutic drugs particularly affects this group as well as those awaiting a transplant. The British Liver Trust has been working with NHSE to improve early diagnosis on three main workstreams: HCC surveillance, community liver health checks, and piloting primary care case finding. In particular, it is hoped that the HCC surveillance standards will improve early detection and reduce variation in care. Because patients with advanced HCC have such a poor prognosis and there are so few treatment options they are usually completely devastated. Patients are often relatively young and are completely shell shocked. Patients also report feeling extremely unwell, very tired and weak. Some quotes from a focus group and one to one interviews with patients and carers include:

	"Emotionally it was tough. I felt like I couldn't cope, and it all just caught up with me. I felt like every time I put my head up above water I got shot down." "Immediately after diagnosis I was shell shocked. I took my house in order, made my will. But I made changes to things. Death was imminent in my mind. Having a transplant makes me realise how lucky I am but I wish there had been another option. Liver disease doesn't seem to get the attention of other cancers." "We were just devastated. My husband was prescribed medication and underwent a radiofrequency ablation procedure. He was extremely tired and in pain. He was put on the waiting list, then he had to be taken off the list as the cancer had grown whilst waiting. He was 42 years old, had never drunk in his life and we were told he would die in about six weeks. The rug was completely taken from under my feet ... my whole life crumbled and ten years on I am still in pain." Relatives have described the condition as "Brutal - the worst possible way to go". When patients are diagnosed with HCC, they often experience depression from the poor prognosis and a range of symptoms including severe pain that cannot be treated without worsening their liver condition. Other severe symptoms include ascites, fluid in the abdomen that can press on the stomach making it difficult to eat and even to breathe. Hepatic encephalopathy can make everyday functions including conversation, writing and staying awake difficult. Only a very few patients are offered curative treatment, and even then, many live with the uncertainty about whether they will receive a liver transplant before the tumour spreads, or whether they will die as a complication of surgery (liver resection has a relatively high mortality rate). 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. Buying extra time for such patients not only can positively impact those individuals but can also have a huge positive impact on families and the wider community, with unquantifiable downstream benefits that can bring. There is also wide variation of care across England and Wales with patients experiencing different standards of care depending on where they live. Our survey of 127 patients with HCC revealed • 90% wanted more information after they left their first appointment at the hospital

- 1 in 5 were not happy with the information they received about treatment options
- Nearly half of respondents (45%) said they asked their doctor for other treatments they had researched that were not initially offered
- More than one in ten (13%) said their liver cancer diagnosis began with a trip to A&E because of symptoms
- One in five (21%) said it took more than six months to get a liver cancer diagnosis after their first visit to the GP
- 44% respondents said they have experienced delays in accessing care since their diagnosis.
- Half of patients (49%) didn't have treatment at their local hospital and over half (55%) said they travelled 20 miles or more for their treatment
- 44% respondents said they have experienced delays in accessing care since their diagnosis.
- Half (51%) said the COVID-19 pandemic has affected their care

An example of a patient who spoke at a recent focus group was a man who had a late diagnosis and been told there were no curative options. The majority of patients calling the helpline have Stage BCLC B or C HCC. The B group are offered TACE, or SIRT and C group systemic therapy if they have preserved liver function. Maintaining preserved liver function can be very challenging with treatments and this can delay HCC treatment. Many patients are diagnosed with a liver condition, cirrhosis and liver cancer at the same time. Additional HCC treatments are urgently needed.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Some patients/carers think that there are no options other than surgery, they ask whether transplant is an option. Others have researched on the internet and are more aware of potential treatment options and trials. There is disappointment and frustration at the lack of treatment options available and the strict entry criteria for trials. It is also true to say that when presented with the statistics of survival on various treatments they wonder whether there is any point proceeding. Some feel they are just being used as a 'guinea pig' others feel that participation in a trial or new treatment will help others further down the line. Most are complementary about the care they receive from medical and nursing staff but fear delays in treatment due to the current state of the NHS – staff shortages, expense of drugs etc. The British Liver Trust has recently worked with NHS England on new
8. Is there an unmet need for patients with this condition?	Yes. HCC has a poor survival prognosis. It is a debilitating condition with many distressing symptoms. These patients have limited treatment options.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The British Liver Trust has not spoken to any patients who have received this treatment in clinical trials. However, patients are desperate for any new treatments and were encouraged by the data that has been published in peer review journals. They saw it as a much needed and welcome additional treatment option for use in adults with HCC. One particular advantage is that the current first line treatment can be challenging if the patient has varices and sometimes, because of this they are not able to have Atezo/Bev. There are limited treatment options currently available and this new treatment does not have the same bleeding risk. Improving quality of life and even small extensions to length of life are of considerable importance to this patient group. HCC patients are very keen to be considered for clinical trials and should have access or be referred for consideration. There are extra benefits in that their travelling costs are met and they receive close monitoring by the research team which can be a huge source of support.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Some patients may be concerned re the reported side effects – however due to the limited number of treatment options many believed that these would be tolerable and acceptable and that any adverse events would be manageable. Patients spoke about being in “last chance saloon” and willing to put up with this for an extended life. Many patients with HCC are relatively young and so they cherished the possibility of having last moments such as “seeing their grandchild” “spending special time with family”. An extension of life was also seen as an opportunity to put “their house in order”. Many patients reported having side effects with existing treatments and talked about how much they would appreciate a further treatment option.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Liver disease and liver cancer disproportionately affects the poorest in society. Many patients with liver cancer come from disadvantaged backgrounds and have complex lives. There are strong links with deprivation (including: homelessness, heavy alcohol and drug use, obesity).

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Liver disease and liver cancer disproportionately affects the poorest in society. Many patients with liver cancer come from disadvantaged backgrounds and have complex lives.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A diagnosis of liver cancer is devastating and the prognosis is very poor (only 13% of patients live for 5 years) • The current first line treatment can be challenging if the patient has varices and sometimes they are not able to have Atezo/Bev - there are limited treatment options currently available and this does not have the same bleeding risk. • Any new treatment that may prolonged their life and provided them with a real chance of survival is desperately needed for these patients • 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 • It would be good to have another immunotherapy option for these patients

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Single Technology Appraisal

Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma

[ID2725]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

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 also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on 6 December 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

Part 1: Treating untreated advanced or unresectable hepatocellular carcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr David James Pinato
2. Name of organisation	Imperial College London and NHS Trust
3. Job title or position	Clinical Reader and Consultant in Medical Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with untreated advanced or unresectable hepatocellular carcinoma? ☐ A specialist in the clinical evidence base for untreated advanced or unresectable hepatocellular carcinoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

8. What is the main aim of treatment for untreated advanced or unresectable hepatocellular carcinoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve patients overall survival from the disease.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Achievement of disease stabilisation or reduction in tumour size (i.e. disease control). In PD-L1 plus CTLA-4 inhibitors, the goal is to extend survival beyond the achievement of a radiologically quantifiable response.
10. In your view, is there an unmet need for patients and healthcare professionals in untreated advanced or unresectable hepatocellular carcinoma ?	Yes. Patients with advanced HCC have limited therapeutic options. Co-existence of cirrhosis and cardiovascular comorbidities limits the utilisation of systemic therapy in these patients, making it a high priority to have multiple therapeutic options to ensure as many patients as possible can benefit from anti-cancer immunotherapy.
11. How is untreated advanced or unresectable hepatocellular carcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The pathway of care for patients with unresectable advanced HCC is well defined. It includes TACE or TARE for patients with liver confined disease and systemic therapy for patients with advanced disease. Guidelines from the Barcelona Clinic Liver Cancer group and from ESMO are generally followed, although access to certain therapies is restricted in the UK. Current systemic therapy options in first line include atezolizumab plus bevacizumab, Lenvatinib and sorafenib. Implementation of durvalumab plus tremelimumab would be advantageous to patients. It will enable individuals who are ineligible to bevacizumab (i.e. high risk of bleeding, cardiovascular comorbidities, wound healing problems, thrombosis) to access combination immunotherapy that has been unequivocally shown to be superior to TKI therapy.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Durvalumab plus tremelimumab will be used in the same way as atezolizumab plus bevacizumab. A potential advantage would be in the less frequent monitoring (every 4 weeks for D+T versus every 3 weeks for A+B currently).

Clinical expert statement

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This treatment should be used in hospital setting on an elective outpatient basis supervised by an oncologist. There is no anticipated investment required to implement this technology in the NHS.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Durvalumab plus tremelimumab is expected to extend the quantity of life of patients who are currently ineligible to combination immunotherapy in the UK (atezolizumab plus bevacizumab). Recent published evidence suggests up to 25% of patients receiving D+T for unresectable/advanced HCC to be alive 4 years after their diagnosis which is a remarkable advancement. Published metanalysis evidence from my research group has shown D+T to have similar survival results in terms of overall risk reduction for death versus sorafenib compared to A+B but a lower risk of high-grade toxicity (i.e. CTCAE G3 or above), making a case for adoption,
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. Durvalumab plus tremelimumab appeared effective across all studied subpopulations within unresectable/advanced HCC.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	No need for additional tests. Treatment will be delivered the same way as current combination immunotherapy with A+B.

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acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. D+T has been shown to delay deterioration in quality of life and lead to a remarkable 25% probability of being alive 4 years after the diagnosis and 20% at 5 years.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	The technology is highly innovative as it brings for the first time a dual immunotherapy approach in the treatment landscape of HCC.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects appeared manageable and in keeping with the mechanism of action of immunotherapy, currently already in use in the NHS.
20. Do the clinical trials on the technology reflect current UK clinical practice?	Although the UK was not part of phase III trials, patient populations are overall reflective of UK practice.

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• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Fulgenzi CAM, Scheiner B, Korolewicz J, Stikas CV, Gennari A, Vincenzi B, Openshaw MR, Silletta M, Pinter M, Cortellini A, Scotti L, D'Alessio A, Pinato DJ. Efficacy and safety of frontline systemic therapy for advanced HCC: A network meta-analysis of landmark phase III trials. JHEP Rep. 2023 Feb 18;5(5):100702. doi: 10.1016/j.jhepr.2023.100702. PMID: 37025943; PMCID: PMC10070142.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA474, TA551, TA666]?	No
23. How do data on real-world experience compare with the trial data?	There is limited real world evidence from the use of durvalumab plus tremelimumab in patients with advanced HCC. My group has published limited evidence in abstract form in year 2024, utilising an international database which did not include UK patients. Data should be appraised with care as they included patients with off label use. However tolerability of the combination appeared in keeping with trial data. Evidence can be found here: https://ascopubs.org/doi/10.1200/JCO.2024.42.3_suppl.501
24. Are the comparators (Atezolizumab + bevacizumab, Lenvatinib and Sorafenib) appropriate and reflect those used in a UK setting?	Yes. In particular my expectation is that D+T would be more useful in patients who are not candidates for bevacizumab, making a stronger case for a direct comparison with sorafenib.

Clinical expert statement

25. Do individuals that have the comparators listed above experience any adverse events or immune-related adverse events and how to they compare to those discussed in the company submission?	A+B may lead to immune related adverse events and risk of bleeding. Bleeding risk and cardiovascular toxicity is not a feature of D+T, making a case for adoption to ensure broader availability of immunotherapy in UK
26. Are you aware of how “people who are ineligible for locoregional therapy and have not undergone systemic treatment” may differ in treatment they receive and their response to that treatment from the more general population of “People with advanced or unresectable hepatocellular carcinoma”.	I would not expect differences in these two populations.
27. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	I do not see any inequalities issues

Clinical expert statement

- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

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

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Durvalumab plus tremelimumab is a novel technology that may broaden the reach of anticancer immunotherapy in the UK

Durvalumab plus tremelimumab has non-overlapping toxicity compared to options available today

Durvalumab plus tremelimumab has compelling 5 years overall survival rates of 20%

Click or tap here to enter text.

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Clinical expert statement

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

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Title: Hepatocellular carcinoma (advanced, unresectable, untreated) - durvalumab (with tremelimumab) [ID2725]- FINAL REPORT

Produced by Warwick Evidence

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Abbreviations

Abbreviations	Definition
ADA	Anti-drug antibody
AE	Adverse event
AFP	Alpha-fetoprotein
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
APC	Antigen presenting cell
AST	Aspartate aminotransferase
AUC	Area under the curve
BCLC	Barcelona Clinic Liver Cancer
BGR	Brook–Gelman–Rubin
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BID	Twice daily
BMI	Body mass index
BMJ	British medical journal
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BSG	British Society of Gastroenterology
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CIC	Commercial in confidence
CR	Complete response
CRD	Centre for Review and Dissemination
CrI	Credible interval
CS	Company's submission
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DBP	Diastolic blood pressure

DCO	Data cut-off
DCR	Disease control rate
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSU	Decision Support Unit
EASL	Eastern Association for the Study of the Liver
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGD	Esophagogastroduodenoscopy
EHS	Extrahepatic spread
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
EQ	EuroQol
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy - General
FAS	Full analysis set
FE	Fixed effects
FWER	Family-wise error rate
GHS	Global Health Status
HBcAb	Hepatitis B surface antigen
HBV	Hepatic B virus
HCC	Hepatocellular carcinoma
HCRU	Healthcare resource utilisation
HCV	Hepatic C virus
HDV	Hepatic D virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
INR	International normalised ratio
INV	Investigator-assessed
IO	Immuno-oncology

IPD	Individual patient data
irAE	Immune-related adverse event
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IWRS	Interactive web response system
LY	Life year
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MASLD	Metabolic dysfunction-associated steatotic liver disease
MCMC	Markov Chain Monte Carlo
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
mTTO	Median time to onset
mTTR	Median time to resolution
MVI	Macrovascular invasion
NCI	National Cancer Institute
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PF	Progression free
PFS	Progression-free survival
PGIC	Patient's Global Impression of Change
PH	Proportional hazard
PHA	Proportional hazard assumption
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PS	Performance status

PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
Q4W	Every four weeks
QALY	Quality-adjusted life year
QLQ-C30	Core Quality of Life questionnaire
QLQ-HCC18	Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
ROBIS	Risk Of Bias In Systematic Reviews
RWE	Real-world evidence
SAE	Serious adverse event
SAS	Safety analysis set
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	36-Item Short Form Survey
SIRT	Selective Internal Radiation Therapy
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMQs	Standardised MedDRA queries
SoC	Standard of Care
STA	Single technology appraisal
STRIDE	Single Tremelimumab Regular Interval Durvalumab
TA	Technology appraisal
TACE	Transarterial chemoembolization
TARE	Transarterial radioembolization
TBL	Total bilirubin
TCR	T cell receptor
TEM	Treatment effect modifier
TIP	Tumour and immune cell positivity
TKI	Tyrosine kinase inhibitor
TRAE	Treatment-related adverse event

Treg	T regulatory cell
TSD	Technology Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
ULN	Upper limit normal
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
VBA	Visual Basis for Applications
VEGF	Vascular endothelial growth factor
WTP	Willingness to pay

Executive Summary

The summary provides an overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.2.1 and 1.2.2 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the view of the EAG, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of the EAG key issues

ID2725	Summary of issues	Report section
Key issue 1: Generalisability of the HIMALAYA trial	Limitations in the generalisability of the HIMALAYA trial population to NHS clinical settings. There were no UK patients in the trial, and the trial as discussed in the patient's characteristics, is unlikely to closely conform to the UK HCC population.	Section 3.2 and 3.2.3
Key issue 2: Company's NMA and modelling OS and PFS	Appropriateness of NMA methods employed. The method used for modelling OS and PFS for STRIDE (using IPD from HIMALAYA) appears to use differing data cut-off (DCO) for OS and PFS. The date of cutoff for comparators atezolizumab + bevacizumab and lenvatinib is noticeably different from that for HIMALAYA where NMA HRs associated with very substantial uncertainty are employed. There is a lack of equity in the handling of STRIDE versus atezolizumab + bevacizumab and lenvatinib.	Sections 3.2.8.1 and 3.2.9.1 and 4.2.6
Key issue 3: Company assumed that TTD for atezolizumab + bevacizumab is equivalent to PFS	The company states that in the absence of TTD information for atezolizumab + bevacizumab and for lenvatinib, they have assumed TTD for these is equivalent to the modelled PFS. However, there are high levels of imprecision associated with the PFS models (employing NMA output HRs) and, in the case of atezolizumab + bevacizumab, bear little resemblance to what is seen in the IMbrave150 trial used for NMA input. The EAG is unconvinced that equivalence of TTD and PFS is a sensible assumption. The EAG	Section 4.2.6

ID2725	Summary of issues	Report section
	is unconvinced that the equivalence of TTD and PFS is a sensible assumption.	
Key issue 4: Utility values	The company assigned the same utility values for patients receiving first-line treatments (e.g., STRIDE) as for those subsequent treatments (e.g., sorafenib). This is inconsistent with the company's treatment-related utility assumptions and neglects the impact of treatment-specific adverse events.	Section 4.2.8
Key issue 5: Severity modifier	The company's use of a QALY weight of 1.2, based on sorafenib, is inappropriate; the QALY weight should reflect established treatments like atezolizumab + bevacizumab currently available in NHS practice.	Sections 4.2.10
EAG, evidence assessment group; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time-to-treatment discontinuation		

Common key issues: clinical effectiveness evidence

Here we outline our key concerns with the clinical effectiveness evidence submitted by the company. These include

- Limitations in the generalisability of the HIMALAYA trial population to the UK NHS HCC patient population.
- Appropriateness of the company NMA and the clarity of its presentation, together with a failure to consider published NMAs addressing the same issues as the company NMA.

Common key issues: cost-effectiveness evidence

Here, we outline our key concerns with the cost-effectiveness evidence submitted by the company. These include:

- Inconsistent use of individual patient data and hazard ratios across treatments results in unrealistic overall survival projections, especially for STRIDE.
- The method used for modelling OS and PFS for STRIDE is different from that used for atezolizumab + bevacizumab and for lenvatinib, where NMA HRs associated with substantial uncertainty are used to estimate the impact. The EAG considers there to be a lack of equity in the modelling of STRIDE compared to that for atezolizumab + bevacizumab and lenvatinib.

- In the absence of time to discontinuation of treatment information for atezolizumab + bevacizumab and an assumed lack of information for lenvatinib, the company has assumed that TTD for these is equivalent to the company-developed models for progression-free survival (PFS). However, there are high levels of imprecision associated with PFS models (employing NMA output HRs) in the case of atezolizumab + bevacizumab bears little resemblance to what is seen in the IMbrave150 trial used for NMA input. The company's NMA output for atezolizumab + bevacizumab PFS is an outsider relative to values in many published NMAs. The EAG is unconvinced that the equivalence of TTD and PFS is a sensible assumption for modelling. The EAG notes that the company states that clinical experts consulted highlighted that the measurement of PFS is challenging, as radiologic progression is a subjective measurement prone to reading errors. And that patients are frequently eligible to continue treatment both within the trial setting and real-world setting even after disease progression. Thus, using PFS as a proxy for TTD is particularly worrying.
- The company assigned the same utility values for patients receiving first-line treatments (e.g., STRIDE) as for those subsequent treatments (e.g., sorafenib). This is inconsistent with the company's treatment-related utility assumptions and neglects the impact of treatment-specific adverse events.
- The source of age-adjustment coefficients for utilities is unclear and these appear overly optimistic.
- The company's use of a QALY weight of 1.2, based on sorafenib, but the QALY weight should have reflected other established treatments (e.g., atezolizumab + bevacizumab) currently available in NHS practice.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions:

Variable	Company's Value	EAG's value
Controls		
Time horizon	40	20

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

Variable	Company's Value	EAG's value
Primary treatment Utilities		
Treatment: sorafenib, lenvatinib	████	Parameter ≤ 5 weeks from death 5-15 weeks from death 15-30 weeks from death >30 weeks from death Estimate ████ ████ ████ ████
Treatment: STRIDE, Atezolizumab plus bevacizumab	████	
Severity weighting		
QALY weight	1.2	1
Age-adjusted coefficients for utilities		
The source of age-adjustment coefficients for utilities	Unclear	Using Ara & Brazier (2010) ¹
Half-cycle correction method for tremelimumab drug costs		
Drug cost of tremelimumab including acquisition and administration costs	Allocating the full cost in the first week, and half the cost in the second week	Using the appropriate coefficients (0.5 for the first and second cycles) leads to allocating half of the costs in the first cycle and the other half in the second one.
Crl, credible interval; EAG, Evidence Assessment Group; HR, hazard ratio; PFS, progression-free survival; QALY, quality adjusted life year; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTD, time-to-treatment discontinuation;		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life represented as quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- By changing the overall survival
- By changing the progression-free survival
- By changing the incidence of treatment-related adverse events

Overall, the technology is modelled to affect costs by:

- Drug acquisition, drug administration, and subsequent treatment costs
- Health state management costs
- End-of-life care costs and adverse event costs

The modelling assumptions that have the greatest effect on the ICER are:

- The assumption of using progression-free survival as a proxy of time-to-treatment discontinuation
- Using the generalised gamma parametric model (based on the HIMALAYA trial) for sorafenib overall survival
- Using the constant hazard ratio for overall survival and progression-free survival derived from a network meta-analysis and applied to STRIDE, atezolizumab + bevacizumab, and lenvatinib.

1.2.1 The clinical effectiveness evidence: summary of the EAG's key issues

Key issue 1: Generalisability of the HIMALAYA trial population to NHS practice

Report section	Section 3.2
Description of issue and why the EAG has identified it as important	The HIMALAYA trial included patients with histologically confirmed HCC, aged ≥ 18 years, weighing >30 kg, and ineligible for locoregional therapy. They had BCLC stage B or C, Child-Pugh class A, ECOG-PS of 0 or 1, and adequate organ and bone marrow function. The generalisability of the HIMALAYA trial population outcomes to the NHS practice may be compromised because the study population does not fully represent the UK, a view that is shared by our clinical experts. Regional variations in the UK include older, predominantly white, overweight (BMI >30), and lower prevalence of viral aetiology.
What alternative approach has the EAG suggested?	Based on the information provided, we consider that there are no feasible alternatives.
What is the expected effect on the cost-effectiveness estimates?	Indeterminate. The EAG are unable to suggest what impact this may have on the cost-effectiveness.
What additional evidence or analyses might help to resolve this key issue?	The HIMALAYA trial is generalisable to only a small portion of the UK's real-world population. Therefore, the EAG considers that additional evidence is required due to the small number of participants providing clinical evidence. This is especially relevant from a UK perspective, as none of the participating centres were from the UK.
BMI, body mass index; EAG, Evidence assessment group; ECOG-PS, Eastern Cooperative Oncology Group- performance status; HCC, hepatocellular carcinoma; NHS, National Health Service	

Key issue 2: Company's network meta-analysis (NMA) and modelling of OS and PFS

Report section	Sections 3.2.8.1, 3.2.9.1 and 4.2.6
Description of issue and why the EAG has identified it as important	The EAG identified several concerns related to the company's NMA including, lack of clarity on the inclusion/exclusion criteria used, no literature search undertaken by the company to identify specific studies to be included in the NMA, data input were sparse and unclear making the analysis difficult to replicate, data input ignored some data from the HIMALAYA trial, no literature search for published NMAs, and no comparison between the company's NMA and those published. We have raised these concerns because the hazard ratio results from the company's NMA are used to model overall survival and progression-free survival over the model time horizon for the atezolizumab + bevacizumab and lenvatinib, and these inputs (OS and PFS) are key drivers of the economic model. Please see below issue about secondary issues relating to the company's NMA. The method used for modelling OS and PFS for STRIDE (using IPD from HIMALAYA possibly at different dates of cutoff for OS and PFS) is different from that used for comparators (atezolizumab + bevacizumab and lenvatinib) where NMA HRs associated with very substantial uncertainty are employed. The EAG considers that there is a lack of equity in the handling of STRIDE versus atezolizumab + bevacizumab and lenvatinib; using the anchored NMA for atezolizumab + bevacizumab and lenvatinib, and independent parametric models for the IPD for STRIDE and sorafenib.

What alternative approach has the EAG suggested?	The EAG has concerns regarding the conduct of and results of the company's NMA that may be addressed in two ways, undertaking an EAG NMA and searching the published literature for relevant NMAs, then choosing an appropriate NMA. We have not undertaken an EAG NMA because we considered it to be outside the remit of critiquing and our effort would be redundant in the view that such analyses have already been undertaken and it would merely be duplicating what has already been published. Hence, we undertook a targeted search of the published literature to identify suitable NMAs (see Section 3.2.10). There are two feasible alternatives to potentially eliminate this inconsistency. First, using NMA-delivered hazard ratios for all compared treatments, including STRIDE. Second, by using trial-based IPD of overall survival and progression-free survival for all compared treatments (i.e., STRIDE, sorafenib, lenvatinib, and atezolizumab + bevacizumab) representing a naïve comparison. The EAG base-case is based on the former. We identified from the published literature an NMA undertaken by Vogel et al. (see Section 3.2.10) and used a constant hazard ratio (vs. sorafenib) for OS and PFS of STRIDE, atezolizumab + bevacizumab, and lenvatinib.
What is the expected effect on the cost-effectiveness estimates?	Collectively, applying different hazard ratios to model OS and PFS will likely lead to an increase in the deterministic incremental cost-effectiveness ratio results.
What additional evidence or analyses might help to resolve this key issue?	The EAG suggests that the NMA should have included all the available information from the included studies, and then used the relevant results as inputs to the economic model. We undertook scenario analyses using hazard ratio results from Wang et al. study to assess the impact on the cost-effectiveness results. However, it would have been beneficial to undertake a survival analysis if IPD were available for OS and PFS for all treatments.
EAG, evidence assessment group; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival	

1.2.2 The cost-effectiveness evidence: summary of the EAG's key issues

In this section, we highlight our concerns with the cost-effectiveness evidence submitted by the company, including:

Key issue 3: Company assumed that TTD for atezolizumab + bevacizumab is equivalent to PFS

Report section	Sections 4.2.6 and 4.2.7 and 5.2
Description of issue and why the EAG has identified it as important	The company assumed TTD for atezolizumab + bevacizumab and lenvatinib to be equivalent to PFS while applying distinct TTD and PFS curves for STRIDE and sorafenib. This assumption stems from a lack of direct TTD data for these treatments, leading to the use of PFS as a proxy. However, the EAG has raised concerns with this approach. Given these discrepancies, the EAG questions the validity of equating TTD with PFS exclusively for atezolizumab + bevacizumab and lenvatinib, as this approach may inaccurately reflect treatment duration and introduce bias in cost-effectiveness estimates.
What alternative approach has the EAG suggested?	The EAG recommends utilising actual TTD data for each treatment where available, rather than assuming PFS is equivalent to TTD. While TTD data exists for lenvatinib, no direct TTD data is available for atezolizumab + bevacizumab. Therefore, the EAG suggests using PFS data but cautions against the company's PFS model. For STRIDE, the EAG also recommends using PFS as a proxy for TTD for consistency, as the company's TTD model for STRIDE seems based on scheduled visit times rather than actual treatment durations.
What is the expected effect on the cost-effectiveness estimates?	The EAG anticipates that the company's assumption of TTD-PFS equivalence may lead to biased cost-effectiveness estimates, particularly in comparisons between STRIDE and atezolizumab + bevacizumab. By using PFS as a proxy for TTD, the company's models may misrepresent actual treatment durations, resulting in distorted costs and outcomes. This could cause an overestimation of costs for atezolizumab + bevacizumab and a reduced ICER for STRIDE compared to atezolizumab + bevacizumab.
What additional evidence or analyses might help to resolve this key issue?	Additional TTD data for atezolizumab + bevacizumab would enhance modelling accuracy and reduce reliance on the PFS-TTD equivalence assumption. Further analyses could involve sensitivity testing to evaluate different HRs in the PFS model and exploring alternative modelling techniques to better capture treatment discontinuation.
TTD, time-to-treatment discontinuation; PFS, progression-free survival; EAG, Evidence Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio	

Key issue 4: Company's use of treatment-related utilities

Report section	Section 4.2.8
Description of issue and why the EAG has identified it as important	Several concerns have been highlighted on the company's preference for assigning utility values. First, treatment-related values are applied regardless of the health-state occupied, and this is not in line with the NICE reference case. Second, treatment-related utility values are applied to people who are in a progression-free health state (on/off) treatment and progressed disease health state (on/off treatment). Third, for people who received subsequent treatment, it was assumed that the utility value remained the same as on primary treatment. The EAG considers that the approach used by the company not to be in line with the NICE reference case.
What alternative approach has the EAG suggested?	The EAG determined that the most appropriate approach is to utilise health state-based utility values in the base case analysis. However, two primary limitations hinder the use of available health state-based utility values: first, there is the unavailability of a suitable source for these utility values, and second, insufficient data regarding the disutilities associated with adverse effects and other patient conditions under various treatments. Given these limitations, the EAG considers the next best alternative to be the use of time-to-death utility values. This approach assigns a consistent utility value for a defined period based on time to death across different treatments, aligning more closely with NICE's reference case by applying the same utility value for identical health states among various treatments. The time-to-death utility values were provided in the company's response to the EAG's clarification questions and were subsequently used for the base case analysis. In the EAG's scenario analyses, four approaches were considered: first, utilising on-treatment time-to-death utility values from TA666; second, employing the company's methodology; third, applying sorafenib utility as the off-treatment utility in the company's approach; and fourth, using utility values from Su et al. 2021,² assigning 0.76 for progression-free disease and 0.68 for progressed disease.
What is the expected effect on the cost-effectiveness estimates?	Keeping all other inputs/assumptions fixed, we would expect that the QALYs yielded by strategy and incremental QALY gain to decrease, leading to an increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	There are several approaches that could be used to resolve this issue. First, using health state utility values for progression-free (on/off treatment) and progressed disease (on/off treatment). Second, on/off-treatment time-to-death utility values from the trial.

Key issue 5: Severity modifier

Report section	Section 4.2.10
Description of issue and why the EAG has identified it as important	The EAG identified that the company used of a severity modifier of 1.2 for QALYs when comparing treatments against lenvatinib and sorafenib, and a modifier of 1 for atezolizumab + bevacizumab. Accurate calculation requires QALYs associated with treatments currently available in NHS practice, which have higher QALY gains.
What alternative approach has the EAG suggested?	We propose that the QALY weight should reflect the established treatment, which has higher QALY gains. This treatment is atezolizumab + bevacizumab, which is currently available in NHS practice.
What is the expected effect on the cost-effectiveness estimates?	The expected effect on cost-effectiveness estimates indicates that using the QALY weight from atezolizumab + bevacizumab shows that [REDACTED]
What additional evidence or analyses might help to resolve this key issue?	Undertaking an analysis where a severity weighting is based on the QALYs expected for people treated with atezolizumab + bevacizumab.

1.2.3 Other issues/remaining uncertainty

Other issues: decision problem

- The decision problem population is narrower than NICE scope.

Other issues: clinical effectiveness evidence

- Concerns regarding potential long-term immune-related adverse effects and immunogenicity from STRIDE.

Other issues: cost-effectiveness evidence

- Previous assessments typically used a 14 to 20-year time horizon, while the company's 40-year proposal was deemed overly optimistic by EAG clinical advisors, especially since only a very small proportion of patients survive beyond 20 years.
- The company's half-cycle correction method for tremelimumab costs overestimates total expenses by misallocating costs, and inflating figures beyond the actual drug cost.

1.3 Summary of EAG preferred assumptions and impact to the company ICER (pairwise comparison)

The EAG made the following changes to the company's model to form the EAG's base-case (see Table 2). The results show the impact of each change to the pairwise incremental cost-effectiveness ratios (ICERs).

Table 2: Summary of EAG's preferred assumptions and ICER

EAG's preferred assumption based on issues	STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company's base case	██████	██	██████	██████	██	██████	██████	██	██████
20-year time horizon	██████	██	██████	██████	██	██████	██████	██	██████
Using the generalised Gamma model (based on the HIMALAYA trial) for sorafenib OS	██████	██	██████	██████	██	██████	██████	██	██████
Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the OS of STRIDE, atezolizumab + bevacizumab, and lenvatinib.	██████	██	██████	██████	██	██████	██████	██	██████
Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the PFS of STRIDE, atezolizumab + bevacizumab, and lenvatinib.	██████	██	██████	██████	██	██████	██████	██	██████
Using PFS as a proxy of TTD in all treatments.	██████	██	██████	██████	██	██████	██████	██	██████
Using the time-to-death utility value (data from the HIMALAYA trial)	██████	██	██████	██████	██	██████	██████	██	██████
Using the QALY weight calculated from atezolizumab plus bevacizumab as the standard treatment in the UK for all comparators.	██████	██	██████	██████	██	██████	██████	██	██████
Using Ara and Brazier (2010) as the source of age-adjustment coefficients for utilities	██████	██	██████	██████	██	██████	██████	██	██████

EAG's preferred assumption based on issues	STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Amendment of the formula for calculating the half-cycle correction for the drug cost of tremelimumab									

1.4 EAG deterministic results

In Table 3 and Table 4, we present the EAG deterministic results based on the EAG's preferred assumptions.

Table 3: EAG deterministic results (pairwise analysis-STRIDE vs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)
STRIDE	████	██	██	█	█	█	█
Sorafenib	████	██	██	████	██	██	████
Lenvatinib	████	██	██	████	██	██	████
Atezolizumab plus bevacizumab	████	██	██	████	██	██	████
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: EAG deterministic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (cost per QALY)
Sorafenib	████	██	██	█	█	█	█
Lenvatinib	████	██	██	████	██	██	████
STRIDE	████	██	██	████	██	██	████
Atezolizumab + bevacizumab	████	██	██	████	██	██	████
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; STRIDE, Single Tremelimumab Regular Interval Durvalumab							

1.5 EAG probabilistic sensitivity analysis

Table 5: EAG probabilistic sensitivity analysis results (pairwise analysis-STRIDE vs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)
STRIDE	████	██	██				
Sorafenib	████	██	██	████	██	██	████
Lenvatinib	████	██	██	████	██	██	████

Atezolizumab + bevacizumab							
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: EAG probabilistic sensitivity analysis results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER
Sorafenib							
Lenvatinib							
STRIDE							
Atezolizumab + bevacizumab							
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab							

1.6 Summary of exploratory analyses undertaken by the EAG

Table 7: EAG's scenario analysis results for STRIDE vs comparators (deterministic)

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
EAG's Base-case		████	██	████	████	██	████	████	██	████
1	Using the company's approach for TTD (Company assumed that TTD for atezolizumab + bevacizumab and Lenvatinib is equivalent to PFS)	████	██	████	████	██	████	████	██	████
2	Using the constant HRs to estimate the OS and PFS of different treatments, based on the company's NMA	████	██	████	████	██	████	████	██	████
3	40-year time horizon	████	██	████	████	██	████	████	██	████
4	10-year time horizon	████	██	████	████	██	████	████	██	████
5	Using on-treatment time-to-death utility values from TA666	████	██	████	████	██	████	████	██	████
6	Using the company's approach	████	██	████	████	██	████	████	██	████
7	Using the sorafenib utility as an off-	████	██	████	████	██	████	████	██	████

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	treatment utility in the company approach									
8	Using the utility values from Su et al., 0.76 and 0.68 are assigned as the proxy of utility values for PFD and PD, respectively.									
9	Using the company approach of age-adjustment coefficients for utilities									
10	Inclusion of vial sharing									
11	PFS extrapolation choice for STRIDE: Splines and knots									
12	PFS extrapolation choice for sorafenib: log-normal									
13	Treatment-specific RDIs									
14	Using the company's approach (splines and knots: normal, 1 knot) for overall survival in STRIDE, sorafenib, and 40-year time horizon									

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
15	Using the overall survival HR of 0.76 from the company's NMA for STRIDE vs sorafenib, and 40-year time horizon									
16	Using the company's NMA OS hazard ratios (Atezolizumab + bevacizumab vs STRIDE and lenvatinib vs STRIDE) applied to the company's spline model for STRIDE to obtain models for atezolizumab + bevacizumab and lenvatinib for sorafenib. Splines and knots is used for sorafenib (see Appendix 9.6)									
17	Using the company's approach for incorporating the severity modifier (1.2 for sorafenib and lenvatinib, and 1.0 for atezolizumab + bevacizumab)									

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
18	Using the severity modifier of 1.2 for all comparisons	████	██	████	████	██	████	████	██	████
ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTD: time to treatment discontinuation										

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

2.1.1 Background

Remit/evaluation objectives

To evaluate the clinical and cost-effectiveness of durvalumab combined with tremelimumab (as Single tremelimumab regular interval durvalumab) hereafter referred to as STRIDE for the first-line treatment of advanced or unresectable hepatocellular carcinoma in adults, within its marketing authorisation.

Condition, symptoms, and incidence

Hepatocellular carcinoma (HCC) is a primary liver malignancy that predominantly affects patients with chronic liver disease and cirrhosis, though up to 25% of cases occur without these risk factors. The global incidence of HCC has been rising over the past 20 years and is expected to continue increasing in many countries. HCC incidence is highest in Asia and Africa due to the high prevalence of hepatitis B and C, both major risk factors for HCC. The incidence of advanced hepatocellular carcinoma (HCC) specifically is rarely reported separately to overall liver cancer statistics; liver cancer incidence in the UK has increased by 177% since the early 1990s, with projections indicating a further 6% rise by 2038-2040.³ Approximately 6,600 new liver cancer cases are diagnosed annually, with higher prevalence in males and older adults.

HCC patients often present with symptoms of advanced cirrhosis, including jaundice, splenomegaly, and hepatic encephalopathy^{4,5} and approximately 41% of HCC cases are estimated to be diagnosed at an advanced or unresectable stage.^{3,6}

Mechanism of action

Durvalumab, a human IgG1 kappa monoclonal antibody, blocks PD-L1 from binding to PD-1 and CD80, enhancing T-cell activation without causing antibody-dependent cytotoxicity. It has a half-life of 21 days and reaches a steady state in 16 weeks. Tremelimumab, a human IgG2 monoclonal antibody, inhibits CTLA-4, releasing T-

cell activation. Both are administered separately via intravenous infusion.⁷⁻⁹ The EAG notes that the mechanism reported in CS Table 2 matches their findings.

Treatment pathway

In the UK, the standard of care for HCC has evolved with advancements in treatment options. Sorafenib was the standard treatment for advanced HCC for many years, having been approved by the National Institute for Health and Care Excellence (NICE) in 2017.^{6, 10, 11}

The combination of atezolizumab and bevacizumab became the new standard of care for advanced or unresectable HCC in the UK following its approval by NICE in December 2020. This combination showed superior overall survival and progression-free survival compared to sorafenib, based on the results of the IMbrave150 study.¹²⁻¹⁴

This combination therapy was approved by the European Medicines Agency (EMA) in late 2020 and is recommended by the European Society for Medical Oncology (ESMO). For patients who do not respond to this first-line treatment, second-line options are considered based on individual patient factors and disease progression. Additionally, the British Society of Gastroenterology (BSG) provides guidelines for the management of HCC, which include evidence-based recommendations for assessment and treatment (CS, Document B, section B.1.3).⁶

Selective internal radiation therapy (SIRT) with QuiremSpheres is recommended by NICE (2021)¹⁵ for patients with Child-Pugh grade A liver impairment when transarterial therapies (TACE) are unsuitable. SIRT, administered via a catheter to the hepatic artery, is particularly considered for patients with large solitary tumours or those with local macrovascular invasion, where systemic therapy tolerance is a concern. Despite limited evidence from randomized controlled trials comparing SIRT and TACE for intermediate-stage HCC, SIRT is an option for treating unresectable advanced HCC in adults with compensated chronic liver disease.^{15, 16}

The systemic treatment algorithm for advanced HCC at BCLC stage C includes several first-line options: atezolizumab/bevacizumab, durvalumab/tremelimumab, sorafenib, and lenvatinib. Atezolizumab plus bevacizumab is recommended for patients with advanced HCC, Child-Pugh class A liver disease, and ECOG performance status 0-1, following management of oesophageal varices. If

contraindications exist, sorafenib or lenvatinib may be offered. Sorafenib is also considered for selected patients with Child-Pugh B liver disease.¹⁷⁻²⁰

Second-line treatments include sorafenib, lenvatinib, regorafenib, nivolumab, pembrolizumab, cabozantinib, and ramucirumab. Tyrosine kinase inhibitors are recommended for patients progressing on first-line atezolizumab plus bevacizumab. Regorafenib is specifically recommended for those who have had sorafenib, with Child-Pugh class A liver impairment and ECOG performance status 0 or 1.

Durvalumab (Imfinzi, AstraZeneca) in combination with tremelimumab has a marketing authorisation for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma.

2.2 Critique of company's definition of decision problem

2.2.1 Population

The NICE final scope defined the population as “People with advanced or unresectable hepatocellular carcinoma”.²¹ The population in the CS decision problem (CS Document B, Table 1) is the same as in the NICE scope but only includes those who are ineligible for locoregional therapy and have not undergone systemic treatment. Specifically, it refers to “Individuals with advanced or unresectable HCC who are ineligible for locoregional therapy and have not undergone systemic therapy” (CS Document B, Table 1).

The criteria for ineligibility for locoregional therapy and lack of prior systemic treatment were added to align with the eligibility criteria of the HIMALAYA trial^{22, 23} (CS Document B, Section B.2.3.1, Table 5). Additionally, the company clarifies that “all individuals have HCC that is either advanced, meaning it has spread extensively, or unresectable, meaning it cannot be surgically removed” (CS Document B, Table 1).

The EAG highlights that NICE's final scope includes a broader population of patients with advanced or unresectable HCC, whereas the company presents evidence of a narrower population.

The EAG clinical expert advised that the HIMALYA trial was designed to benefit patients most likely to respond to the STRIDE regimen as the first line of systemic therapy. This includes patients with advanced or unresectable HCC who are

ineligible for locoregional treatment due to disease progression. STRIDE is recommended as the first line of systemic therapy, justifying the lack of prior systemic therapy for these patients. The criteria for ineligibility for locoregional therapy and the absence of prior systemic therapy are supported by the EAG's clinical advisor. The EAG agrees with this recommendation.

2.2.2 Intervention

The company's decision problem intervention(s) aligns with the NICE final scope.²¹

The company also describes the technology and mechanism of action of durvalumab and tremelimumab (CS Document B, Section B.1.2, Table 2), which is consistent with the summary of product characteristics (SmPC).

2.2.3 Comparators

The company's decision problem comparators were narrower than the NICE final scope.²¹

The company's decision problem includes only atezolizumab + bevacizumab, lenvatinib, and sorafenib (CS Document B, pg. 15).

Based on BSG guidelines and the company's clinical expert opinions, the company explains that atezolizumab combined with bevacizumab is considered the standard of care (SoC) for first-line treatment in NHS clinical practice (see AstraZeneca Data on File. HIMALAYA Clinician Validation Interviews, supplied in the CS reference pack).¹⁶ Therefore, it is the main comparator in the company's submission. For patients who cannot use atezolizumab plus bevacizumab or prefer oral treatment over intravenous therapy, the BSG guidelines recommend lenvatinib and sorafenib as alternative first-line options.^{10, 14, 16, 24} The EAG supports this view, citing the BMJ Best Practice (2024) for hepatocellular carcinoma.¹⁹ Specifically, atezolizumab/bevacizumab is the SoC for first-line treatment according to the treatment algorithm for BCLC stage C (advanced disease).

The company notes that their comparators differ from NICE's scope because the patient population is ineligible for locoregional therapies like selective internal radiation therapy (SIRT). They argue that best supportive care (BSC) should complement main treatments rather than serve as a standalone comparator. The EAG clinical experts highlighted that while evidence for locoregional therapy is limited, it is administered before systemic treatment. Additionally, BSC is provided for

all patients as part of NHS practice and is not considered a separate comparator. The EAG agrees.

2.2.4 Outcomes

The company's decision problem outcomes align with the NICE final scope.²¹

2.2.5 Other relevant factors

The company's decision problem (CS Document B, section B.2.7) states that clinical efficacy subgroup analyses show the efficacy of STRIDE across various patient characteristics, including:

- HCC aetiologies
- ECOG Performance Status (PS)
- Presence of macrovascular invasion (MVI)
- The specific subgroups reported are:
 - Sex
 - Age at randomisation
 - PD-L1 expression
 - Aetiology of liver disease
 - ECOG PS at baseline
 - MVI
 - Extrahepatic spread (EHS)
 - Region
 - Alpha-fetoprotein (AFP) at baseline
 - BCLC score

These details can be found in CS Document B, Table 1.

The EAG agrees with the company. NICE has not considered any subgroups for this population. However, based on the literature²⁵⁻²⁷ and EAG clinical expert, there are subgroups and prognostic factors that affect the treatment and prognosis of patients that should be considered.

2.2.6 Summary section

The company's decision problem specifies a population with advanced or unresectable HCC who are ineligible for locoregional therapy and have not undergone systemic treatment, aligning with the HIMALAYA trial criteria. The EAG

agrees with the provided justification although the population is narrower than NICE final scope. The intervention, STRIDE, aligns with the NICE final scope. However, the company's comparators (atezolizumab + bevacizumab, lenvatinib, and sorafenib) are narrower than the NICE final scope. The EAG finds the company's justifications for excluding locoregional therapies and BSC sufficient. The outcomes align with the NICE final scope, and the company presents subgroup analyses across various patient characteristics. The EAG notes that NICE has not considered subgroups.

Table 8: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with advanced or unresectable HCC	Individuals with advanced or unresectable HCC who are ineligible for locoregional therapy and have not undergone systemic therapy	The population largely aligns with the NICE final scope and incorporates additional specifications to match the eligibility criteria of the HIMALAYA trial (see Section B.2.3.1). Importantly, all individuals have HCC that is either advanced, meaning it has spread extensively, or unresectable, meaning it cannot be surgically removed (see Section B.1.3.2). The patient population of interest must also be ineligible for locoregional therapies. ²⁸	The company's population is narrower than NICE's scope. The EAG's clinical advisor confirmed the company's justification. The EAG finds the company's justification acceptable.
Intervention	Durvalumab plus tremelimumab	STRIDE: durvalumab (1,500 mg Q4W) and a single dose of tremelimumab (300 mg)	The intervention is in line with the final scope. In the HIMALAYA trial, patients were randomised into one of four treatment arms, with one of these arms supporting the licensed dose for STRIDE. ^{9, 29}	Aligns with NICE final scope
Comparator(s)	• Atezolizumab + bevacizumab • Lenvatinib • Sorafenib	• Atezolizumab + bevacizumab • Lenvatinib • Sorafenib	The comparators considered within this submission align with current UK clinical practice for the treatment of patients with advanced or	The company's comparators are narrower than NICE's final scope. The EAG agrees with the company that BSC is complementary treatment and

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• SIRT including SIR-Spheres and TheraSphere • QuerumSphere (subject to ongoing NICE evaluation at the time the final scope was published) • BSC		unresectable HCC who are ineligible for locoregional therapy.¹⁶ The selection of these comparators was validated through interviews with HCC specialists based in the UK (AstraZeneca Data on File. HIMALAYA Clinician Validation Interviews, supplied in the CS reference pack) • In line with BSG guidelines and clinical expert opinion, atezolizumab + bevacizumab is considered the SoC in first-line NHS clinical practice based on its superior efficacy to sorafenib and lenvatinib.¹⁶ Therefore, it represents the primary comparator within this evaluation. • When individuals are contraindicated to atezolizumab + bevacizumab or would prefer to receive an oral treatment instead of IV therapy, lenvatinib, and sorafenib are the recommended alternative first-line options as per the BSG guidelines.^{10, 14, 16, 24}	should not be considered the main comparator. Locoregional therapy is typically administered before systemic therapy, whereas the HIMALAYA trial included patients who were ineligible for locoregional therapy.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			•Although SIRT is included in the NICE final scope, it is not a relevant comparator in this evaluation. As described above, the patient population relevant to this submission consists of individuals who are not candidates for locoregional therapy. This may be because of their tumour burden, level of liver function, and/or vascular invasion, among other factors.¹⁶ Since SIRT falls under the category of locoregional therapies, it may not be used in the patient population of interest to this evaluation, rendering SIRT an irrelevant comparator. Recent interviews with clinicians confirmed that only individual's ineligible for SIRT will be considered for STRIDE, further emphasising that SIRT is not a relevant comparator (AstraZeneca Data on File. HIMALAYA Clinician Validation Interviews, supplied in the CS reference pack) •With regards to BSC, patients with advanced or	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			unresectable HCC should be referred to palliative care services alongside their active cancer treatment. Therefore, palliative care should be administered alongside systemic treatment rather than considered as a comparator.¹⁶ Patients who receive BSC alone would only do so because they are ineligible for active therapy, and therefore standalone BSC is not considered a relevant comparator.	
Outcomes	The outcome measures considered: • OS • PFS • TTP • Response rates • AEs • HRQoL	The outcome measures considered: • OS • PFS • TTP • Response rates, specifically ORR, DoR and DCR • AEs • HRQoL, including EORTC QLQ-C30, EORTC QLQ-HCC18 and EQ-5D-5L	In line with the NICE final scope	Aligns with NICE final scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Subgroups	No subgroup analyses were recommended in the NICE scope.	Clinical efficacy subgroup analyses have been presented in CS Document B, section B.2.7, to demonstrate the efficacy of STRIDE across HCC aetiologies, ECOG PS, and the presence of MVI, among other patient characteristics.	In line with the NICE final scope	The company's subgroups are broader than NICE final scope. The EAG agrees with the company's approach conducting subgroup analyses.
Special considerations including issues related to equity or equality	N/A	N/A	N/A	N/A
AE, adverse event; BSC, best supportive care; DCR, disease control rate; EAG, evidence assessment group; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; MVI, Macrovascular invasion; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; STRIDE, single tremelimumab regular interval durvalumab; TTP, time-to-progression				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS presents a systematic literature review (SLR) of clinical trials on patients with advanced or unresectable HCC. The scope of the SLR has evolved over time.

3.1.1 Searches

The bibliographic searches were conducted at three different times, with initial searches missing some key terms, potentially overlooking earlier studies. Subsequent updates improved the comprehensiveness and sensitivity of the searches by including a broader range of terms. All searches were restricted to the English language and specific study types. Additional searches included clinical trial registries and conference abstracts, though details on some methods were limited. No searches of health technology assessment (HTA) sources were reported. Supplementary bibliography searches were conducted to address some of the initial search limitations but concerns about the overall sensitivity of the searches remain. For a detailed critique of bibliographic searches, please refer to Appendix 9.1.

3.1.2 Systematic literature review methods

A summary of the EAG critique for each step of the SLR and cross-references to the relevant section in the CS is presented in Table 9.

The full EAG assessment using the modified ROBIS³⁰ can be found in the Appendix 9.2. Overall, the EAG found the risk of bias in the company's SLR to be of high concern.

Table 9: Summary of the EAG's critique of company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS Appendix D, Table 14	High concern
Searches and selection of studies	CS Appendix D, Sections D.1.1-D1.2 and D.1.3 CS Document B, section B.2.9	Unclear concern
Data extraction and risk of bias assessment	CS Appendix D, Sections D.1.3, D.1.5, D.1.6, D.1.7	Low risk of bias
Evidence synthesis	CS Document B, section B.2.9	High concern

	CS Appendix D, Sections D.1.5-D.1.10 and D.3	

The EAG conducted a quality appraisal of the company's SLR using the ROBIS tool.³⁰ The review's objectives were clearly defined but evolved over time. The pre-defined eligibility criteria were broader than the NICE final scope, and later have been adjusted to better align with NICE's requirements. These criteria were used to select studies for a network meta-analysis (NMA), focusing on overall survival (OS) and progression-free survival (PFS), while other outcomes such as objective response rates (ORR), tolerability, or safety were not reported.

The eligibility criteria were unclear. The company's inclusion/exclusion criteria for the NMA lacked detail and proper justification, making it difficult to determine the appropriateness of excluded studies.

The bibliography searches for SLRs and NMAs were incomplete. The original SLR searches missed important synonyms for hepatocellular carcinoma, potentially overlooking relevant studies. Although updated searches improved term variety, they still excluded terms for SLRs and NMAs, potentially missing some relevant studies useful for reference checking. Database searches covered the period from 2016 to April 2024.

Study characteristics and results were adequately reported. The RoB assessment used by the company was the NICE STA template, also reported in the guidance by the Centre for Reviews and Dissemination (CRD) at the University of York.³¹ The EAG has asked the company to clarify (A14) the RoB tool that has been used. The company responded that it was Cochrane RoB2. The company's claim doesn't align with the statement in the CS, section D.1.3, Appendix D.

The company's unclear inclusion/exclusion criteria for the NMA led to limited data, resulting in wide confidence intervals and no statistically significant OS comparisons. The synthesis used only three studies with two interventions each, neglecting additional evidence and resulting in imprecise outputs unsuitable for extrapolation. The EAG noted the lack of steps to address heterogeneity, the absence of funnel plots, limited sensitivity analyses, and low precision in NMA results. Bias was not incorporated, and methodological inadequacies were present.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Overview of key points in the EAG's critique of key trial - HIMALAYA

Design

The HIMALAYA trial was a phase III, open-label, multicentre, RCT sponsored by AstraZeneca. The 181 sites were distributed globally across 170 centres with patients enrolled from North America, South America, Asia and Europe. There were no sites in the UK and no patients from the UK, and consequently, the generalisability of findings from HIMALAYA to the UK HCC population is questionable.

Intervention

Patients were randomised 1:1:1:1 to one of four treatment arms:

- A. Orally administered Sorafenib (400 mg twice daily),
- B. IV administered durvalumab (1,500 mg every four weeks)
- C. IV administered a combination of a single dose of tremelimumab (300 mg) plus IV durvalumab (1,500 mg every four weeks); a treatment regimen labelled STRIDE.
- D. IV administered combination therapy of tremelimumab (75 mg) every four weeks for four doses plus IV durvalumab at 1,500 mg every four weeks; a treatment labelled T75+D

The T75+D treatment arm was discontinued early (with 153 patients randomised) because an interim analysis indicated a lack of efficacy versus durvalumab alone. The EAG is unsure if these patients subsequently received second-line therapy (e.g. oral sorafenib or IV atezolizumab + bevacizumab) or became eligible for reallocation of treatment within HIMALAYA, although the former seems more likely. The company submission does not present data for the durvalumab only arm or interim results for the T75D arm.

Population

The company states that the trial is representative of the UK population with advanced or unresectable HCC, supported by a multicentre audit of 361 patients across 11 UK centres.³²

The EAG think the recruited population in HIMALAYA was unlikely to reflect the generality of UK HCC patients in several respects:

- A. Ethnicity (proportion of Asian, Japanese and Chinese patients);
- B. Age at diagnosis (HIMALAYA recruited some adults diagnosed with HCC at age ≥ 18 years whereas guidelines from the British Society of Gastroenterology¹⁶ (see Figure 1) indicate that diagnosis in the UK at age < 30 years is very rare; median age at diagnosis in HIMALAYA is lower than in the UK);

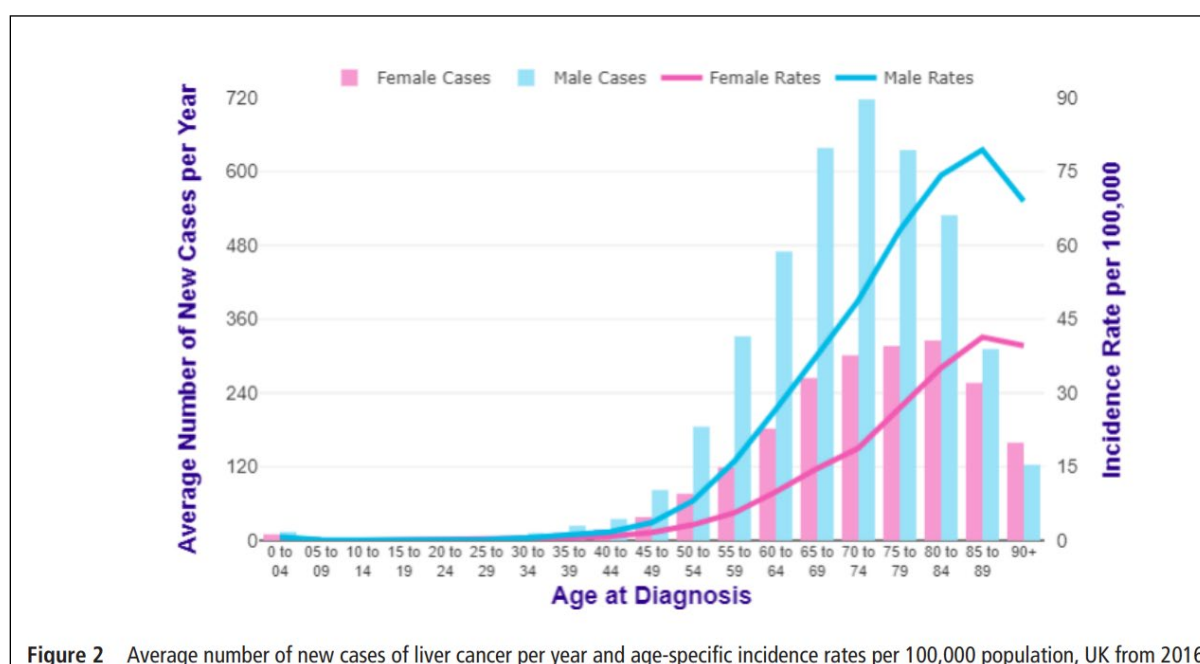


Figure 1: Incidence of liver cancer, by age and sex in the UK

The EAG's clinical advisor concurred with this EAG assessment.

C. Gender imbalance

HCC is more common amongst men than women. Gender dimorphism of the liver may render males more susceptible to develop HCC.³³

HIMALAYA was weighted heavily with male participants, the ratio men to women was 5.66:1. UK HCC incidence per 100,000 people reported by Cancer Research

UK was 6.2 for women and 14.3 for men, equating to 30.5% female,¹⁶ a ratio of 2.28:1, less than half that in HIMALAYA. This gender imbalance between UK and HIMALAYA populations may limit the generalisability of HIMALAYA findings to the UK clinical setting.

Sexual dimorphism of the liver and gender dependent immunological differences infer it is feasible that gender differences in response to HCC treatments may exist. Since HIMALAYA is more heavily weighted with men relative to women than the UK HCC population, gender differences in response would skew outcomes in HIMALAYA relative to those expected in the UK clinical setting.

The company's exploratory subgroup analysis of overall survival suggests that, in contrast to men, in women sorafenib and STRIDE are equally effective. This analysis is severely underpowered because of low recruitment of women. Balcar et al., 2024³⁴ used five Phase III "landmark" RCTs in random effects meta-analysis to investigate possible gender differences in overall survival response to first line treatments; they reported pooled estimates suggestive of marginally better response in men (HR 0.79; 0.73, 0.86 || versus HR 0.85; 0.7, 1.03). In all included RCTs women were under-represented; lack of gender data resulted in exclusion of most RCTs.

Balcar et al., 2024³⁴ also reported results from a retrospective real-world analysis of overall survival after atezolizumab + bevacizumab; patients from North America, Europe and Asia were included. The study lacked a control arm, the results suggest no gender difference in response. Real world studies for other interventions are lacking.

In Summary, gender differences in response to first line treatments are feasible. As such the imbalance in gender ratio in HIMALAYA relative to the UK setting would skew outcome estimates. Evidence for differing gender response is weak because trials heavily weight recruitment toward males so that response estimates for women are very uncertain.

D. ECOG PS

In the UK audit the company provided, patients with the ECOG PS ≥ 1 are above 79% while in the HIMALAYA trial only has 37% in both arms. HIMALAYA may not have included any participants with ECOG PS ≥ 1 .

E. Body mass index (BMI)

Only 14.2% and 12.3% of STRIDE and sorafenib recipients respectively in HIMALAYA have BMI above 30, while our clinical advisors said that most patients have BMI above 30. This seems relevant to the fitness of patients and their response to treatments.

F. Demographic profile: inclusion and exclusion criteria exercised during recruitment result in a demographically narrower population than in the UK.

The EAG notes that a recent real-world study of UK HCC that included 2160 patients suggests that more than half of the patients receive no specific cancer therapy.³⁵

Randomisation and allocation of treatment

Randomisation was not completely random. Patients were stratified using three demographic factors deemed important influencers of outcome and randomisation used a block system to guard against imbalance in the number of patients recruited to each trial arm. Randomisation was implemented using an Interactive Web Response System (IWRS); allocation of treatment was determined by IWRS and communicated to the centres that recruited patients. EAG assume that investigators then correctly allocated treatment; according to company data on file, only a limited number of patients received the wrong treatment.

Concealment of allocation

HIMALAYA was an open-label trial and as such no attempt was made to conceal treatment received by patients from either patients or the treatment team. Many decisions taken by the treatment teams and/or by patients, such as whether progression has occurred, whether treatment should continue or stop, and responses by patients to questions for patient-reported outcomes will potentially be influenced by knowledge of the treatment received. The EAG considers that this introduces a definite risk of bias in outcome results from the trial including any patient-reported outcomes about quality of life.

Comparators

Discounting the discontinued T75+D arm, HIMALAYA encompassed three interventions, two of which, sorafenib and durvalumab, were available for comparison with the STRIDE regimen. The company only reported on STRIDE

versus sorafenib. The EAG consider one remit of the submission to be the estimation of the clinical effectiveness of STRIDE versus alternative first-line treatments. In this respect, EAG would welcome data for durvalumab at the latest cut-off (DCO March 1st 2024). EAG recognise that durvalumab may not be a UK-approved first-line intervention for HCC, but thinks it reflects a decision by the company not to pursue that option with licensing authorities. The EAG notes that published meta-analyses and network meta-analyses aimed at comparing first-line treatments for HCC include durvalumab as a first-line option; in EAG's opinion, the company's handling of comparators reflects an over-narrow interpretation of the submission's remit.

Outcomes

The company specified that the key outcome was overall survival, and this was identified as the “primary objective” of the trial. The company's first submission (dated 13th August 2024) presented a CIC analysis of overall survival using the latest cutoff (March 1, 2024) encompassing 6 years (approximately 72 months) maximum follow-up. In a follow-up submission (dated 30th September 2024) the same data was presented but no longer CIC (referenced as Rimassa et al., 2024 ESMO Barcelona 2024). Both submissions lacked analysis of durvalumab, considered by EAG to be an omission of data.

Five key secondary outcomes were identified. Two of these, progression-free survival (PFS) and time to discontinuation of treatment (TTD) are used in the company's economic analysis.

The EAG notes that the company presented a PFS analysis derived from an earlier cut-off (i.e., 27th August 2021 with a maximum follow-up of approximately 42 months) than that was used for overall survival. The EAG are unclear on the reason for using early data cut-off and considers this a potential omission of relevant data. No PFS data for durvalumab was presented. The public domain (Sangro et al., 2024)²² has OS data from a later cutoff (23 January 2023) than 27th August 2021 but PFS analysis was not presented. The EAG are unclear why no PFS analysis appears to have been undertaken after the cut-off of January 2021 but think it may relate to multiple testing strategies for the trial. The company stated that their clinical experts highlighted that the measurement of PFS is challenging as radiologic progression is a subjective measurement prone to reading errors and that they noted

that patients are frequently eligible to continue treatment both within the trial setting and real-world setting even after disease progression. These statements bring into question the reliability of estimates of this outcome, and since economic modelling PFS is used as a proxy for TTD this also brings into question results for TTD.

3.2.2 HIMALAYA trial design

The EAG's summary of the key features of HIMALAYA, based on the company's submitted information, is summarised in Table 10.

Table 10: EAG Summary of HIMALAYA design

Method step	Summary of the approach used
Method of randomisation	Randomisation to 4 treatment arms in a 1:1:1:1 ratio using IWRS, stratified by MVI (Yes or No), aetiology of liver disease (HBV vs. HCV vs. others), and ECOG performance status (0 or 1)
Eligibility criteria	Patients with histologically confirmed HCC, aged ≥ 18 years, weighing >30 kg, and ineligible for locoregional therapy. They had BCLC stage B or C, Child-Pugh class A, ECOG-PS of 0 or 1, and adequate organ and bone marrow function were included. Patients with unresolved toxicity, concurrent cancer therapy, recent major surgery, active GI bleeding, uncontrolled hypertension, confirmed coinfection with both HBV and HCV, and pregnant lactating were excluded.
First-line treatment regimens	1] STRIDE. 2] Sorafenib 3] Durvalumab 4] TD75+D
Measured outcomes	Primary: OS Secondary: OS at 18, 24, and 36 months; PFS, TTP, ORR, DCR, DoR, Secondary and exploratory PRO: EORTC QLQ-C30, EORTC QLQ-HCC18, EQ-5D-5L Safety: AEs
Statistical analysis	Analyses using a stratified log-rank test, adjusting for liver disease aetiology, ECOG PS, and MVI. The effect of STRIDE versus sorafenib was estimated with a stratified Cox proportional hazards model, and Kaplan-Meier plots were used to visualize survival times. The efficacy analysis included all randomized patients (ITT population), while the safety analysis included all patients who received at least one treatment dose.

The HIMALAYA trial design was presented in CS 3 (CS Document B, section B.2.3.2). Of 1,324 patients recruited to four separate arms 153 were allocated the TD75+D regimen, 393 the STRIDE, 389 sorafenib, and 389 durvalumab.

The T75+D treatment arm was closed due to insufficient clinical activity,^{22, 36} The final patient distribution was STRIDE (393), sorafenib (389), durvalumab monotherapy (389), and T75+D (153). The T75+D and durvalumab monotherapy results were not reported as they were deemed irrelevant to the submission. The company's analyses were restricted to STRIDE and sorafenib arms.

The reasoning behind the chosen dose regimens is detailed in the trial protocol informed by data based on pharmacokinetic and pharmacodynamic studies of prior trials (Study D4190C00006) (see AstraZeneca. Data on File: HIMALAYA Clinical Study Protocol (CSP) (2019), supplied in the CS reference pack).³⁷

The CS Document B, section B.2.3.2, outlines the stratification factors for randomisation: macrovascular invasion (MVI), aetiology of liver disease (HBV vs. HCV vs. others), and Eastern Cooperative Oncology Group (ECOG) performance status (PS).³⁸⁻⁴⁰ The rationale is detailed in the study protocol, only these three factors were chosen from the variety of prognostic factors of potential importance. Geographic region was excluded as a stratification factor.

Table 11 presents the EAGs summary of the company's stated key endpoints for HIMALAYA based on submitted information.

Table 11: EAG summary of key endpoints of HIMALAYA

Objectives	Endpoint Description	Assessment	Chosen assessment time points
Primary	OS efficacy of STRIDE vs. sorafenib	IPD from maximum of 72 months follow-up*.	18, 24, 36, 48, 72 months
Secondary: Efficacy	To assess the efficacy of STRIDE vs. sorafenib: PFS, TTP, ORR, DCR, and DoR	IPD by investigator assessment PFS*, TTP* ORR, DCR, and DoR according to RECIST 1.1 by Investigator assessment	Every 8 weeks (± 1 week), for the first 48 weeks from randomization, and then every 12 weeks (± 1 week). Then until confirmed PD
Secondary: PROs	To assess disease-related symptoms, impacts, and HRQoL in STRIDE vs. sorafenib: Time to deterioration in global health status /QoL, functioning (physical), multi-term symptom (fatigue), single-item symptoms (appetite loss, nausea)	Questionnaire-assessed using the EORTC QLQ-C30 and EORTC QLQ-HCC18*	Every 8 weeks (± 7 days), relative to Cycle 1 Dose 1 date) for the first 48 weeks then every 12 weeks (± 7 days), thereafter until treatment discontinuation.
Key exploratory: PROs	To assess physician-reported patient outcomes in STRIDE vs. sorafenib: EQ-5D-5L	EQ-5D-5L were collected in the trial and were cross-walked to the EQ-5D-3L for the economic model, following NICE's recommendation and Hernández-Alava et al.'s ⁴¹ methods	Every 8 weeks (± 7 days), relative to Cycle 1 Dose 1 date) for the first 48 weeks And then every 12 weeks (± 7 days) thereafter until treatment discontinuation.
Safety	To assess the safety and tolerability profile of STRIDE vs.	Endpoint variables include categories of AEs, most frequently reported AEs, serious AEs, fatal AEs, AEs	At all visits (Visits continue every 4 weeks)

Objectives	Endpoint Description	Assessment	Chosen assessment time points
	sorafenib AEs and laboratory findings	leading to discontinuation of study treatment (TTD), other AEs, AEs of special interest, and immune-related AEs (irAE)	
* Used by the company's economic analyses			

3.2.3 Patient characteristics

The baseline characteristics of the HIMALAYA trial, detailed in CS Document B, section B.2.4, show balanced treatment arms regarding demographics and general characteristics. The company states that the trial is representative of the UK population with advanced or unresectable HCC, supported by a multicentre audit of 361 patients across 11 UK centres.³²

The EAG notes that the submission's UK audit and the HIMALAYA trial have several key differences. HIMALAYA includes younger patients and more people with HBV and HCV. The audit also shows that UK patients have a more severe disease status profile. The audit lacks data on ethnicity, BCLC stage, and other factors. These differences threaten the validity of applying the trial results to the UK population.

Baseline characteristics for HIMALAYA trial and as found in the UK audit are presented in Table 12.

Table 12: Key baseline characteristics reported in HIMALAYA and the UK audit as the representative of the UK population in the CS

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

Parameter	HIMALAYA trial		UK audit (n=361)
	STRIDE (n=393)	Sorafenib (n=389)	
Nonviral	161 (41.0)	166 (42.7)	196 (54)
Unknown	NR	NR	18 (5)
BMI group (kg/m2), n (%)			
<18.5	■	■	NR
≥18.5 - <25.0	■	■	NR
≥25.0 - <30	■	■	NR
≥30.0	■	■	NR
BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reported			

3.2.3.1 Key differences in patient characteristics between the HIMALAYA trial and the UK audit

In the UK, nearly 43% of new HCC cases are diagnosed in individuals aged 75 and over. The HIMALAYA trial population is younger, with a median age of 65.

The audit includes PS 0 (21%), PS 1 (62%), and PS 2 (17%), while the HIMALAYA consists of only PS 0 and PS 1, with about 62% in PS 0.³² These differences highlight the lack of comparability between the audit and RCT.

The UK audit lacks baseline data on

■, and PD-L1, so it was not possible to compare these factors with the HIMALAYA trial. Additionally, the UK audit³² does not capture the BCLC staging system. In terms of these specific factors, it is not possible to draw firm conclusions about the generalisability of the HIMALAYA trial to the UK population reflected by the audit data.

The EAG's clinical expert noted that the HIMALAYA trial population is unlikely to fully represent the UK. Regional variations in the UK include older, predominantly white, overweight (BMI >30), and a lower prevalence of viral aetiology. Based on some studies found by the EAG, almost 55% of the UK population with HCC are over 69 years old.

■.⁴²⁻⁴⁴ The population enrolled in the HIMALAYA study differs from the UK audit population in a number of characteristics including age, ■, and aetiologies. The audit encompassed only 361 patients.

3.2.4 Risk of bias in HIMALAYA

In CS Document B Table 10, the company provided a summary of its view of the quality of the HIMALAYA trial. The company stated that *“the trial may be considered at low risk of bias”*. However, two entries in Table 10 contradict this: [a] *“no details were provided about allocation concealment”*; [b] *“high risk”* of bias because the trial was open-label and investigator assessed.

The EAG agrees with the entries in CS Document B Table 10 and consequently considers HIMALAYA at substantial risk of bias.

The EAG independently assessed the HIMALAYA trial using Cochrane RoB version 2, available in Appendix 9.3.

Although the baseline characteristics (section 3.2.3) do not show significant imbalances between STRIDE and sorafenib, and the cumulative impact of several key prognostic factors in favour of STRIDE, raises concerns that stratification may not have identified the most appropriate factors for randomisation to avoid bias. Bias due to HIMALAYA's open-label unblinded design presents an appreciable risk of bias, particularly for patient-reported outcomes and from unblinded assessors of progression, time-to-discontinuation of treatment and overall response rate (ORR). The blinded independent central review (BICR) evaluated the exploratory analysis and outcomes, but no data or further information on BICR was reported in the company submission. Therefore, the extent and direction of bias between investigator assessment and BICR assessment cannot be determined. ITT analysis was used and there was no risk of bias from missing data.

The EAG requested the tabulation of all safety and adverse event data for the 5-year data cut-off (DCO) and beyond. In response, the company presented an overview of serious TRAEs and AEs that were not treatment-related from the updated analysis II (1st March 2024). However, no further information on delayed treatment events after five years or beyond was provided. The EAG finds the overview with general results and frequencies inadequate and insufficient. Concerns about long-term TRAEs remain.

In conclusion, the EAG considers the HIMALAYA trial to have an appreciable risk of bias.

3.2.5 Clinical effectiveness results of the HIMALAYA trial

3.2.5.1 Primary outcome (overall survival; OS)

CS Document B, Figure 4 provided the OS Kaplan-Meier results to the maximum follow-up of 60 months; median survival was 16.43 months and 13.77 months respectively for STRIDE and sorafenib.

Median overall survival results are also reported in the main publication of the trial by Abou-Alfa et al³⁶ as 16.43 months (95% confidence interval [CI], 14.16 to 19.58) for STRIDE, and 13.77 months (95% CI, 12.25 to 16.13) for sorafenib.

The CS reports percentage survival for each arm at 18, 24, 36, 48, and 60 months: at 18 months, 24 months and 36 months stating that OS rate ratios for STRIDE compared to sorafenib are 1.17, 1.24, and 1.54 respectively. Survival rates for STRIDE and sorafenib respectively were reported by Abou-Alfa et al³⁶ as 48.7% (95%CI, 43.6, 53.5) and 41.5% (95%CI, 36.5, 46.4) at 18 months, 40.5% (95%CI, 35.6, 45.3) and 32.6% (95%CI, 27.9, 37.4) at 24 months, and 30.7% (95%CI, 25.8, 35.7) and 20.2% (95%CI, 15.8, 25.1) at 36 months, respectively, demonstrating a statistically significant survival benefit for STRIDE versus sorafenib at 36 months.

Irrespective of maximum follow-up the tail of the OS STRIDE plot exhibited many censorings but few events.

3.2.5.2 Secondary outcomes

The CS and Abou-Alfa et al.³⁶ reported on five secondary endpoints: PFS, TTP, ORR, DoR, and DCR.

3.2.5.2.1 Progression-free survival (PFS)

CS Document B Figure 6 showed the Kaplan-Meier plot for PFS at maximum follow-up of approximately 42 months based on Abou-Alfa et al.³⁶ The median PFS for STRIDE was 3.78 (95%CI:3.68, 5.32) months and for sorafenib was 4.07 (95%CI: 3.75, 5.49) months with hazard ratio reported as 0.90 (95%CI:0.77, 1.05) for STRIDE versus sorafenib.

3.2.5.2.2 Time-to-progression (TTP)

CS Figure 7 provided a Kaplan-Meier plot for time to progression (CS Document B, section B.2.6.2.2). Median TTP was similar for each arm.

3.2.5.2.3 Response rates (ORR, CR, DOR, DCR)

CS Document B, section B.2.6.2.3 reports response rates classified into four levels: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

The objective response rate (ORR), assessed by the investigator using RECIST 1.1 criteria, was significantly higher in the STRIDE treatment arm (20.1%) compared to the sorafenib arm (5.1%), with an odds ratio (OR) of 4.69 suggesting patients given STRIDE were approximately 4.69 times more likely to respond than those given sorafenib treatment (<0.0001).

Abou-Alfa et al.³⁶ report that the proportion of patients remaining in response at 12 months was 65.8% for STRIDE and 63.2% for sorafenib.

CR was observed in 3.1% of patients (12 out of 393) in the STRIDE treatment arm and none in the sorafenib treatment arm.

The company suggests that achieving a CR is strongly associated with longer OS in patients although this is achieved by a relatively small proportion of patients, an interpretation reported in a systematic review and meta-analysis ($R^2 = 0.905$).⁴⁵

At the final data cut-off, the STRIDE arm had a median duration of response (DoR) of 22.3 months compared to 18.4 months for sorafenib, with the STRIDE arm showing a quicker median time to onset of response. However, the low numbers of responders introduce uncertainty in these median estimates.

3.2.5.3 Patient-reported Outcomes (PRO)

The HIMALAYA trial included several Patient-Reported Outcome (PRO) tools, such as EORTC QLQ-C30, EORTC QLQ-HCC18, EQ-5D-5L, PRO-CTCAE, and Patient global impression change (PGIC).

The EORTC instruments aimed to assess disease-related symptoms and quality of life, with STRIDE showing higher physical functioning but lower global health status scores than sorafenib. STRIDE resulted in a longer median time to deterioration in most PRO measures, except jaundice. The EQ-5D-5L, used to determine health state utility values, was detailed in the trial protocol but not extensively covered in the CS Document. Mean EQ-5D-5L and EQ-VAS scores by treatment status taken from the CS are summarised by the EAG (Table 13 and Table 14).

Table 13: Mean EQ-5D-5L scores by treatment status in HIMALAYA (primary analysis; Full analysis set (FAS)) (DCO: 27th August 2021)

[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Table 14: Mean EQ-VAS scores by treatment status in HIMALAYA (primary analysis; FAS) (DCO: 27th August 2021)

[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

The company provided data on the proportion of patients with moderate to extreme problems before and after treatment in Figure 12 (CS Document B), based on the DCO of August 27, 2021. The EAG has extracted this data and presented it in Table 15.

Table 15: The proportion of patients in HIMALAYA with moderate to extreme problems before (on-treatment) and after treatment discontinuation (off-treatment)

[REDACTED]	[REDACTED]			
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Because of the open-label design of HIMALAYA, the EAG considers these outcome results to be at serious risk of bias.

3.2.6 Subgroup analysis

The company's subgroup analysis compared the OS benefit of STRIDE versus sorafenib across various clinical and demographic subgroups (CS Document B, section B.2.7). The company suggest that the OS benefit of STRIDE was generally consistent across most subgroups. In response to clarification request from EAG, the company affirmed that the subgroup analysis was not powered for formal comparisons, and no multiplicity adjustments were made. The EAG's clinical expert confirmed that the HIMALAYA trial was not powered for subgroup analyses.

3.2.7 Adverse effects

The company concluded (CS Document B, section B.2.10) that in the HIMALAYA trial, the STRIDE regimen exhibited a favourable safety profile. The EAG discusses some uncertainties in the interpretation of adverse events findings below.

3.2.7.1 Dose interruptions, reductions and discontinuations

The CS Document B, section B.2.10.2 reports that dose delays and infusion interruptions caused dose interruptions in the HIMALAYA. In CS document B, section B.2.10.2, the company states that durvalumab-related dose delays in the STRIDE treatment affected [REDACTED]. In CS document B, section B.2.10.3, the company reports that [REDACTED] discontinuations due to any adverse event leading to the discontinuation of the study treatment. The company only considers [REDACTED] of these cases as possibly related to treatment, which the EAG finds not justified. The reported proportions are calculated and captured by investigators who were not blinded, making the results prone to bias. Therefore, the EAG cannot fully agree that all of these AEs leading to discontinuation are possibly treatment-related.

3.2.7.2 Treatment-related adverse events

In Table 28 of CS Document B, section B.2.10.3, the company summarises treatment-related adverse effects (TRAEs) for the HIMALAYA trial, categorising them as “TRAEs of any cause” and “TRAEs”. The EAG requested definitions and lists of AEs in these categories for clarification (A7). The company provided a brief explanation of how AEs were interpreted by the investigators, however, details anticipated by the EAG were not provided.

The CS reports that patients in the STRIDE arm suffered a higher incidence of adverse events in both categories of TRAE compared to sorafenib, although the Abou-Alfa et al paper³⁶ based on much shorter maximum follow-up reported that Grade 3/4 treatment-emergent adverse events occurred for 50.5% of patients with STRIDE, and 52.4% with sorafenib. Relative to sorafenib, STRIDE exhibited higher rates of serious TRAEs, immune-mediated TRAEs requiring high-dose steroids, and grade 3 or 4 immune-mediated TRAEs, raising the EAG’s concerns. Immune-mediated TRAEs leading to death were observed in STRIDE but not in sorafenib. STRIDE also had a higher incidence of grade 3 or 4 hepatic TRAEs.

High rates of both treatment-related and non-treatment-related AEs for both STRIDE and sorafenib are illustrated in CS Document B Figure 19. The EAG sought clarification on non-treatment-related AEs, which was provided. However, Table 20, Appendix I of the clarification responses, lacks results for common non-treatment-related serious adverse events (SAEs) from the HIMALAYA trial.

Notwithstanding, the reported AE results for durvalumab, tremelimumab, and sorafenib, coupled with their severity, raise the EAG's concerns about the safety profile of STRIDE.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. The company reported serious TRAEs and non-treatment-related AEs after five years (Clarification responses A15, Figure 1), showing an increase in non-treatment-related SAEs in both STRIDE and sorafenib. The EAG's concerns about STRIDE's safety persist.

Figure 20 of CS Document B details the time to onset of common TRAEs.

Immunotherapy treatments, including those in the STRIDE regimen, can cause irAEs, potentially leading to autoimmune diseases even years after treatment. The EAG is concerned about chronic or unresolved irAEs and requested clarification (A8). The company claimed all irAEs are manageable. The EAG also requested the latest adverse event data due to long-term risk concerns. The company's response to A15 indicates that irAEs from STRIDE can occur anytime, mainly within the first 3 months, but does not address long-term TRAE and irAE concerns. The company has only reported serious AE after 4 years in the CS, appendix F, table 32. While most irAEs manifest during or shortly after treatment, some autoimmune complications, such as colitis, hepatitis, pneumonitis, and endocrine disorders, may arise a year or more later.

Therefore, patients treated with immune checkpoint inhibitors may develop autoimmune conditions even after five years post-treatment.

The EAG evaluations indicate that immunotherapy treatments, particularly immune checkpoint inhibitors like nivolumab (Opdivo) and pembrolizumab (Keytruda) (like durvalumab and tremelimumab), can cause irAEs, potentially leading to autoimmune

diseases even years after treatment.⁴⁶⁻⁵⁶ These irAEs occur due to the enhanced immune system activity, which can sometimes attack healthy cells. While most irAEs manifest during or shortly after treatment, some autoimmune complications, such as colitis, hepatitis, pneumonitis, and endocrine disorders, may arise a year or more later. The STRIDE regimen, combining tremelimumab (anti-CTLA-4) with durvalumab (anti-PD-L1) for unresectable HCC, also carries this risk. Therefore, patients treated with immune checkpoint inhibitors may develop autoimmune conditions even five years post-treatment.^{46-53, 56-58}

3.2.7.3 Haemorrhagic events

For the haemorrhage-related TRAEs (CS Document B, Table 29), sorafenib showed

[REDACTED]

[REDACTED] No other haemorrhagic events were reported. Additionally, there were no treatment-related deaths due to haemorrhage-related AEs in the STRIDE arm.

3.2.7.4 Hepatic events

Based on the CS B.2.10.3.3, Tables 30 and 31, the hepatic AEs and hepatic treatment-related AEs, as captured by hepatic Standardised MedDRA queries (SMQs), were comparable between STRIDE and sorafenib. In HIMALAYA (clarification response A5), hepatic AEs were defined as any worsening of Common Terminology Criteria for Adverse Events (CTCAE) grades from the start of treatment until 90 days after the last dose or until the initiation of subsequent therapy (see HIMALAYA Clinical Study Protocol (2019) supplied in the CS reference pack).^{59, 60} Consequently, irAEs occurring beyond this period or overlapping with subsequent treatments were not captured.^{61, 62} The company asserts that these hepatic AEs were tolerable for STRIDE. The EAG notes that STRIDE has a higher overall incidence of hepatic AEs than sorafenib. Severe hepatic AEs (Grade ≥ 3) are more frequent for STRIDE than sorafenib (refer to the additional hepatic AEs in Table 1 and Table 19 based on the CTCAE grade in response to (clarification question A5). Overall, sorafenib demonstrates better tolerability regarding hepatic AEs, with lower percentages in most categories, particularly in severe cases and specific conditions like hepatitis.

3.2.8 Ongoing studies

The company asserts that there are currently no ongoing studies of relevance to this evaluation. The EAG searched and did not identify any further ongoing studies. In particular, the EAG investigated whether the company had discovered any further relevant studies or NMAs had been published.

3.2.8.1 Conclusion of the clinical effectiveness section

The HIMALAYA trial faced several limitations, particularly due to its strict eligibility criteria, which may affect the generalisability of its results to the UK population. The NICE final scope was broader and more representative of the UK's population compared to the company's narrower scope, making the NICE scope more relevant for the UK context. The HIMALAYA trial's criteria focus on cancer progression, favouring fitter and younger patients compared to the UK's population. However these approaches are standard in trials, the EAG raised concerns about the trial's participant characteristics and baseline differences compared to the UK audit, challenging the company's claim of generalisability. The EAG clinical advisor mentioned that oncologists may hesitate to treat older patients not represented in trials, but if these patients are fit and without significant comorbidities, they may still be considered for treatment as clinicians become more familiar over time with the regimen.

There are concerns about safety. Tolerability and TRAEs, associated with STRIDE, especially irAEs, which can be recurrent and life-threatening. Given the evolving nature of this field, patients on STRIDE need close monitoring. Adverse events have been tracked by the company only up to 90 days post-treatment or until subsequent therapy begins, which may not capture all irAEs or those overlapping with new treatments. The company's responses to the EAG's safety concerns were not adequate. However, the EAG's clinical expert commented that, given the poor prognosis of patients, the survival benefits of STRIDE outweigh the risks of long-term side effects.

While the STRIDE regimen improved overall survival compared to sorafenib, and most adverse events were tolerable and manageable, concerns remain about its generalisability to the UK population and long-term irAEs.

None of the graphics in CS Document B have associated 95%CIs or 95%CrIs. The Appendix Figures 15 and 17 show 95%CIs for reconstructed KM plots for PFS and OS in the REFLECT RCT of lenvatinib versus sorafenib, but this data does not appear to have been utilised in modelling.

The method used for modelling OS and PFS for STRIDE (using IPD from HIMALAYA possibly at different DCO for OS and PFS) is different to that used for comparators (atezolizumab + bevacizumab and lenvatinib) where NMA HRs associated with very substantial uncertainty are employed. There is a lack of equity in the handling of STRIDE versus atezolizumab + bevacizumab and lenvatinib.

The KM plot for TTD of STRIDE has an unusual trajectory that appears to be influenced by visit times. Using precise dates for discontinuation that should be available to the investigators would represent an improvement.

The company states that in the absence of TTD information for atezolizumab + bevacizumab and for lenvatinib, they have assumed that TTD for these is equivalent to the PFS the company developed. However, the PFS models (employing NMA output HRs) are associated with severe imprecision and in the case of atezolizumab + bevacizumab bears little resemblance to what is seen in the IMbrave150 trial used for NMA input. The EAG is unconvinced that the equivalence of TTD and PFS is a sensible assumption for modelling.

The EAG is not convinced that there is a complete lack of information about TTD for the comparators atezolizumab + bevacizumab and lenvatinib.

3.2.8.2 Summary of clinical effectiveness

- The HIMALAYA trial population is a doubtful match for the UK HCC population eligible for first-line treatment making generalisability of findings from the trial outcomes doubtful.
- The open-label design of HIMALAYA results in an appreciable risk of bias particularly applying to the mutual decisions between patients and investigators and the responses of patients to questionnaires regarding health-related quality of life (HRQoL).
- Decisions regarding progression and discontinuation of treatment were dependent on trial investigators rather than an independent body.

- The company states that establishing when progression has occurred is difficult and subject to error.
- Some issues regarding the long-term safety of STRIDE treatment remain unresolved and this is a limitation.

3.2.9 Company NMA and their sources of information

The submission itemises analyses of OS and PFS at several different cutoff dates. The relevant information is summarised in Table 16 using data in CS Appendix M Tables 55, 56, and CS Document B Table 11. CS Appendix D Table 20 provides references to studies included in the company's NMA. Several analyses report a 0.76 HR with various 95% CIs.³⁵ From information provided in the submission the EAG is unclear which HR and associated 95% CIs were used for the company's NMA and what justified this choice. The publication of Sangro et al., 2024²² appears to have the same cutoff date and number of events as provided in Appendix M Table 56, 23 January 2023 entry but they have differing point estimates of HR, although the 95% CIs (to 2 decimals) are identical. Appendix M Table 56 for the 23 January 2023 states '*Hazard ratio stratified by factors based upon the categories used in the randomisation system.*' The Sangro paper states '*OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology of liver disease (hepatitis B or C virus or other/nonviral), ECOG performance status (0 or 1), and macrovascular invasion (yes or no).*' This may explain the different HR estimates.

Table 16: Cutoff dates itemised in the submission

Date of cutoff <i>Date of publication</i>	STRIDE events/ Patients	Sorafenib events/ Patients	HR (95% CI)	STRIDE Median follow-up in all patients (95% CI) months	Sorafenib Median follow-up in all patients (95% CI) months
27 August 2021 * 2022	262 / 393	293 / 389	0.78 (0.65, 0.93)	33.18 (31.74, 34.53)	33.18 (31.74, 34.53)
23 January 2023 ** NR	291 / 393	316 / 389	0.76 (0.67, 0.92)	49.1 (47.0, 50.2)	47.3 (45.1, 49.2)
1 March 2024 *** 2024	309 / 393	332 / 389	0.76 (0.65, 0.89)	62.49 (59.47, 64.79)	59.86 (58.32, 61.54)
Publication specified as data source for the company NMA (Table 20 CS Appendix D; Reference number 4)					
Reference 97 of CS Document B: Sangro et al., 2024a Ann Oncol 35, 448 – 457.					
23 January 2023 ^	291 / 393	316 / 389	0.78 (0.67, 0.92)		

2024					

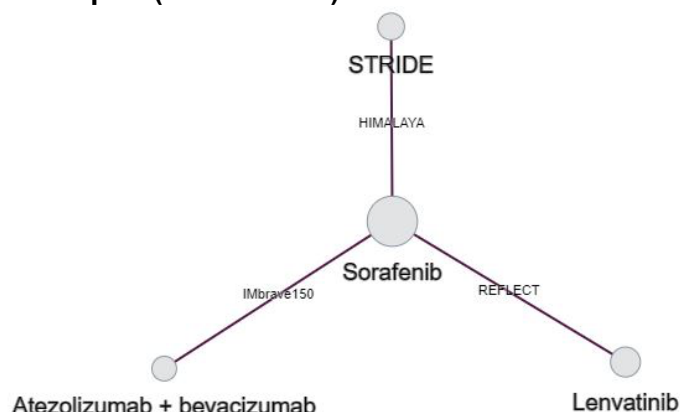
* Publication source *Abou-Alfa, G. et al. 2022b. (Figure 1A, pg6)*. ** Publication not specified. *** Source submission Document B. [^] Sangro et al., 2024a Ann Oncol 35, 448 – 457. NR not reported.

The EAG notes that the difference in events (patient deaths) between the 23 January cutoff for Sangro et al., and the latest cutoff (1 March 2024) is 18 for STRIDE and 16 for sorafenib and that this also influences the resulting HR.

3.2.9.1 NMA; the company's inclusion of evidence

The brief description of the inclusion criteria specifies that only Phase III RCTs were eligible for inclusion in the company's NMA.

The NMA diagram (see Figure 3) (CS Document B Figure 14) shows three different interventions were linked via sorafenib. Each of these three links used data from one study each (so three studies were included in the NMA in total).

Figure 2: Network plot (PFS and OS)

Footnotes: Node size indicates the number of patients receiving each intervention.

Abbreviations: OS: overall survival; PFS: progression-free survival.

Table 17: Summary of eligibility criteria for the NMA

Domain	Eligibility Criteria
Population	Advanced or unresectable HCC
Intervention/Comparator	Reporting on at least two interventions/comparators of interest: ^a • STRIDE • Atezolizumab + bevacizumab • Lenvatinib • Sorafenib Not including any combinations with other therapies
Outcomes	OS and/or PFS INV
Study design	Phase III RCTs

Footnotes: ^aStudies identified by the SLR were investigated to determine if additional evidence could be included in a network via a comparator not of interest, this was not possible, so the network only includes STRIDE, atezolizumab + bevacizumab and lenvatinib.

Abbreviations: HCC: hepatocellular carcinoma; INV: investigator-assessed; OS: overall survival; PFS: progression-free survival; RCTs: randomised control trials; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Figure 3: Network plot (OS and PFS) (obtained from CS Document B Figure 1 and Table 17)

The eligibility criteria for the NMA lacks detail. There appear to be no exclusion criteria other than that implied by: “*Not including any combinations with other therapies*”. Little justification for this restriction is offered. There is also no clear guidance on whether abstracts or conference proceedings of Phase III RCTs were or were not included.

The inclusion criteria specified by the company for its NMA do not indicate how published subgroup analysis studies for Phase III RCTs were to be handled (i.e., included or excluded).

The EAG found it difficult to interpret the footnote to CS Table 17 ‘*Studies identified by the SLR were investigated to determine if additional evidence could be included in*

a network via a comparator not of interest, this was not possible so the network only includes STRIDE, atezolizumab + bevacizumab and lenvatinib. With respect to this footnote the EAG notes:

- a. The literature searches for the company's original systematic literature review (SLR), which (along with the SLR updates) informed the NMA, were not specifically designed to identify studies for the NMA (they are missing terms for the intervention and important synonyms for hepatocellular carcinoma,
- b. The company did not perform a literature search to identify published NMA studies of first-line treatments for hepatocellular cancer,
- c. The company did not mention the existence of published NMA studies in which analyses of first line treatments were linked by their common use of sorafenib as a comparator.

The results from the company NMA were summarised in CS Document B Figures 15 and 16. Overall survival point estimates of HR (sorafenib versus comparator) indicate that all comparators were superior to sorafenib. The company noted that there were no statistical differences in pairwise results between comparators. This may be attributable to the limited data feeding into the NMA. The STA examining atezolizumab + bevacizumab versus sorafenib reported a statistically significant HR of 0.58 (95%CI: 0.42, 0.79)¹⁴ which seems considerably different to the inference of insignificance and HR of 0.66 from the company NMA. The wide CIs highlight the considerable imprecision associated with the NMA results.

Details of the company's NMA methodology were presented in Appendix D Tables 20, and 24 through to 27. Table 18 implies that the published data in Abou-Alfa et al., 2022 was used for HIMALAYA. This paper, however, reports an adjusted HR of 0.78 (95%CI: 0.65, 0.93) for overall survival of STRIDE versus sorafenib, whereas the HR estimate used in the NMA appears to be 0.76, derived from the latest cut-off analysis presented in CS Document B.

Table 18: (relevant information about studies used in the NMA) (Company Appendix Table 20)

Study	References used
HIMALAYA ³⁶	4. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM evidence 2022;1:EVIDo2100070

IMbrave150 ^{63, 64}	5. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. <i>New England Journal of Medicine</i> 2020;382:1894-1905. 6. Cheng A-L, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. <i>Journal of hepatology</i> 2022;76:862-873.
REFLECT ⁶⁵	7. 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. <i>The Lancet</i> 2018;391:1163-1173.

Footnote to Company's Appendix D Table 20: "eligibility criteria for each study were checked to confirm inclusion/exclusion on several tumour location considerations".

The HIMALAYA study Abou-Alfa 2022 (maximum follow-up 40 months) was specified as the relevant study (CS Appendix D Table 2), the HR input for OS appears to have come from a later cutoff analysis of HIMALAYA. Because the company's NMA diagram specifies selected interventions (i.e. only sorafenib and STRIDE) from HIMALAYA (CS Document B Figure 4) the date of cut-off used for data extraction remains unclear.

In the EAG's opinion, this statement conflates the distinction between studies and interventions and is confusing. Inclusion for the company's NMA appears to be based on "*studies*", but the resulting NMA analyses are based on the company's selection of *interventions* used in those studies. For example, for the HIMALAYA trial, data from the durvalumab arm were excluded from the NMA. The company's exclusion of durvalumab was based on the fact that it is unlicensed in the UK and on clinical advice that because of lack of license it was unused in UK clinical practice.

The available evidence from HIMALAYA is based exclusively on non-UK patients and the company's exploratory subgroup analysis of HIMALAYA suggests that the outcome depends on the geographical location of participants. However, the EAG notes that a recent study estimated that more than 50% of HCC cases in England receive no cancer-specific treatment at all.³⁵ Patient mix of treatments receivers and non-treatment receivers is unknown. In the HIMALAYA trial, virtually all participants receive treatment; so there is a much broader mismatch between the RCT and real-world treatment in the UK. (Please section 3.2.3)

Several recently published NMAs include much more data than the company's NMA. Consequently, most of these HR estimates have a narrower 95%CrI estimate.⁶⁶⁻⁷⁷ All except Celsa et al. and Leigh et al. reported HRs with CrIs.

The EAG suggests that the NMA should include all the available data from the included studies and that the results relevant to the economic model and decision problem should then be selected for input to the economic model. The NMA appears to ignore potentially relevant evidence and may have missed the purpose of the NMA, namely, to synthesise all evidence bearing on the performance of first-line interventions in studies for the defined population.

In agreement with the EAG for TA666, we consider that it is not unreasonable to conduct an NMA of HRs for the purpose of answering the question whether there is evidence of an average treatment effect ignoring any treatment-by-time interaction over the duration of the observed studies. However, using HRs from NMAs in the context of an economic evaluation is inappropriate in order to estimate population mean benefit.

The CS Document B lacks any mention of the potentially relevant published NMAs. The company did not specifically search for NMAs. The absence of any consideration of previous NMAs may overlook the existence of potentially important evidence. Given the number of published NMAs and the wider number of interventions they have included, the EAG considers this an omission. In conducting the NMA, the EAG suspect that the decision problem has been over-narrowly interpreted.

3.2.10 EAG's selection and use of published NMAs

Considering the limitations addressed in sections 3.1.2 and 3.2.8.1, and after further evaluations, the EAG decided to consider a substitute NMA instead of the company's. The EAG undertook a targeted search of the epistemonikos database (<https://www.epistemonikos.org/>) on 24/09/2024 to identify NMAs that included the intervention and comparators of interest. See Appendix 9.4 for the search strategy. Of the 52 records identified in the search, 12 were selected as potentially relevant and checked against pre-specified inclusion/exclusion criteria.⁶⁶⁻⁷⁷

A table of eligibility criteria was constructed by the EAG to include the most relevant NMAs to the topic (see Table 19). Out of the 12 NMAs found, four^{68, 71, 72, 74} were excluded as they did not use the more up-to-date results for the atezolizumab + bevacizumab intervention.⁶⁴ Five further studies were excluded due to inadequate methodology for statistical analyses.^{67, 69, 70, 73, 77} All included the Abou-Alfa et.al. 2022⁷⁸ as their source for the HIMALAYA trial, but did not report the recent publication which included additional HIMALAYA trial results.⁷⁹ All twelve published NMA studies reported on OS and PFS in some form, but none reported TTD.

After evaluating the NMAs against the eligibility criteria, three studies^{66, 75, 76} were included and assessed using the ROBIS risk of bias tool (see Table 20).

Table 19: The eligibility criteria for EAG's NMA selection

Study design	RCTs
Data source	Data should be sourced from the latest results of main trials as follows: Atezolizumab + Bevacizumab: Refer to Cheng et al. 2022⁶⁴ and any other primary/updated publications STRIDE: Refer to Abou-Alfa 2022³⁶ and any other primary/updated publications
Population	Patients with advanced or unresectable HCC who have not received prior systemic therapy
Interventions	- STRIDE, - Atezolizumab + bevacizumab, - Lenvatinib - Sorafenib
Outcome	Primary outcome of interest: OS, and PFS Secondary outcome: Time to Treatment Discontinuation (TTD) (if available)
Statistical analysis	The NMAs should report sensitivity and heterogeneity analyses. The choice between a fixed-effect or random-effect model should be based on the results of the heterogeneity analysis.

Table 20: ROBIS risk of bias for the three included NMAs

ROBIS Domain and Signalling Questions	Celsa-2024⁶⁶	Vogel-2023⁷⁵	Wang-2024⁷⁶	Comments
1: Study eligibility criteria				
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes	Yes	Yes	All studies adhered to their pre-defined objectives and eligibility criteria.

ROBIS Domain and Signalling Questions	Celsa-2024⁶⁶	Vogel-2023⁷⁵	Wang-2024⁷⁶	Comments
1.2 Were the eligibility criteria appropriate for the review question?	Yes	Yes	Yes	Eligibility criteria were appropriate for the review questions in all studies.
1.3 Were eligibility criteria unambiguous?	Yes	Yes	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably Yes	Yes	Probably Yes	Both Wang's 2024 and Celsa's 2024 studies have limited their studies to only phase III trials. They have not missed the data sources of interest.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably yes	Yes	Probably yes	English Language-only publications for Celsa and Wang 2024 were included. However, the reported studies match the data sources of interest.
Concerns regarding specification of study eligibility criteria	Low	Low	Low	All studies had clear and appropriate eligibility criteria.
2: Identification and selection of studies				
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes	Yes	Yes	
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	Yes	Probably no	No additional searches other than of 2 conferences were conducted for Wang 2024.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably Yes	Yes	Probably Yes	The search strings for each database for Celsa (2024) are not provided and it is unclear how Boolean operators are used in relation to the reported search terms. The Embase search for Wang (2024) is unclear. The numbers for database searches in both PRISMA flow diagrams suggest the searches were structured appropriately. Search strategies for Vogel (2024) were well-structured and sensitive.
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	Yes	Yes	Restrictions were appropriate and justified.

ROBIS Domain and Signalling Questions	Celsa-2024⁶⁶	Vogel-2023⁷⁵	Wang-2024⁷⁶	Comments
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Yes	Yes	Efforts were made to minimize errors in study selection.
Concerns regarding methods used to identify and/or select studies	Low	Low	Low	Wang (2024) did not conduct additional searches; however, the EAG did not identify any missing studies related to this concern. Therefore, all relevant studies have been captured.
3: Data collection and study appraisal sections				
3.1 Were efforts made to minimise error in data collection?	Yes	Yes	Yes	Standardized methods were used to minimize errors.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Yes	Yes	Detailed study characteristics were provided.
3.3 Were all relevant study results collected for use in the synthesis?	Yes	Yes	Yes	All relevant results were collected and used.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	Probably yes	Yes	Vogel 2023 has used the Centre for Reviews and Dissemination (CRD risk of bias). ³¹
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	Yes	Yes	Multiple reviewers independently assessed the risk of bias.
Concerns regarding methods used to collect data and appraise studies	Low	Low	Low	
4: Synthesis and findings				
4.1 Did the synthesis include all studies that it should?	Yes	Yes	Yes	All relevant studies were included in the synthesis.
4.2 Were all predefined analyses followed or departures explained?	Yes	Yes	Yes	Predefined analyses were followed, and departures were explained.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes	Yes	Yes	The synthesis was appropriate and accounted for study similarities.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	Yes	Yes	Heterogeneity was addressed using appropriate methods.

ROBIS Domain and Signalling Questions	Celsa-2024⁶⁶	Vogel-2023⁷⁵	Wang-2024⁷⁶	Comments
4.5 Were the findings robust, e.g., as demonstrated through funnel plot or sensitivity analyses?	Yes	Yes	Yes	The findings were robust and supported by sensitivity analyses.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes	Probably yes	Yes	Necessary assessments have been properly taken to minimize the risk of bias.
Concerns regarding the synthesis and findings	Low	Low	Low	The synthesis and findings were robust and appropriately addressed biases.
Risk of bias	Low	Low	Low	Overall, all studies demonstrated a low risk of bias.

Of the three selected published NMAs that satisfied the EAG inclusion criteria two reported HR and 95%CrIs for PFS and OS^{75, 76} while the third⁶⁶ reported restricted mean survival data (OS to 30 months, and PFS to 16 months) because of worries about violation of proportional hazards. Since the company's NMA reports HRs the EAG selected the Vogel and Wang NMAs for further investigation.

Vogel et al NMA⁷⁵

Table 21 compares the HR results for atezolizumab + bevacizumab versus sorafenib output from Vogel's NMA with that from the company's NMA. The OS HRs are similar but PFS HRs are different (█ company vs 0.66 for Vogel).

Table 21: Comparison of hazard ratios from the company's NMA and that of Vogel et al.,⁷⁵

Vogel OS HR Atezolizumab + bevacizumab vs. sorafenib	Company OS HR Atezolizumab + bevacizumab vs. sorafenib	Vogel PFS HR Atezolizumab + bevacizumab vs. sorafenib	Company PFS HR Atezolizumab + bevacizumab vs. sorafenib
0.68 (0.42, 1.1)	█	0.66 (0.27, 1.59)	█
Vogel OS HR STRIDE vs. sorafenib	Company OS HR STRIDE vs. sorafenib	Vogel PFS HR STRIDE vs. sorafenib	Company PFS HR STRIDE vs. sorafenib
0.782 (0.66, 0.93)	█	0.9 (.62, 1.35)	█
HR, hazard ratio; OS, overall survival; PFS, progression-free survival			

Since the Vogel NMA was industry sponsored, the EAG looked at other NMAs to see if one or the other HR for PFS (Atezolizumab + bevacizumab versus sorafenib) might be an outlier. The results are listed in Table 22.

Table 22: PFS hazard ratios reported for the comparison atezolizumab + bevacizumab* vs sorafenib

NMA	HR	95%CrIs
Company submission (Table 16)	■	■
Vogel ⁷⁵	0.66	0.27, 1.59
Chen ⁶⁷	0.65	0.52, 0.84
Ding ⁶⁹	0.64	0.52, 0.79
Fulgensi ⁷¹	0.59	0.46, 0.75
Liu ⁷³	0.65	0.53, 0.80
Peng ⁷⁴	0.59	0.46, 0.75
Zhang ⁷⁷	0.65	0.54, 0.79
Wang ^{*76}	0.60	0.36, 0.99

* Wang made a “treatment class” comparison; the immunotherapy + angiogenic agent class HR input was pooled from atezolizumab + bevacizumab and sintilimab + bevacizumab studies. The NMA published by Ciliberto et al., 2023 reported HRs vs placebo; for PFS the EAG could not identify from the publication what data source was used; Ciliberto reported a PFS HR of 0.96 for the comparison sorafenib vs. placebo that seems implausible.

The NMA PFS input (■) for IMbrave was taken from the supplementary appendix of Finn et al., An updated analysis of PFS by Cheng et al., with longer follow-up than Finn and more mature data reported a Stratified HR 0.65 (95%CI: 0.53, 0.81).

In the opinion of the EAG this 0.65 value from mature data is more appropriate than the investigator assessed ■ input.

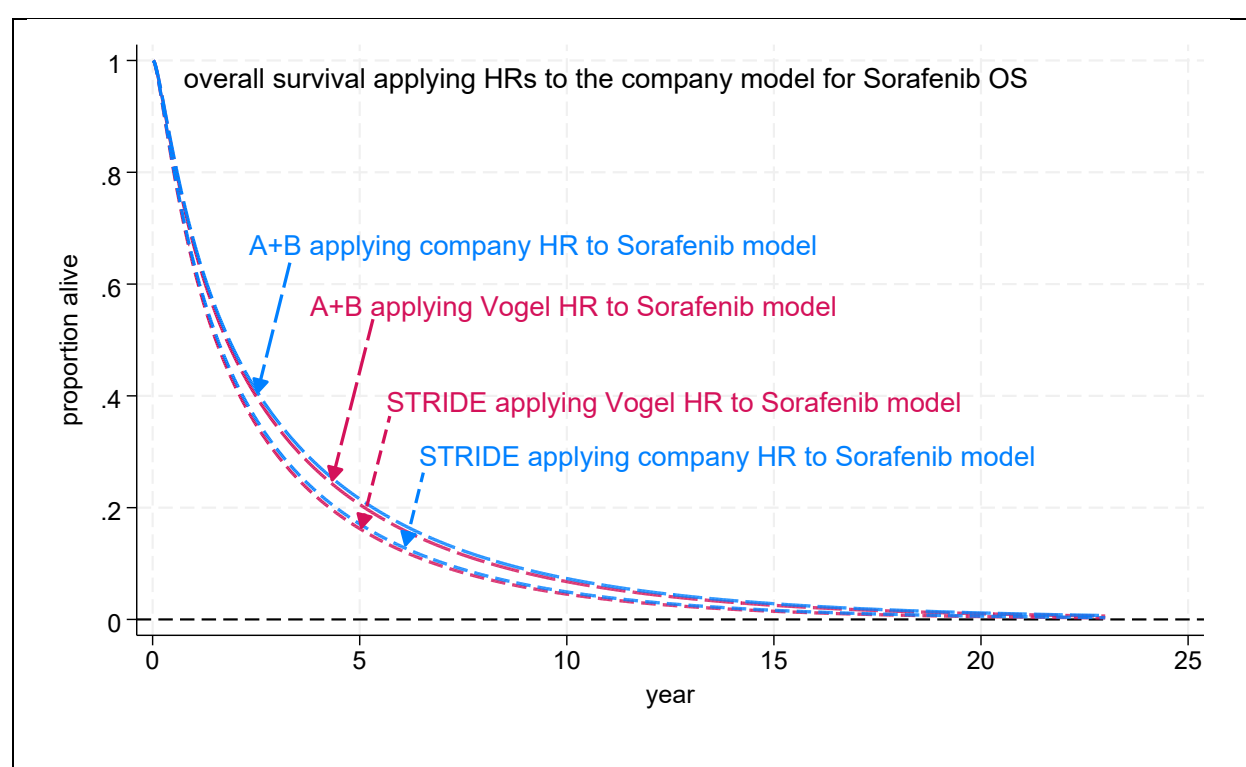
It also aligns with the Vogel NMA output of 0.66 (95%CrI: 0.27, 1.59).

The listed NMAs were a mixture of fixed and random effects models. The results indicate that the company NMA PFS HR estimate for the comparison of atezolizumab + bevacizumab versus sorafenib is an outlier when compared to those reported in other published NMAs.

The impact of the differences in HR between the Vogel NMA and the company’s NMA was investigated by applying the relevant hazard ratios to the company’s sorafenib models of OS and PFS. The results are shown in Figure 4. The small difference in HRs for OS can be seen to have a negligible influence on overall survival curves, with all models predicting that there are very few survivors beyond 20 years. Similarly, the lack of difference in the company and Vogel PFS HRs for the

comparison of STRIDE vs sorafenib means virtually identical models for this comparison.

However, a large difference can be seen between the company and Vogel et al., models for the PFS for atezolizumab + bevacizumab versus sorafenib. Because the company HR (■■■) clearly appears to be an outlier, the EAG believe that this introduces a bias that may have impacted the economic model.



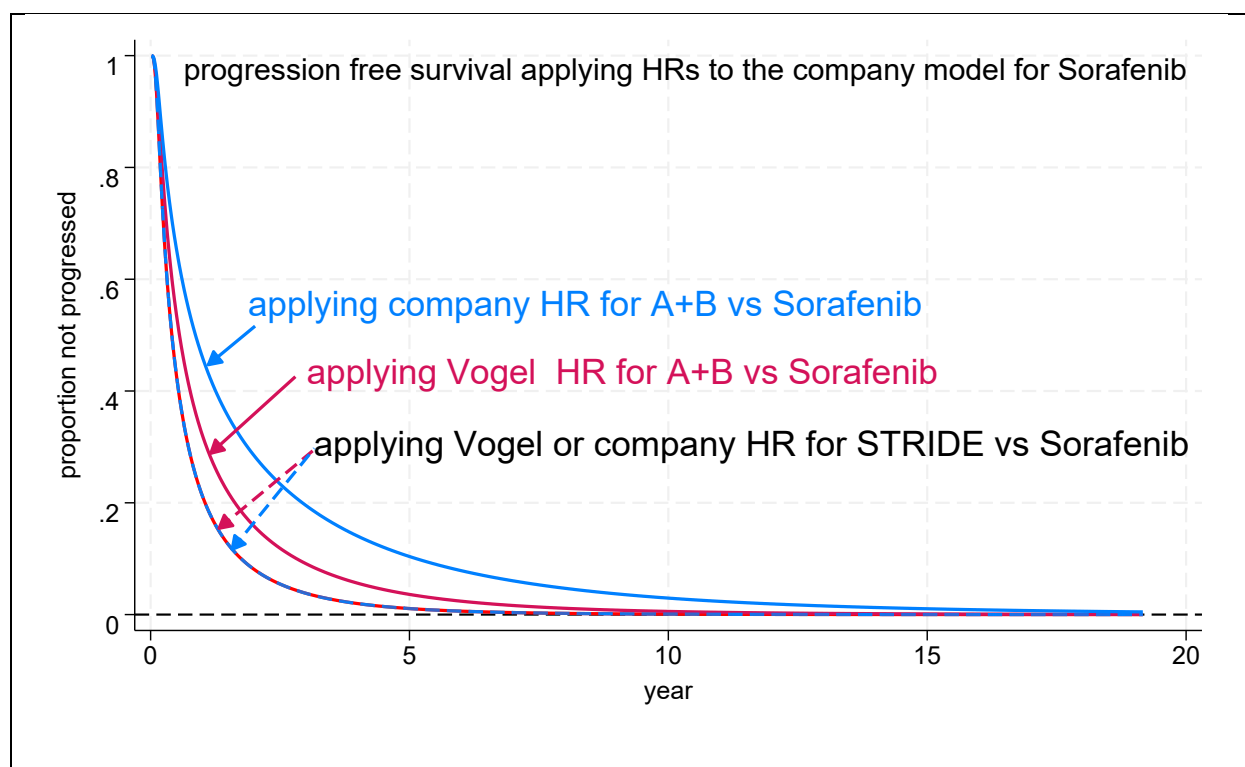


Figure 4: Impact of applying Vogel et al. hazard ratios

Wang et al., NMA⁷⁶

The EAG performed the same analysis using Wang et al.'s NMA as described above for the Vogel et al., NMA. It should be noted that Wang et al., performed an NMA comparing classes of first line treatments for HCC that a) the REFLECT study was not included; b) data from HIMALAYA arm with durvalumab alone was not included. Of interest is the comparison of “immunotherapy (e.g. atezolizumab or sintilimab) + anti-angiogenetic agent” versus “combined therapy” such as tremelimumab combined with durvalumab (i.e., STRIDE). Application of Wang et al.'s HRs to the company sorafenib models of OS and of PFS produced model curves shown in Figure 5.

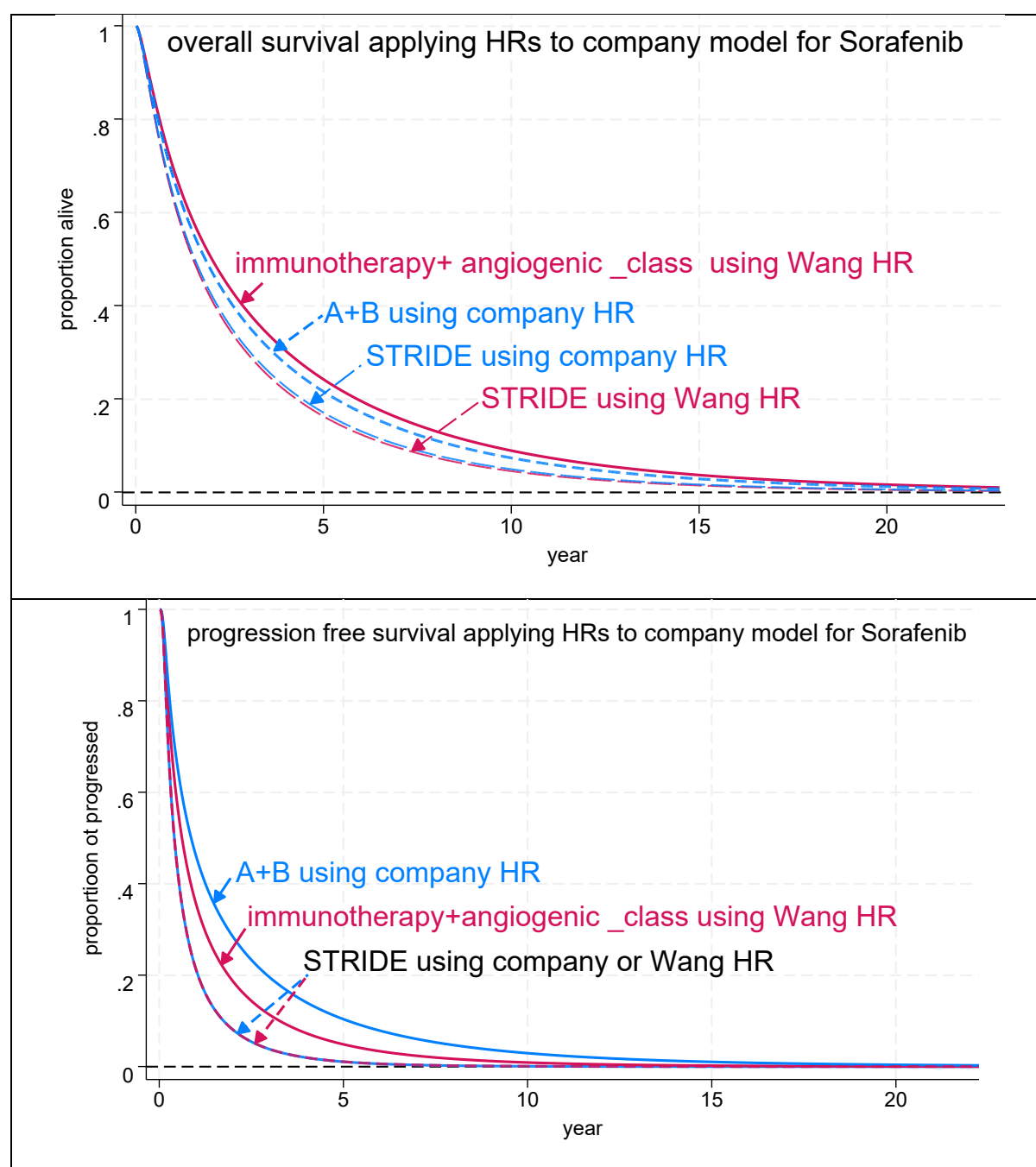


Figure 5: Impact of applying Wang et al., hazard ratios

The results from applying Wang et al.'s HRs mirror the results from Vogel, indicating that the company estimates for PFS may introduce bias for the comparison of STRIDE versus atezolizumab + bevacizumab.

Summary of EAG issues regarding the company's NMA

1. Reporting of the methodology used to conduct the company NMA was lacking detail and was incomplete. The company's justification for the inclusion and

exclusion criteria for studies lacked detail and justification. It would be difficult to replicate the NMA.

2. No literature searches were conducted for published NMAs on this topic. Consequently, no comparison was undertaken between the company's NMA and those published on the same topic; there was no mention of the existence of other NMAs.
3. The data used in the NMA was very sparse and all pairwise comparisons resulted in HRs that were not statistically significant; any modelling undertaken with these NMA results will be associated with considerable uncertainty.
4. Some data from the HIMALAYA trial was not included in the NMA.

3.2.11 Conduct of the company's NMA

In Table 23 lists EAG concerns regarding the conduct of the company's NMA.

Table 23: EAG points of concern for the company's NMA

<i>Study type</i> The use of Phase III RCTs ensures a high level of evidence quality. However, the company did not clearly justify why they limited only to Phase III RCTs. Differences between the study variables such as region (% Asia-Pacific), HBV aetiology, and macrovascular liver invasion may introduce variability that impacts the comparability of outcomes across studies. The company did not justify omitting the durvalumab arm of the HIMALAYA.
<i>Treatment effect modifiers (TEMs)</i> The company acknowledge and explore potential TEMs; however, the inability to adjust for TEMs due to a small number of studies limits the robustness of the NMA. Variations in HBV prevalence, MVI, and regional representation across trials may have introduced bias. The decision not to conduct more complex adjustments, like meta-regression or population adjustment methods, leaves some residual confounding unaddressed.
<i>Proportional hazards (PH) assumption</i> The proportional hazard assumption was violated for REFLECT and HIMALAYA. For REFLECT, the exploration of time-varying hazards as undertaken by the company showed that the application of a constant HR for lenvatinib in the economic model may overestimate the long-term effect of treatment, and therefore yields conservative cost-effectiveness estimates when compared to STRIDE. The company found the proportional hazard violation for STRIDE versus sorafenib (from HIMALAYA) for PFS and OS, and for lenvatinib vs sorafenib (from REFLECT) for PFS and OS. There was no evidence of a proportional hazard

violation for atezolizumab plus bevacizumab versus sorafenib (from IMBrave150). As there was evidence of non-proportional hazards for REFLECT, the company presented an analysis in which a time-varying treatment effect for the efficacy of lenvatinib versus sorafenib was explored (Appendix N). This showed that the application of a constant HR for lenvatinib in the economic model may overestimate the long-term effect of treatment, and therefore yields conservative cost-effectiveness estimates when compared with STRIDE.

PFS assessment consistency

The company used investigator-assessed PFS across all studies to align with the data from HIMALAYA, to ensure consistency. However, the use of different criteria for PFS assessment (RECIST 1.1 versus mRECIST) across studies could still affect comparability. While RECIST and mRECIST may have similar performance, mRECIST includes extra factors that could potentially impact the results. Furthermore, reliance on investigator assessments, rather than blinded independent review, introduces subjectivity and potential bias.

Differences in follow-up

HIMALAYA has a much longer follow-up time compared to IMbrave150 and REFLECT. The variability in follow-up duration across studies complicates direct comparisons of outcomes. The NMA did not fully adjust for these differences, which could impact the results' accuracy, particularly when assessing longer-term outcomes.

Use of informative priors

The use of a published informative prior for the RE models that did not converge is a sound approach and improved model stability. However, the appropriateness of the informative priors is debatable, as their applicability to hepatocellular carcinoma-specific (NICE scope; Table 1) settings may be limited. The sensitivity of the results to the choice of priors introduces additional uncertainty, as different priors could yield varied outcomes. The impact of the model not converging with non-informative priors could have been delineated more clearly.

HBV, Hepatic B virus; NMA, network meta-analysis; PFS, progression-free survival; PH, proportional hazard; RCT, randomised-controlled trial; TEM, treatment effect modifiers

4 COST-EFFECTIVENESS

This section focuses on the economic evidence submitted by AstraZeneca and, additional information received in response to the EAG's clarification questions. The EAG critically appraised the evidence submitted and examined the company's electronic model. We provide a summary and critique of the company's economic evidence, including the company's systematic review(s), methods, and results (base-case, sensitivity and scenario analyses) as reported in the CS Document B using frameworks on best practices for reporting economic evaluation and economic modelling to assess the overall reporting quality and validity of these analyses. In the subsequent section, where possible, the EAG have addressed the concerns raised in the form of additional analyses undertaken, which concludes with the EAG base-case.

The submission received by the EAG included:

- A systematic review of the economic evidence
- Methods used to undertake the economic analysis, the company's base-case and sensitivity analysis results
- Electronic version of the de novo Markov model built in Microsoft Excel

4.1 EAG comment on company's review of cost-effectiveness evidence

The company undertook systematic literature reviews (SLRs) to identify evidence on resource use, costs, and the cost-effectiveness of standard of care in patients with treatment-naïve advanced or unresectable HCC in the UK. Additionally, a systematic review was undertaken to identify studies that reported health-related quality of life (HRQoL) in the same population, also limited to the UK. The searches for both SLRs were undertaken in June 2024, with a date limit of 20 October 2021. The SLR methods in the company appendix refer to a previous, broader SLR (searches run May 2020, from database inception) and 1st update (searches run Oct 2021), which also sought HRQoL studies (see CS Document B, section B.3.1) and was not limited to the UK.

To obtain relevant studies, the company searched MEDLINE and Embase databases, as well as identifying records through searching UK HTA agencies via a database (INAHTA), relevant conferences, checking bibliographies of relevant SLRs, NMAs and economic evaluation. HTA bodies were not searched separately, which would have been ideal. Population terms in combination with disease terms and its stages, and economic terms were considered reasonable.

In total, seven studies were considered relevant for the systematic review, five obtained from the database searches and two from supplementary searches. The company stated that no economic evaluation was identified that compared STRIDE to another relevant comparator as first-line treatments in adults with advanced or unresectable HCC. They identified previous appraisals of atezolizumab + bevacizumab, lenvatinib and sorafenib all of which included an economic model. The conduct of these economic analyses was reported in CS Document B, Table 32, pages 91-93.

EAG summary: Because a geographic search filter for the United Kingdom was applied, searches will have likely missed relevant economic evaluations and HRQoL studies from other countries. Hence, it would have been beneficial to broaden the search by not limiting it to UK-based studies to potentially widen the evidence-base.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The EAG reviewed AstraZeneca's economic evaluation model against NICE standards. A *de novo* cost-effectiveness model was developed to assess the cost-effectiveness of STRIDE in adult patients with advanced or unresectable HCC, in line with the HIMALAYA patient population, licence and decision problem for this submission. The EAG summarised the model structure and evaluated clinical evidence (e.g., efficacy, treatment discontinuation, mortality) and economic evidence (e.g., drug costs, health state resource use and costs, utilities). The EAG critiqued the methods and inputs used in the analysis.

4.2.1 NICE reference case checklist

The EAG undertook an evaluation of the company's submission against the NICE reference case. Findings are summarised in the Table 24.

Table 24: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE.	Decision problem clearly stated and is in line with the scoped developed by NICE.
Comparator(s)	As listed in the scope developed.	Comparators included in the company's economic analysis included sorafenib, lenvatinib and atezolizumab + bevacizumab. The company excluded selective internal radiations therapies (SIRT) including SIR-Spheres and TheraSphere, QuirumSpheres and BSC. (see section 4.2.4)
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	All relevant health effects that occur following treatment have been considered in the economic analysis.
Perspective on costs	NHS and PSS.	Resource use and costs adopts the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	Cost-effectiveness analysis. The company reported pairwise comparisons as well as fully incremental results.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	40-year time horizon.
Synthesis of evidence on health effects	Based on systematic review.	For the indirect treatment comparison, the company has conducted a systematic literature review (SLR) with a network meta-analysis (NMA).
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The company's preferred measure is in line with the NICE final scope.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L utility data were collected in the HIMALAYA trial. In the model, utilities were treatment-dependent, meaning there was a possibility of having different utility values for the same health state.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The EQ-5D-5L health utility values were cross-walked to the EQ-5D-3L using the algorithm described by Hernández-Alava et al.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company has incorporated the QALY weight into the model.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use clearly reported and valued appropriately using current prices and is in line with the NHS and PSS perspective.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate based on a 3.5% per annum for both costs and benefits used.
EQ-5D-5L, EuroQoL five dimension five levels; NHS, National Health Service; NMA, network meta-analysis; PSS, personal social services; QALYs, quality-adjusted life years		

4.2.2 Model structure

The company conducted a cost-effectiveness analysis using a partitioned survival model (PSM) to reflect disease progression and patient survival patterns in those treated with STRIDE and comparator therapies for advanced or unresectable hepatocellular carcinoma (HCC). The company stated that this model aligns with previous NICE evaluations, making it the most appropriate choice based on the available clinical data.^{10, 14, 24} The PSM structure uses time-to-event data from the HIMALAYA study, focusing on overall survival (OS) and progression-free survival (PFS). The HIMALAYA trial provides five-year survival data. The company addressed uncertainties through consultations with UK experts on advanced or unresectable HCC. The model includes three health states: progression-free (PF),

post-progression (PD), and death. Figure 6 provides a simplified schematic of the model, illustrating the possible transitions between these health states.

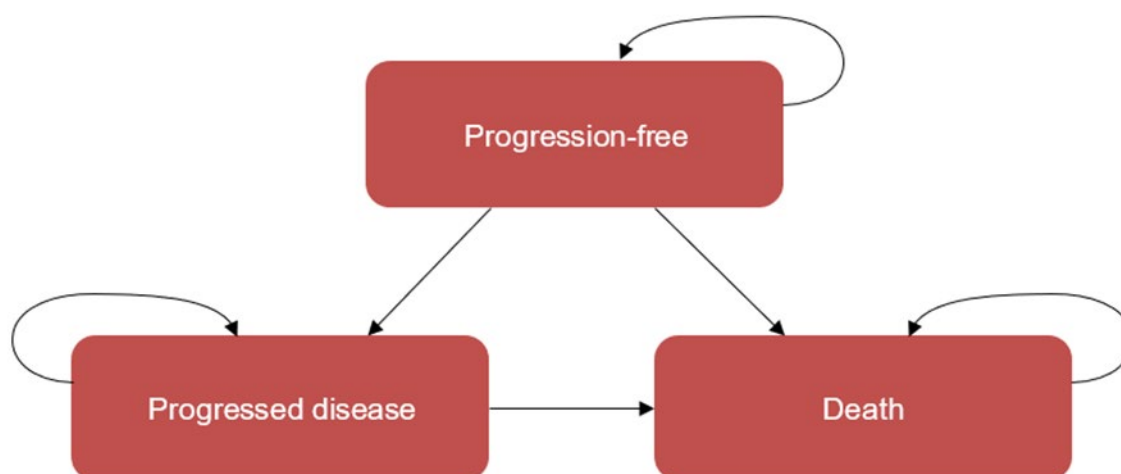


Figure 6: Simplified model schematic (Figure 22, CS Document B, page 89)

The company model starts with patients in a 'progression-free' state, receiving either STRIDE or a comparator treatment (atezolizumab + bevacizumab, sorafenib, lenvatinib). Patients may progress or die, and those with progressed disease may either remain alive with progression or die, with no improvement in health state. In the model, patients in the 'progression-free' and 'progressed disease' health states can be either on or off treatments.

EAG comment: The EAG identified two concerns regarding the company's model structure.

First, in the definition of health states, the model structure does not account for important subgroups within the "progression-free" and "progressed disease" health states. Specifically, there are two sub-states for each of these: "on treatment" and "off treatment." "On treatment" refers to patients who are still receiving the primary treatment (e.g., STRIDE), while "off treatment" refers to those who have discontinued primary treatment and are undergoing subsequent treatments. The costs associated with patients on primary treatment and those on subsequent treatments differ substantially. The EAG argues that collapsing these subgroups into single health states oversimplifies the illustrative model structure, especially when a considerable proportion of patients in the progression-free state transition to subsequent treatments.

Second, the company assumed that progression-free survival (PFS) serves as a proxy for time-to-treatment discontinuation (TTD) in treatments of atezolizumab + bevacizumab and lenvatinib. This implies that all patients in the progression-free state remain on primary treatment, while all patients in the progressed disease state receive subsequent therapies. The EAG contends that this approach introduces inconsistencies across treatments, which could lead to bias and ultimately weaken the robustness of the model.

4.2.3 Population

The economic evaluation focuses on adults with advanced or unresectable HCC classified as BCLC stage B or C. The analysis is based on the HIMALAYA patient population, which aligns with the licensed indication for STRIDE. The evaluation specifically excludes patients eligible for locoregional therapy due to factors such as tumour burden, liver function, and vascular invasion.²⁸ The company quotes recent input from UK clinician experts to support this approach, emphasising that systemic therapy is only considered when locoregional options like SIRT are either not suitable or unavailable (see AstraZeneca, Data on File, HIMALAYA Clinician Validation Interviews, supplied in the CS reference pack). The evaluation also specifically excludes patients who have received prior systemic therapy.

The clinical efficacy of STRIDE is examined demonstrated through subgroup analyses in terms of HCC aetiologies, ECOG performance status, and the presence of macrovascular invasion, among other factors. The company reported that the OS benefit of STRIDE versus sorafenib was consistent across most pre-specified subgroups, with HR estimates falling within the 95%CI of the overall population. Some variability occurred, particularly in the female subgroup and patients with HCV, where the 95%CI included one, indicating no significant difference in effectiveness. The company stated, in females, this was likely due to the small sample size (<100 per arm), while post-hoc analysis for HCV revealed imbalances. Despite this, OS benefit remained consistent across subgroups and at the primary DCO. The baseline characteristics used in the economic model are based on the HIMALAYA trial (see Table 25) and the company stated based on clinical expert feedback are deemed generally representative of patients in UK clinical practice (see AstraZeneca, Data on File, HIMALAYA Clinician Validation Interviews, supplied in the CS reference pack).

Table 25: Baseline characteristics for the model population (obtained from Table 33 CS Document B, page 94)

Model parameter	Value	Source
Mean age, years	■	HIMALAYA (FAS)
Percentage male, %	■	HIMALAYA (FAS)
Mean weight, kg	■	HIMALAYA (FAS)
Mean height, cm	■	HIMALAYA (FAS)
Patient BSA, m ²	■	HIMALAYA (FAS)
BSA: body surface area; FAS: full analysis set.		

EAG summary: The primary source of effectiveness evidence for STRIDE versus sorafenib is derived from the HIMALAYA trial. However, as highlighted in section 3.2.3, there are some limitations in the trial's population that warrant consideration: The trial population appears younger than what would be expected in a real-world UK clinical context. The mean age of modelled participants in the trial is ■ years, whereas UK clinical experts indicate that the average age of HCC patients in practice is closer to 70 years. This age discrepancy raises concerns about the generalisability of the results to the UK population. Further details on other characteristics of differences between the HIMALAYA trial and UK population are outlined in Section 3.2.3. This presents challenges in generalising the findings of the HIMALAYA trial, including its economic evaluation, to the UK context.

4.2.4 Interventions, comparators and subsequent treatments

Interventions

The intervention under review is durvalumab plus tremelimumab (STRIDE), consistent with the final scope. The HIMALAYA trial supports the approved dosing of STRIDE, where patients receive durvalumab (1,500 mg Q4W) and a single 300 mg dose of tremelimumab. STRIDE is administered until disease progression or unacceptable toxicity occurs, as per the European Medicines Agency.^{9, 29}

Comparators

The comparators include atezolizumab + bevacizumab, lenvatinib, and sorafenib, which the company states reflect current UK clinical practice for advanced or unresectable HCC, particularly for those ineligible for locoregional therapies. Atezolizumab + bevacizumab is the standard of care due to its superior efficacy over lenvatinib and sorafenib. Lenvatinib and sorafenib serve as alternative first-line therapies for patients for whom atezolizumab + bevacizumab is contraindicated or who prefer oral treatment.

Other comparators, such as selective internal radiation therapy (SIRT) and best supportive care (BSC), are excluded by the company. The company states that SIRT is irrelevant to this analysis because it is classified as locoregional therapy, which is unsuitable for this patient population due to tumour burden or liver function. The rationale for excluding BSC is that, while essential for symptom management, it is only offered to patients who are ineligible for systemic treatment, rather than as an alternative to active therapy.

Subsequent treatments

The company's approach to subsequent treatments within the model ensures that once patients discontinue their primary treatments, including interventions and comparators, they do not receive the same treatment in later lines. Instead, patients transition to specific subsequent therapies based on their initial treatment. For instance, patients who receive STRIDE as their primary treatment may move on to ■■■, ■■■■■■■■, or ■■■■■■■■. All patients are assumed to receive BSC, either alone or in combination with other subsequent treatments, for the remainder of their lifetime. Since the model only accounts for first and second lines of therapy, it is assumed

that patients will not continue their primary treatment as a subsequent therapy. The distribution of patients progressing to each subsequent treatment, based on the first-line therapy they received, is provided in Table 26.

Table 26: Subsequent treatment distribution (obtained from Table 55 CS Document B, page 142)

Subsequent treatment	Primary treatment (%)			
	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
BSC	■	■	■	■
Cabozantinib	■	■	■	■
Lenvatinib	■	■	■	■
Regorafenib	■	■	■	■
Sorafenib	■	■	■	■

The company has used the duration of therapy for subsequent treatments based on the median progression-free survival reported in the most relevant clinical trial identified for the treatment, given the setting (see Table 38).

EAG summary: As noted in Section 2.2.3, the EAG agrees with company's approach for not considering locoregional therapy and BSC as main comparators. This approach is confirmed by the EAG's clinical advisor and the previous STA (TA666).

4.2.5 Perspective, time horizon and discounting

The company adopted the perspective of the NHS and Personal Social Services (PSS) for costs and outcomes, following the NICE reference case. A lifetime time horizon of 40 years was selected to account for patient outcomes up to age 100 (it goes to age 103 according to company's survival modelling). Based on the overall survival model employed in the base-case analysis, the company stated that this time horizon was deemed appropriate, as 4% of patients in the intervention arm are projected to survive beyond 20 years, ensuring the model captures all costs and QALYs across treatment arms. A one-week cycle length was used, aligning with the frequency of clinical events and treatment regimens. The company stated this

approach is consistent with the latest NICE evaluation in advanced HCC.¹⁴ A half-cycle correction was applied. Costs and effects were discounted at 3.5% annually, as recommended by the NICE reference case.

EAG summary: The perspective and discount rate used by the company are in line with the NICE 2022 recommendations and are appropriate to the decision problem. The time horizon of the model was 40 years. However, previous STAs for similar treatments have typically used shorter time horizons of 14 to 20 years.^{10, 14} In its submission to CADTH for STRIDE, the company also opted for a 15-year time horizon.⁸⁰ The EAG submitted a clarification request to the company regarding the use of different time horizons in both the previous CADTH submission and the current one. However, the EAG found the company's response unconvincing.

The EAG believes that a 20-year time horizon would sufficiently capture differences in costs and benefits of treatments, aligning with the NICE reference case. Additionally, adopting a 20-year time horizon would be consistent with previous STAs for advanced HCC treatments and is compatible with the advice of the EAG clinical advisors, especially given the age distribution of relevant UK patients.

As described subsequently in this report, the EAG's amendment to the modelling assumptions lead to around 1% of people are projected to survive beyond 20 years. Given this, extending the time horizon to 40 years, compared to 20 years, is likely to have a negligible impact on the ICER.

4.2.6 Overall survival, progression-free survival and time-to-treatment discontinuation

Overall survival

The company conducted an overall survival (OS) analysis using individual patient data (IPD) from the HIMALAYA trial, with a median follow-up of 5 years for OS. Parametric survival models were applied to the Kaplan-Meier data for STRIDE and sorafenib. The proportional hazards assumption, evaluated through multiple statistical methods, was found to be violated. As a result, the company used independently fitted models for each treatment arm, rather than joint models, to minimise assumptions. The company used splines and knots for STRIDE and sorafenib. For comparator treatments, atezolizumab + bevacizumab and lenvatinib,

network meta-analysis (NMA)-derived hazard ratios (HRs) were applied to the sorafenib arm. However, proportional hazard violations for lenvatinib vs. sorafenib indicated potential bias, leading the company to apply a constant HR of one for OS, acknowledging lenvatinib's non-inferiority to sorafenib in the REFLECT trial. For atezolizumab + bevacizumab, the absence of the proportional hazard violation allowed for the reliable use of the NMA-derived HR. Constant HRs were applied by the company for lenvatinib and atezolizumab + bevacizumab. See Figure 7 for the KM plots for STRIDE and sorafenib and parametric curves fitted.

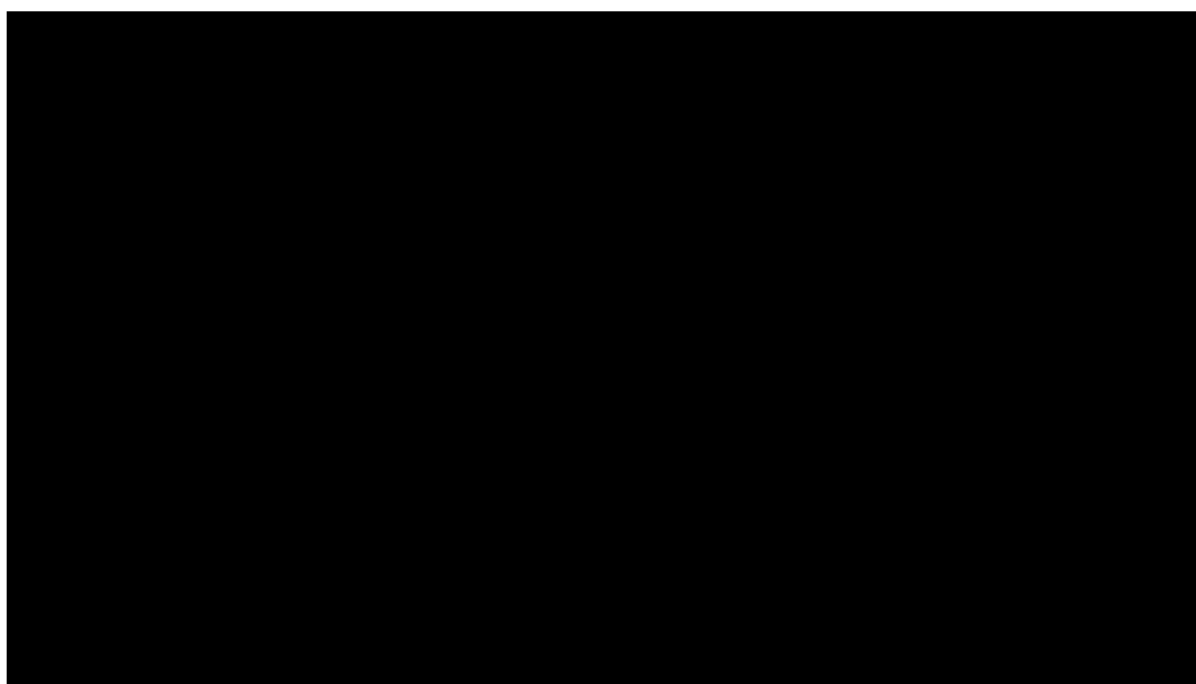


Figure 7: Company base-case OS parametric survival extrapolations (STRIDE, atezolizumab + bevacizumab, sorafenib and lenvatinib) (Figure 35, CS Document B, page 113)

STRIDE and sorafenib

Figure 8 shows the KM plot of OS for STRIDE and sorafenib at the latest cut-off. Beyond about 56 months (4.66 years) there are few events and many censorings. The plot for the third arm of HIMALAYA (Durvalumab) is not shown. Survival is superior for STRIDE versus sorafenib and an adjusted HR of 0.76 (95% CI 0.65 to 0.89) versus sorafenib is reported. This HR is less than the HR of 0.78 reported at a maximum follow-up of five years by Sangro et al., 2024.²²

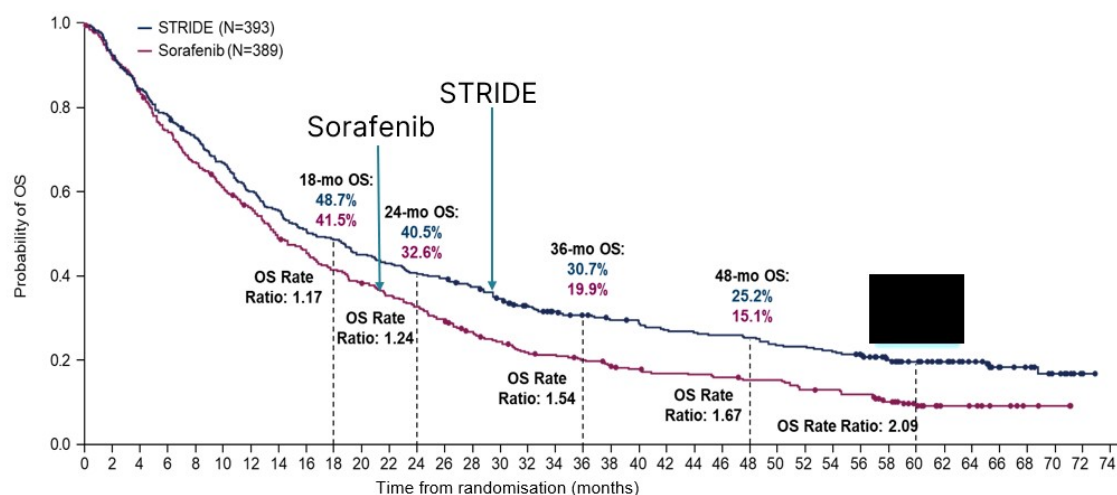


Figure 8: Kaplan-Meier plot of HIMALAYA OS results (updated analysis II:^a FAS) (DCO: 1st March 2024) (obtained from CS Document B, Figure 4)

Footnote: ^aThe updated analysis II was not powered for statistical analysis.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; OS: overall survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.

Source: Rimassa et al., 2024.⁷⁹

In Figure 8 the KM plots do not have 95% CIs. The EAG reconstructed the individual patient data (IPD) for STRIDE and sorafenib using the Guyot et al., 2012⁸¹ method to be able to illustrate the 95% CIs associated with the KMs.

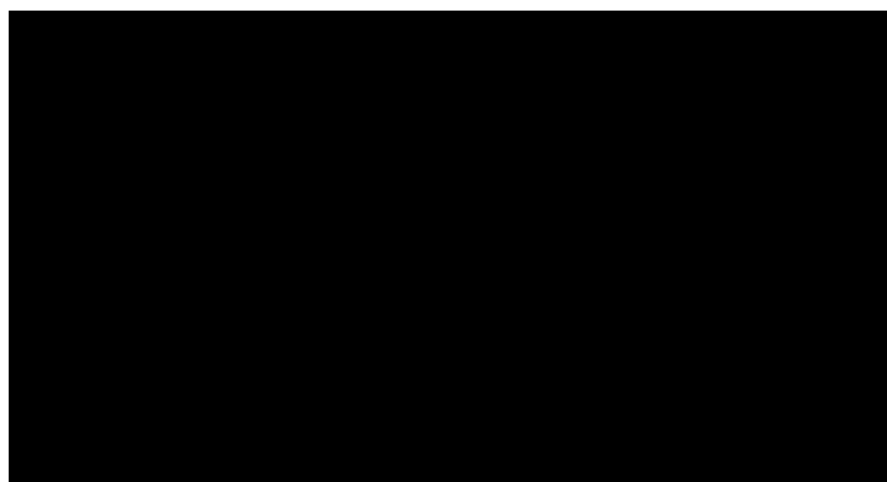


Figure 9: EAG reconstructed Kaplan-Meier plots (OS sorafenib)

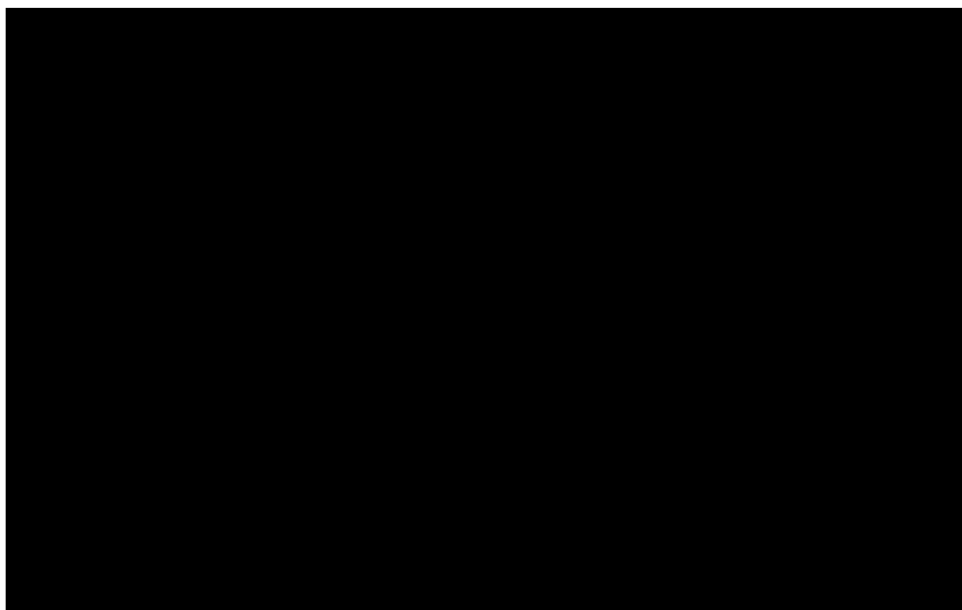


Figure 10: EAG reconstructed Kaplan-Meier plots (OS STRIDE)

Because the proportional hazards assumption was violated, the company fitted parametric models separately to each arm of HIMALAYA (latest cut-off). The models selected as “best” were then extrapolated approximately 6.5-fold to a lifetime horizon of 40 years. The criteria the company used to select its “best” models were:

- A. AIC/BIC scores of models over the observation period (CS Document B Tables 34 and 36).
- B. Judgement regarding the degree of visual alignment of smoothed hazard versus modelled hazard (CS Document B Figure28); no statistical test for this was presented.
- C. “Validation” using clinical plausibility (essentially expert clinical opinion).

In CS Document B Figure 28, the EAG notes that models fit well to the smoothed hazard (dotted line) over years one to three but less well at other times. Smoothed hazard plots vary according to the assumptions underpinning the smoothing and consequently, it is possible to generate different smoothed plots.

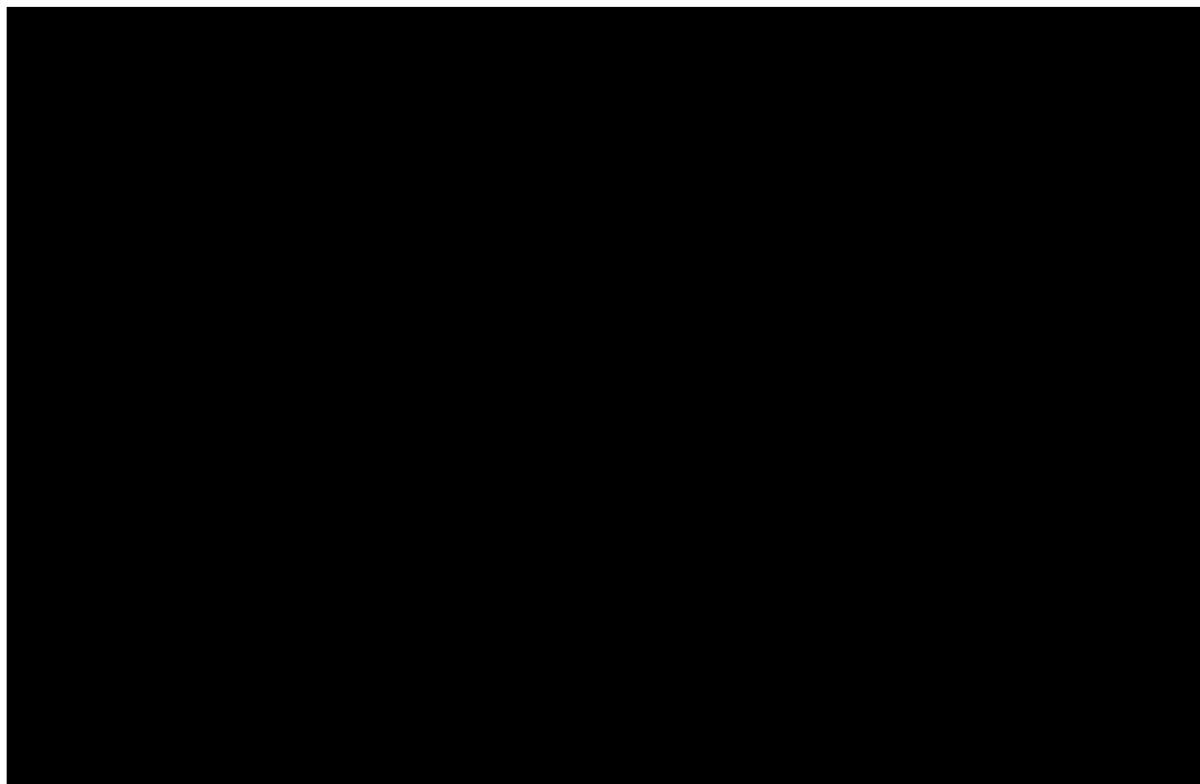


Figure 11: Smoothed hazard plots for OS for STRIDE (Normal models and smoothed hazard (dotted line) (Company submission Document B Figure 28)

AIC/BIC values for the company's spline model for STRIDE are summarised in Table 27 and compared with the values for standard parametric models for STRIDE presented in the submission Appendix.

Table 27: Model fit statistics for OS parametric survival functions for STRIDE (Table 34: Model fit statistics for OS parametric survival functions for STRIDE and Appendix O)

Function	AIC	Rank (AIC)	BIC	Rank (BIC)
1 knot spline model STRIDE	██████	█	██████	█
Exponential	2755.4	7	2759.4	7
Weibull	2746.1	5	2754.1	5
Log-normal	2715.4	1	2723.4	1
Log-logistic	2721.3	3	2729.3	3
Gompertz	2727.6	4	2735.6	4
Generalized gamma	2716.9	2	2728.8	2
Exponential	2755.4	7	2759.4	7
Gamma	2751.3	6	2759.3	6

The EAG notes that the generalised gamma and log-normal models attain superior scores compared to the Normal 1-knot spline model selected for the base-case by the company. The loglogistic model delivers similar scores. If AIC BIC values are a guide to “good” models, this suggests that some standard models might have equal or greater modelling utility as the spline model. Model fit for “standard” parametric distributions were presented in submission Appendix O Figure 19 (see Figure 12).

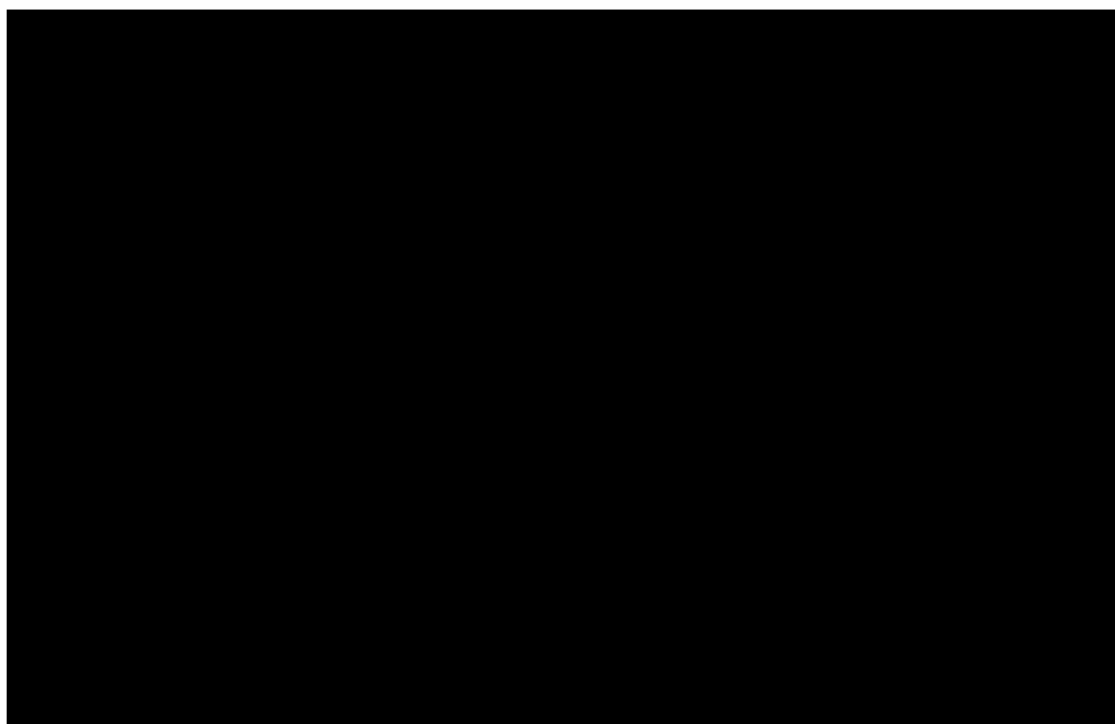


Figure 12: Overall survival for durvalumab and tremelimumab (CS Appendix O, Figure 19)

Of the models in CS Appendix Figure 19, four models Gompertz, lognormal, loglogistic and generalised gamma appear strongly influenced by the tail of the KM plot and predict survivors beyond 40 years (as does the company’s spline model) and as such suggest some patients are “cured by treatment”. The Gompertz model also follows the KM tail and predicts nearly 10% of patients are essentially immortal. All other standard models predict almost zero survivors beyond 20 years. An EAG clinical advisor stated that it is possible that some patients in HIMALAYA may experience cure and survive 40 years from start of treatment particularly if they are young at the start of treatment. The EAG notes that HIMALAYA included patients in the age range of 18 to 85 years, but no UK patients. A cured patient of 18 years at randomisation would reach 58 years after 40 years, and a cured patient aged 85 at

randomisation would reach 125 after 40 years. Clearly if some experience “cure” they are likely to be young patients.

In practice the company spline model(s) and generalised gamma models predict very similar lifetime survival that in the case of STRIDE suggests apparently “cured” patients (see Figure 13).

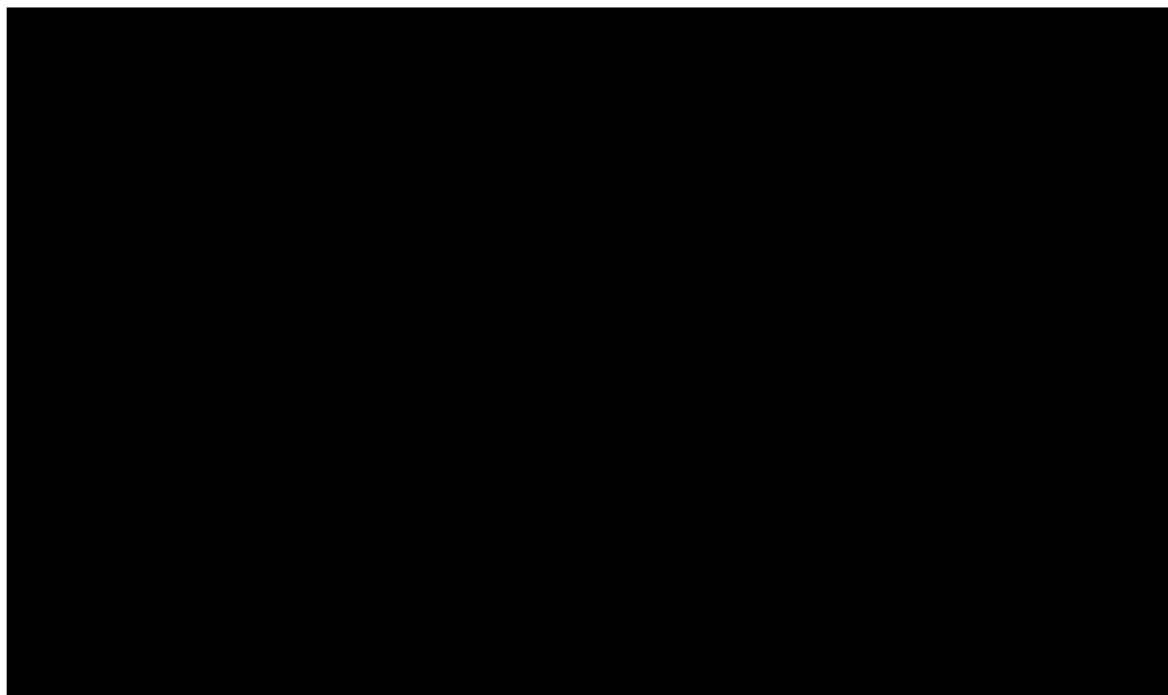


Figure 13: EAG representation for company's spline and generalised gamma models for STRIDE and sorafenib with EAG reconstructed KM plots and 95% CIs.

Lenvatinib and atezolizumab + bevacizumab

The company's NMA uses HR inputs from three included studies (four interventions), irrespective of the proportional hazards violation. The NMA delivers hazard ratio estimates that are then used for modelling overall survival and progression-free survival over a lifetime for the comparators lenvatinib and atezolizumab + bevacizumab but not for STRIDE which is modelled independently on the IPD from HIMALAYA.

The EAG have noted demographic differences between HIMALAYA and the UK population (age, gender mix, ethnicity and other factors that were not employed in stratification at randomisation). A problem of using IPD from HIMALAYA is that the population is not representative of that encountered in UK clinical practice.

The company use IPD for each arm of HIMALAYA to model OS for STRIDE and OS for sorafenib. The approach used to model OS for the comparators atezolizumab + bevacizumab and Lenvatinib is to apply NMA HRs to the sorafenib IPD. Two different approaches may lead to inconsistency.

Similarly, the EAG for the atezolizumab + bevacizumab STA remarked that it is inappropriate to estimate the relative treatment effects of lenvatinib versus atezolizumab + bevacizumab using an HR from a random effects NMA, whilst estimating the effect of sorafenib versus atezolizumab + bevacizumab using arm-based parametric survival model.

The EAG for the atezolizumab + bevacizumab STA additionally considered that using HRs from NMAs in the context of an economic evaluation is inappropriate in order to estimate population mean benefit.

The company sorafenib OS model is a spline 1-knot model. Applying a fixed HR (be it 1 or another value) to this model will generate another spline model. Thus, the survival models the company has generated for the comparators atezolizumab + bevacizumab and for lenvatinib are spline models. The base-case model for STRIDE is derived in a different way to the comparators, namely by generating a spline 1-knot model using HIMALAYA IPD. If the NMA point estimate [REDACTED] HR for STRIDE versus sorafenib is applied the resulting spline model aligns well with the IPD model over the bulk of the observed data but differs during the 6.4-fold extrapolation to a 40-year time horizon (Figure 14). Note that the 95%CrIs for the [REDACTED] HR were wide: [REDACTED].

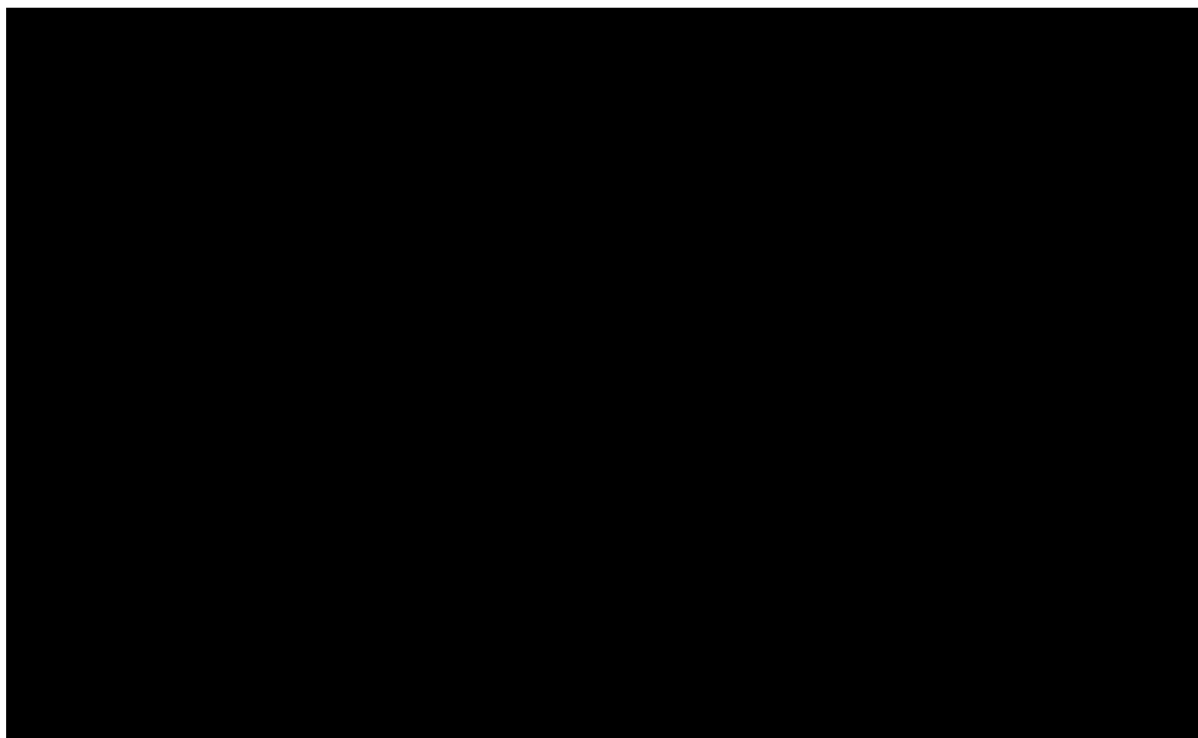


Figure 14: EAG comparison of STRIDE survival based on IPD and that using the NMA HR

Figure 15 shows modelled survival for STRIDE and comparators versus sorafenib when the company's NMA HRs versus sorafenib are used equivalently for all interventions. The only model indicating survivors to 40 years is the STRIDE spline model based on HIMALAYA IPD at the latest cutoff. Other models have diminished proportions alive beyond 30 years.

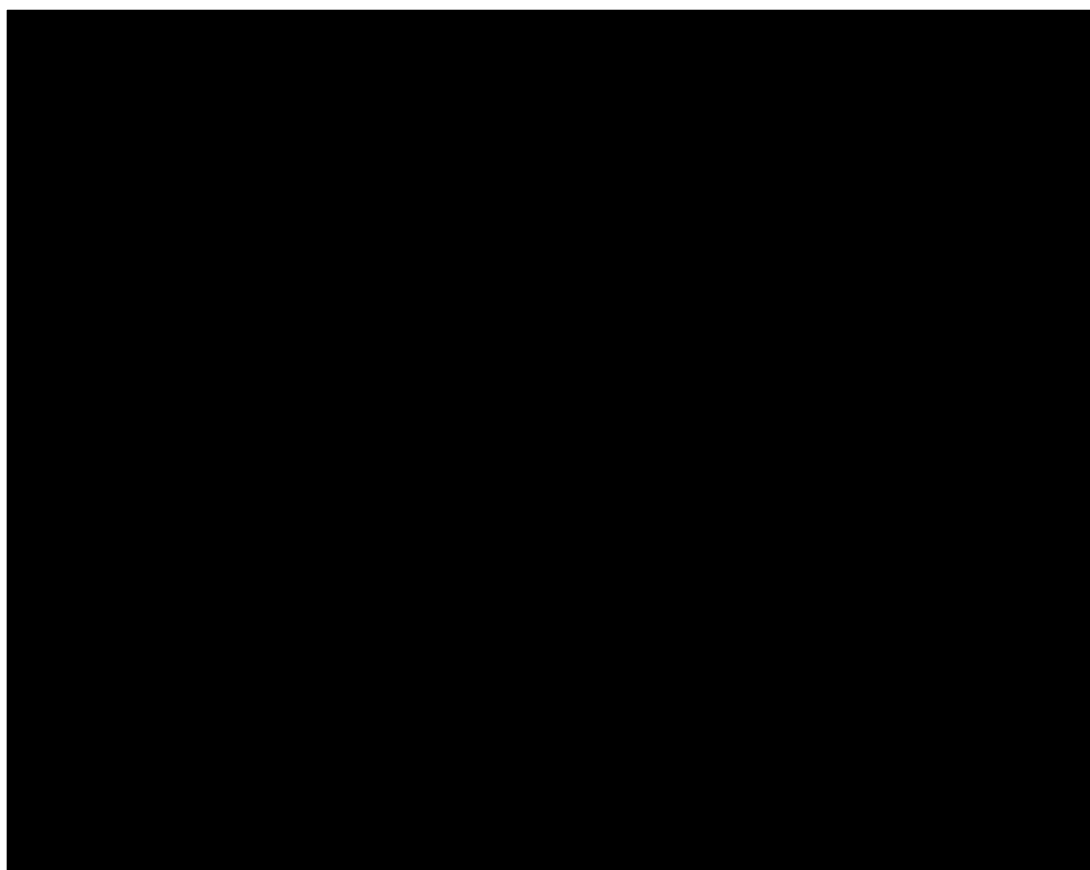


Figure 15: EAG comparison of survival of comparators using NMA HR adjustment

Progression-free survival STRIDE; key secondary endpoint

The company assessed PFS for STRIDE and sorafenib using IPD from the HIMALAYA trial. The formal assessment of the proportional hazards assumption revealed a violation, based on visual inspection of KM curves, the log-log plot, Schoenfeld residuals plot, and Grambsch and Therneau test.⁸²⁻⁸⁵ Due to this violation, the company opted to use independently fitted models for each treatment arm rather than joint models to minimise assumptions (see Figure 16). For PFS, the company applied splines and knots to the parametric survival models as follows: three knots for STRIDE and two knots for sorafenib. For comparators, atezolizumab + bevacizumab and lenvatinib, constant hazard ratios (HRs) were used. This approach was chosen to account for the observed proportional hazard assumption violation and ensure accurate modelling of PFS outcomes across the different treatments.

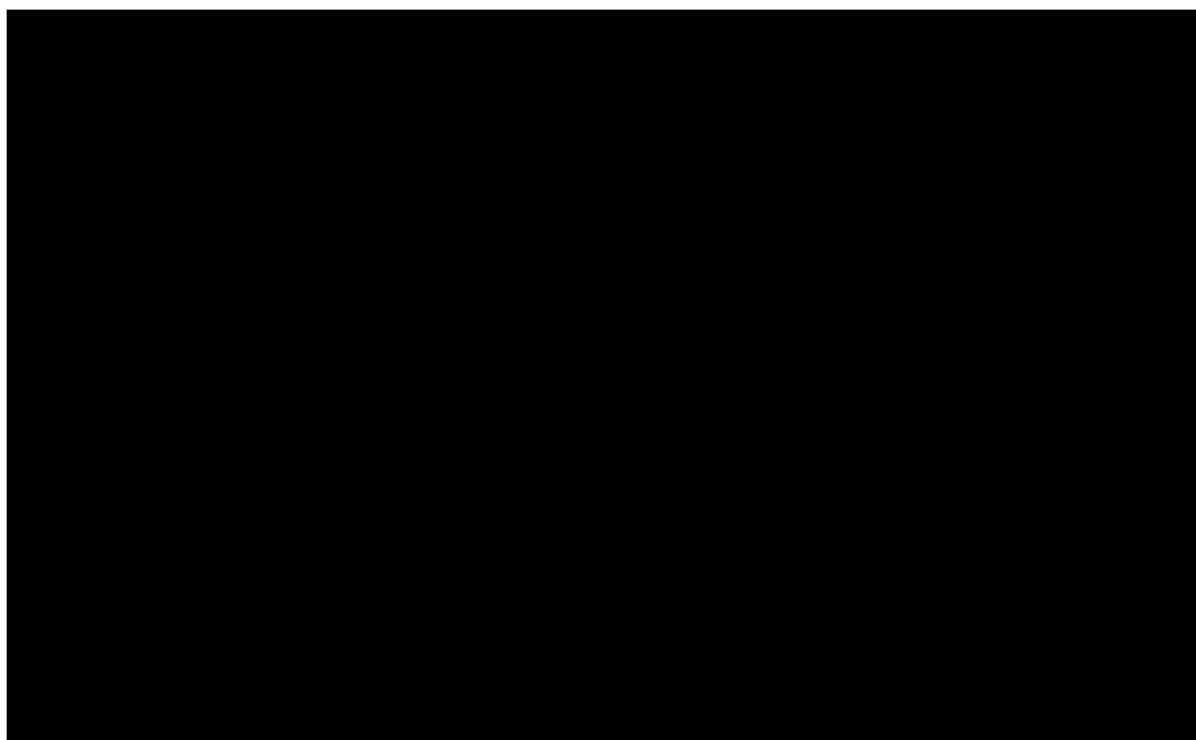


Figure 16: Company base-case PFS parametric survival extrapolations for STRIDE, atezolizumab + bevacizumab, sorafenib and Lenvatinib (Figure 47, CS Document B, page 126)

The STRIDE Kaplan-Meier plot

The event for this analysis was defined as objective progression or death, whichever occurs first.

Figure 6: Company submission Kaplan-Meier plot of HIMALAYA PFS results (primary analysis; FAS) (DCO: 27 th August 2021)

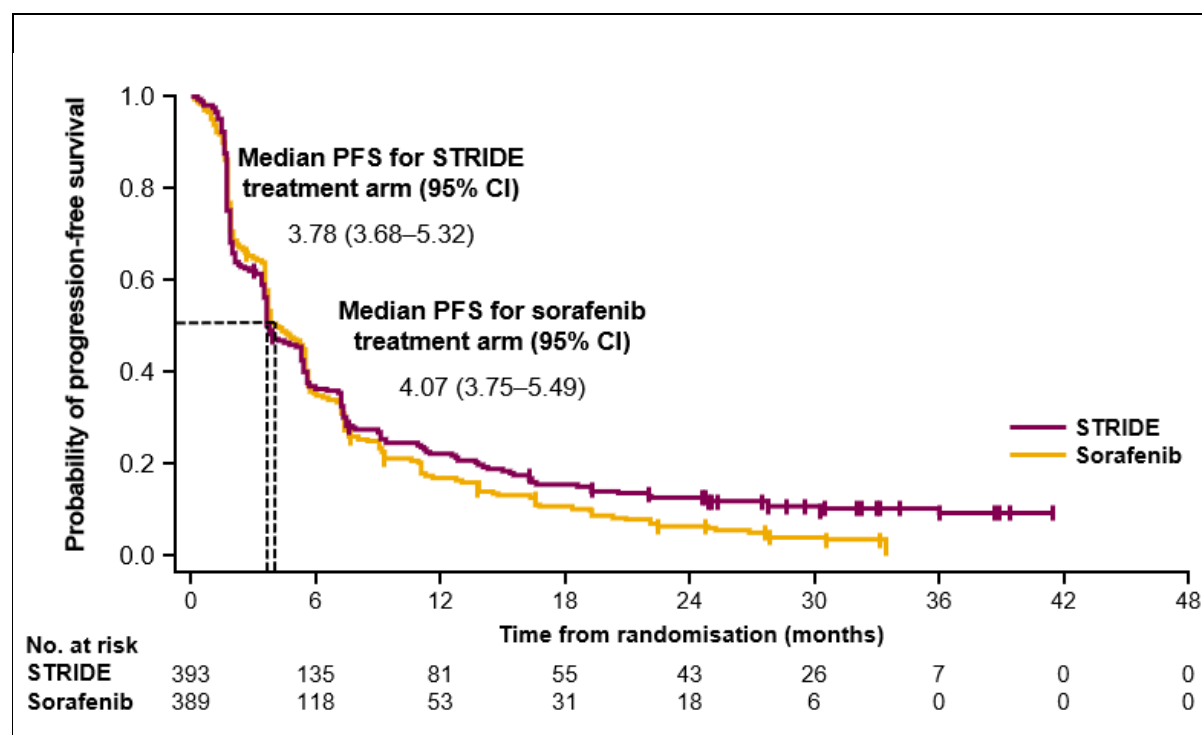


Figure 17: Kaplan-Meier plot of HIMALAYA PFS results (obtained from CS Document B, Figure 6)

According to Figure 17 (CS Document B, Figure 6; DCO August 2021), within the first 12 months, 79.4% of STRIDE patients have already progressed, after which the incidence of progression greatly slows leading to a long flattish tail to the plot from about 16 to 18 months when only 14% remain at risk (86% already progressed) and extending to 41.8 months. The KM plot is apparently strongly influenced by the 14% of patients remaining at risk beyond approximately 17 months to 41 months that contributes about 58% of the total 41.8 months of observed PFS and most of any chosen modelled extrapolation to a lifetime horizon.

As is characteristic of many PFS KM plots the company's PFS plot has notable "bends" in trajectory reflecting the timing of visits to assess whether progression has occurred. Such plots obviously cannot accurately reflect "true" progression times (irrespective of how judged) which will be far more randomly distributed than implied by the "bends" due to imposed assessment times. The KM plot is compounded by a combination of assessment intervals plus actual progression times and is a combination of the two.

"Standard" parametric models have consistent trajectory through time (i.e., are not characterised by multiple bends) and as such will deliver relatively poor AIC BIC values because they will not follow the bends in the observed plot. Such "bendy"

trends in observed KM can be more closely fitted using spline models with increasing number of knots that will tend to deliver improving AIC BIC values with increasing number of knots. However, close fitting to a bendy trajectory clearly will not reflect the reality of actual progression times because the event times of patients will be more randomly distributed than implied by the “observed” bendy plot which is compounded by assessment times and actual progression. In general, the closer the spline model is to the bendy PFS plot, the less likely it will reflect actual progression times and in extrapolation beyond 41.8 months of observation the more likely it will be influenced by the last bend(s) captured by the spline model’s knots or by the long flat tail of the KM from approximately 18 months.

In brief, because of the uneven (bendy) trajectory of the observed data, it is unlikely that AIC BIC values will necessarily be meaningful in determining “a good” model of actual progression times (i.e. reflective of event times).

COMPANY MODEL OF PFS *STRIDE*

The company’s spline model of PFS was based on the alignment of modelled hazard with “observed” smoothed hazard shown in Figure 18 (CS Document B Figure 39) and on the AIC BIC values from spline and other models. It was unclear to the EAG whether data from the DCO in Figure 6 or from a later DCO was used. The relevant part of CS Document B Figure 39 aligns observed hazard (shown as a dotted line) with the spline models’ hazard. In the EAG’s opinion, none of the spline hazard models shown fit particularly well after six months. For reasons explained above spline models although delivering favourable AIC BIC scores may risk over influence from the imposed visit times.

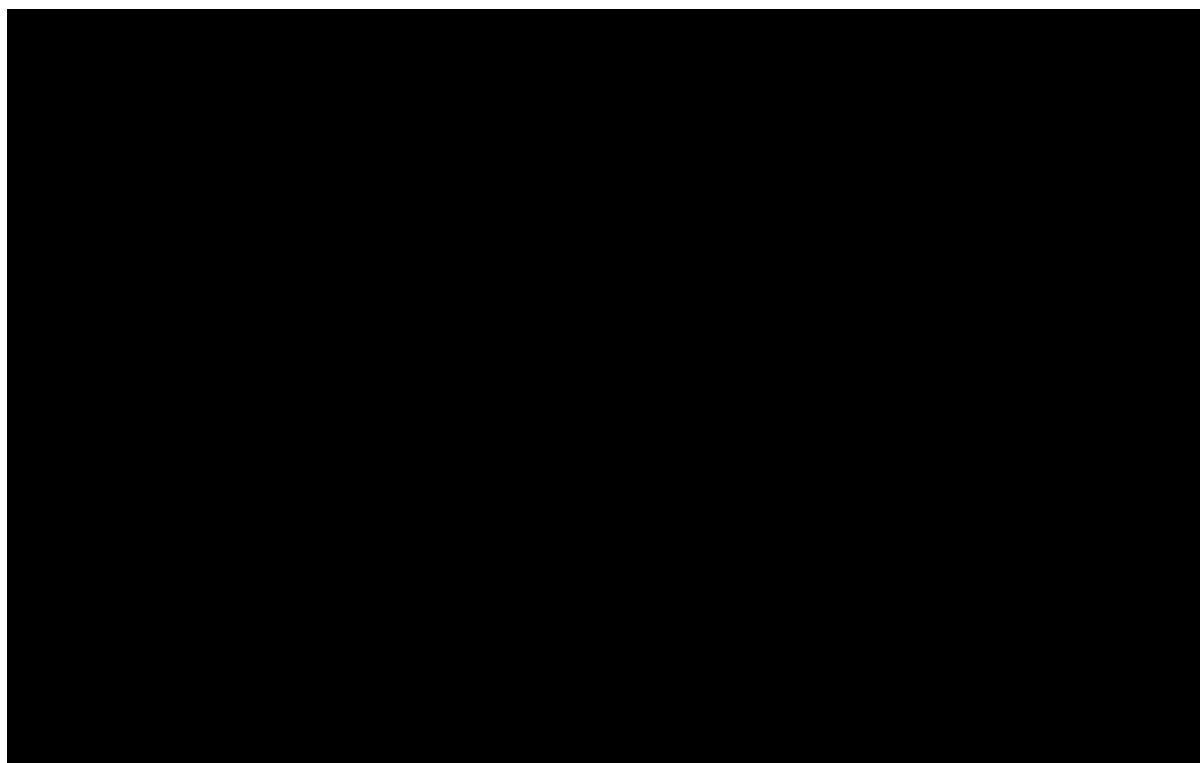


Figure 18: Company model of PFS STRIDE (alignment of modelled hazard with “observed” smoothed hazard, truncated by EAG at 36 months)(Obtained from CS Document B, Figure 39)



The EAG reconstructed the IPD underlying the KM to provide 95% CIs and compared the reconstructed KM with the KM data from the company’s economic model. The comparison showed a close correspondence between the two (see Figure 19).

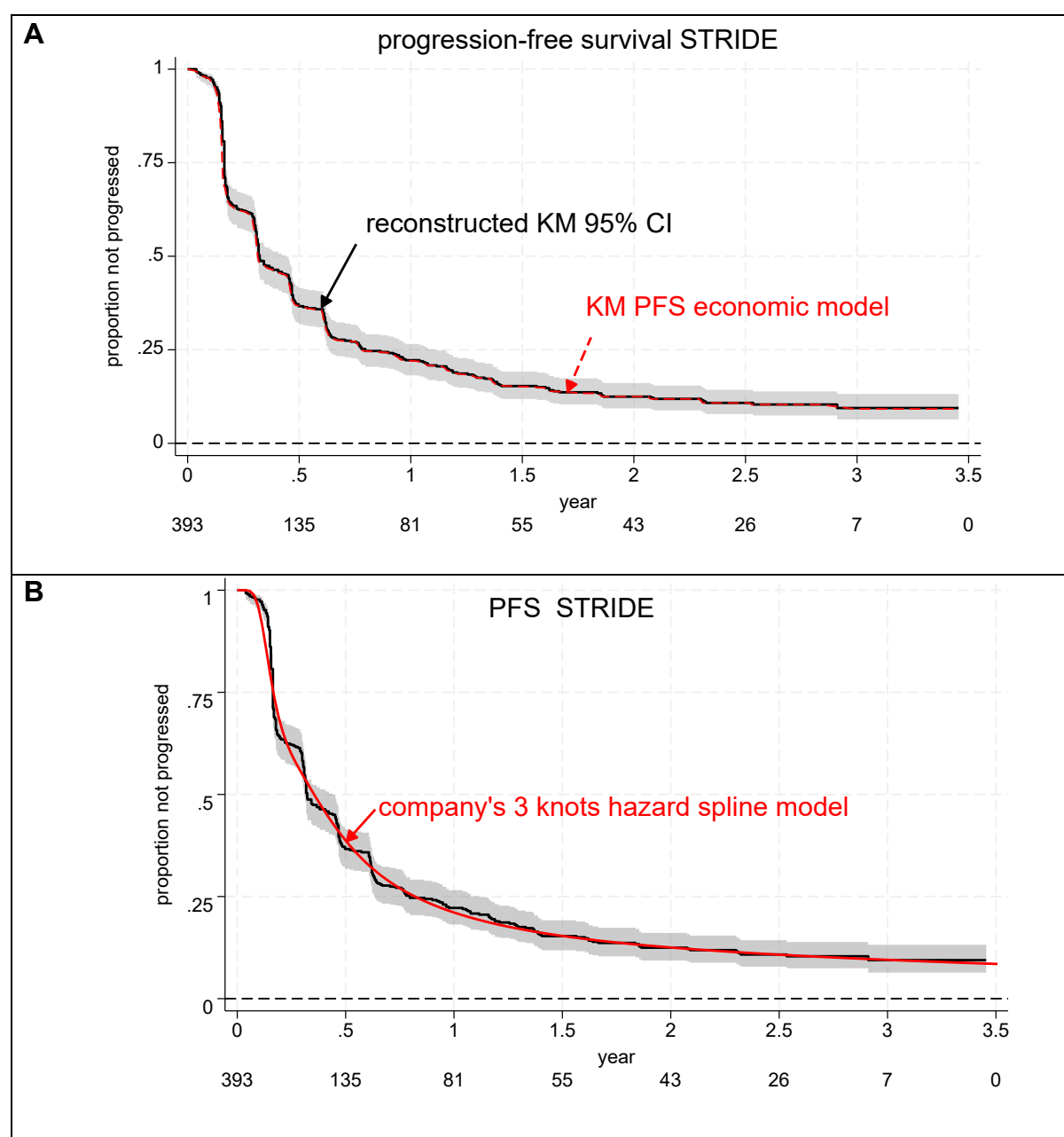


Figure 19: EAG Reconstructed KM (STRIDE PFS) and 95% CIs (A) with company spline model (B).

The company's selected a 3-knot spline model (shown in Figure 19) exhibited AIC BIC scores of 1959.3 and 1979.1 respectively (CS Document B Table 40), lower values than those delivered by "standard" models (Appendix O 2.1 Table 61) shown in Table 28.

Table 28: AIC/BIC values generated by fitting standard parametric models (CS Appendix O section 2.1, Table 61)

Submission Appendix O section 2.1, Table 61				
Function	AIC	Rank (AIC)	BIC	Rank (BIC)
3-knot spline model*	1959.3	-	1979.1	-
Exponential	1956.89	6	1960.85	6
Weibull	1958.04	7	1965.97	7
Log-normal	1899.04	1	1906.97	1
Log-logistic	1901.98	3	1909.91	2
Gompertz	1951.44	4	1959.37	4
Generalized gamma	1899.44	2	1911.33	3
Gamma	1952.67	5	1960.60	5

*EAG addition to table

When extrapolated to a 20-year time horizon the company's spline models of hazard exhibit an almost unchanging flat trajectory at a very small hazard from 10 years to the 40-year time horizon (e.g., CS Document B Figure 39).

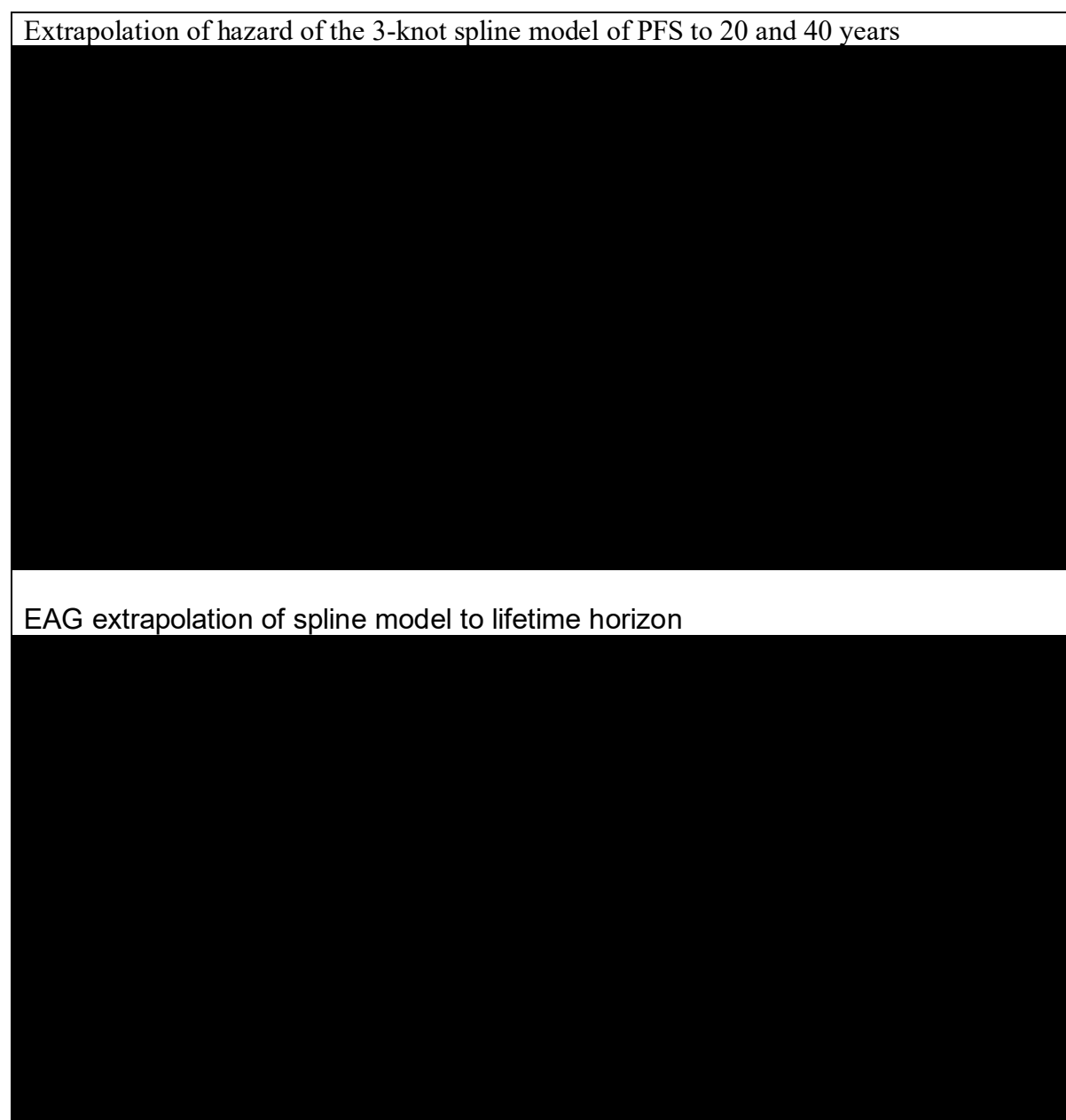


Figure 20: Smoothed hazard plots for PFS for STRIDE (obtained from CS Document B, Figure 39)

When extrapolated further to the 40-year lifetime horizon modelled hazard remains nearly flat. This results in little progression after 10 years as seen in Figure 21 (obtained from CS Document B, Figure 38), with a small number of patients remaining un-progressed even after 40 years.

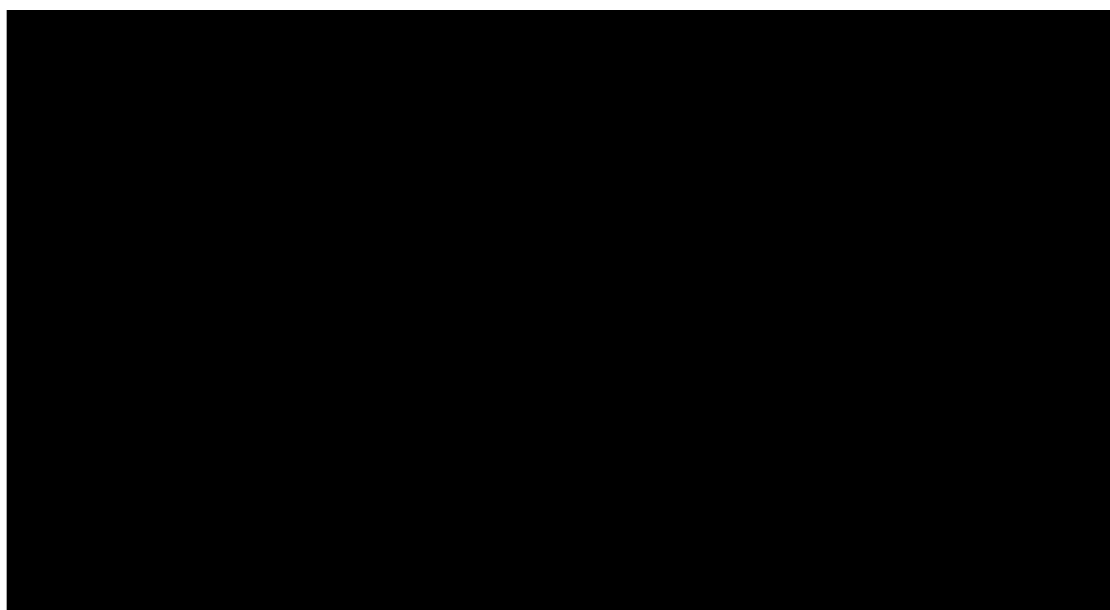


Figure 21: PFS for STRIDE with parametric survival function extrapolations (obtained from CS Document B, Figure 38)

In the opinion of the EAG, the company model with three knots may “overfit” the observed data and may not reflect the progression of an average 64-year-old patient since the model is influenced strongly by imposed visit times and by the post 17-month PFS data that relies on only 14% of the population.

In contrast, standard models with the exception of generalised-gamma and Gompertz predict that progression is complete within approximately five to ten years as shown in Figure 22 (Appendix Document Figure 23). The Gompertz and generalised-gamma models are influenced strongly by the tail of the KM plot predicting some individuals not progressed after 40 years. These two models give a lot of weight to the post-17 months part of the KM plot after which only 14% patients remain at risk.

Company Appendix DOC Figure 23 STRIDE PFS parametric survival extrapolations

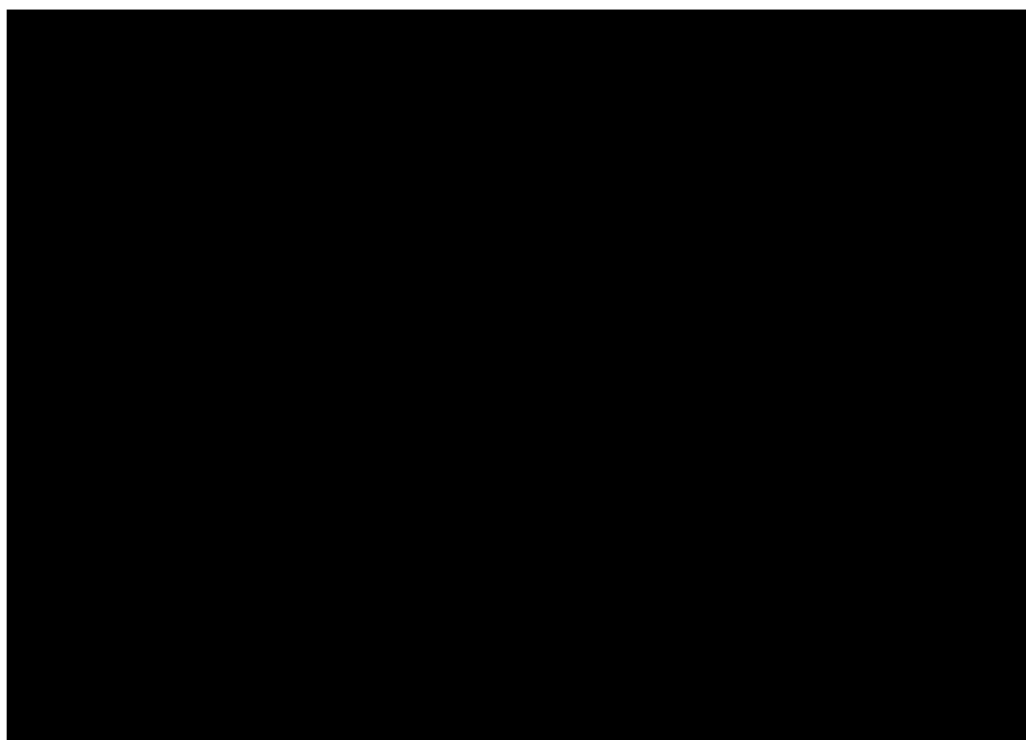


Figure 22: PFS for STRIDE with parametric survival function extrapolations (obtained from CS Document B, Figure 38)

EAG summary: Most parametric models of the company's 42-month observed PFS predict completion of progression events within 5 to 15 years. Much more optimistic models including the company's spline models, the Gompertz and generalised-gamma models, predict that some patients remain in an "unprogressed status" after 40 years; these models may seem unrealistic, however the EAG clinical advisor stated that it is possible some patients may experience "cure" particularly if of a young age. The EAG note that HIMALAYA included patients less than 20 years of age. For reasons explained above, although these models deliver superior AIC BIC values, these scores are not necessarily a useful guide to a "good" model.

Patient characteristics of the 14% patients at risk beyond approximately 17 months would be of interest; the company did not report a subgroup analysis for their 3-knot spline PFS model and "best performer patients" remain unidentified.

Company model of PFS sorafenib

The company used IPD from HIMALAYA to develop a 2-knot spline model. The DCO used appears to be later than that shown in CS Document B Figure 6 since the KM

plot shows almost complete progression. Many models will generate good fit to this mature data and the spline model selected by the company is acceptable.

Reconstructed Kaplan Meir (95% CIs) and the company model are shown in Figure 23.

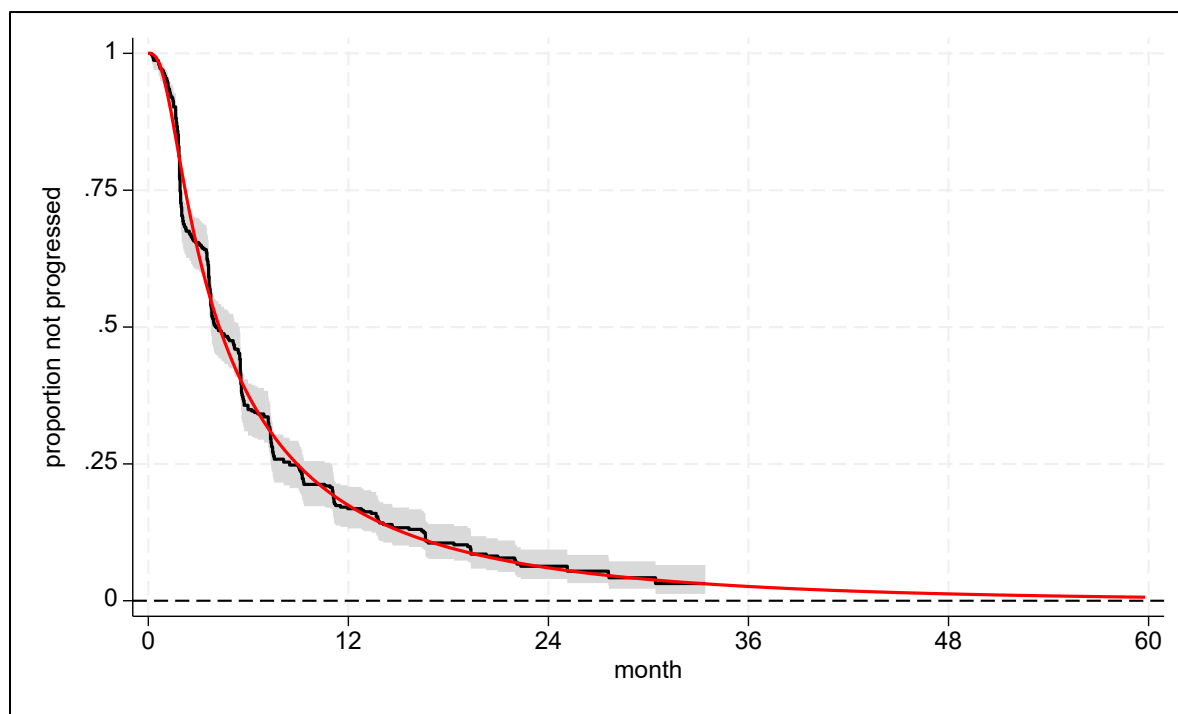


Figure 23: PFS KM plot and company spline model

PFS: comparators atezolizumab + bevacizumab and lenvatinib

Models of PFS were developed using anchored NMA HR outputs applied to the cubic spline model for sorafenib PFS (Figure 24) that used IPD from HIMALAYA (DCO used unclear but probably not Aug 27, 2021).

The PFS NMA inputs are summarised in Table 29 together with the NMA outputs from CS Document B Figures 15 and Figure 16.

Table 29: Summary of input and output from NMA for PFS

Regimen	HR input to NMA*	HR 95%: CrIs output from NMA
STRIDE	0.76 (0.65, 0.89)	
Atezolizumab + bevacizumab	0.66 (0.52, 0.85)	
Lenvatinib	0.92 (0.79, 1.06)	

* Inputs based on CS Appendix Table 22

It should be noted that the 95% CrIs associated with output are very wide and that models based on NMA output will be subject to considerable imprecision (see EAG Figure 37 and Figure 38).

The company's approach led to median PFS values for lenvatinib and atezolizumab + bevacizumab listed in Table 30 that also lists the medians reported in the REFLECT and IMbrave150 RCTs. As can be seen there are differences between RCT and company model medians that are particularly large for atezolizumab + bevacizumab. The differences exist even though HRs from IMbrave150 and REFLECT were input to the NMA and a naïve expectation the relationship of medians would be more consistent.

Of particular concern is the low HR PFS output for atezolizumab + bevacizumab versus sorafenib of [REDACTED] based on investigator assessment of PFS rather than from a blinded independent board. This has implications for the cost-effectiveness analysis where PFS is used as proxy for TTD, since [REDACTED] indicates prolonged treatment that accumulates considerable cost for atezolizumab + bevacizumab.

Compared with HR reported in published NMAs (including Vogel et al.), the [REDACTED] HR from the company NMA might be considered an outlier.

Table 30: NMA HR modelled median PFS and naïve comparison with RCT reported median PFS

Regimen	RCT reported	Company modelled HR PFS/AstraZeneca model
STRIDE* Sorafenib*	3.78 months 4.07 months	4.25 months 4.25 months
Atezolizumab + bevacizumab^ Sorafenib^	6.9 months 4.3 months	10.12 months 4.25 months
Lenvatinib [∞] Sorafenib [∞]	7.4 months 3.7 months	6.44 months 4.25 months

* Data from Figure 6 (DCO 27th Aug 2021)

^ Cheng et al., 2022 Update of IMB 150 *Journal of Hepatology* 76: 862-873

∞ Kudo et al., 2018 *Lancet* 2018; 391: 1163–73

The company's method for developing PFS models for STRIDE and sorafenib was different from that used for atezolizumab + bevacizumab and for lenvatinib. The

former used IPD direct from the HIMALAYA RCT, while the latter applied the company's interpretation of output from the company anchored NMA. The EAG considers the difference in methods may lead to inequitable comparison between STRIDE vs atezolizumab + bevacizumab and between STRIDE versus lenvatinib. The EAG therefore investigated using the same method for atezolizumab + bevacizumab and lenvatinib PFS as that used by the company for STRIDE

Figure 24 shows the EAG reconstructed PFS KM for IMbrave150 RCT PFS compared with the atezolizumab + bevacizumab PFS modelled by the company, together with the best fit (generalised gamma) for the IMbrave150 KM. As can be seen the company model seems optimistic relative to RCT-observed data.

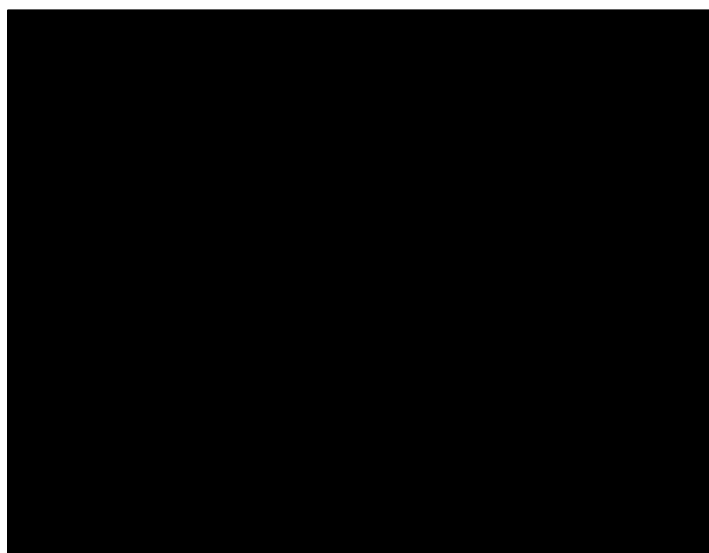


Figure 24: Reconstructed KM PFS IMbrave150 based on Finn et al. Naïve comparison versus company model of atezolizumab + bevacizumab

The EAG performed the same analysis for PFS from the REFLECT RCT. The reconstructed KM plot based on Kudo et al., 2018⁶⁵ is shown in Figure 25.

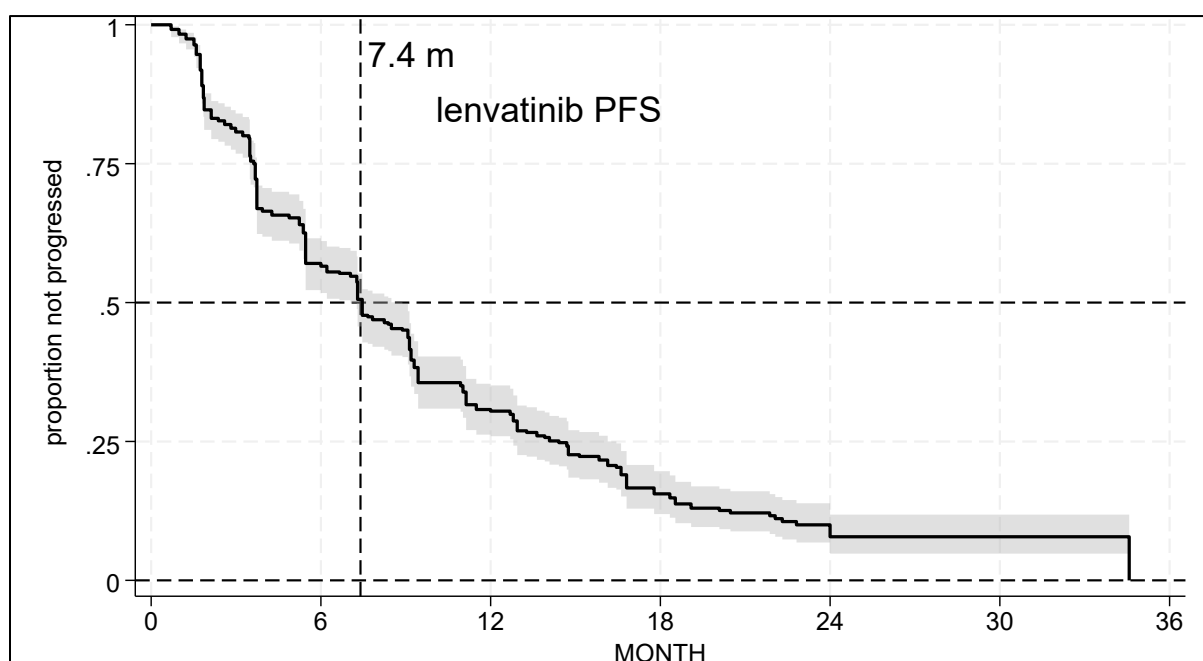


Figure 25: Reconstructed KM 95%CI PFS lenvatinib based on REFLECT RCT

The company model for lenvatinib PFS was derived by applying a [REDACTED] HR to the HIMALAYA IPD-based spline model for sorafenib. The input to the NMA was [REDACTED] (CS Appendix Table 22). The company's NMA HRs and their use in PFS modelling are summarised in Table 31.

Table 31: Summary of HR inputs outputs from the company's NMA for PFS

Company NMA	HR input	HR output	HR used to model PFS
Lenvatinib vs sorafenib	[REDACTED]	[REDACTED]	[REDACTED]
A+B vs sorafenib	[REDACTED]	[REDACTED]	[REDACTED]
STRIDE vs sorafenib	[REDACTED]	[REDACTED]	Not used ^{‡‡}

** these HRs were applied to the HIMALAYA IPD derived spline model of sorafenib PFS.*

‡ this HR is an outlier when compared to input used in published NMAs. It is based on IMbrave investigator PFS rather than on blinded independent assessment.

‡‡ the company modelled PFS for STRIDE using IPD from HIMALAYA latest cut off.

Time-to-treatment discontinuation (TTD) STRIDE

Tremelimumab is provided as a single one-off dose and TTD for STRIDE refers to discontinuation of durvalumab. Some patients in HIMALAYA were rechallenged with

STRIDE including tremelimumab, but EAG understanding is that rechallenge was not encompassed in TTD analysis. As with OS and PFS modelling the company's TTD involved judging alignment of smoothed hazard with modelled hazard (CS Document B Figures 48 and 50). The main difference in approach for TTD relative to that for OS and PFS being that spline models were not explored for TTD. Using visual alignment of hazard models with smoothed hazard, and AIC BIC scores, the company selected the Weibull model from amongst 8 models explored as potential base case. Company models including Weibull are depicted in Figure 26 (CS document B Figure 49) (EAG have added an arrow to identify the Weibull line). The second best fit (generalised gamma was used in scenario analysis).

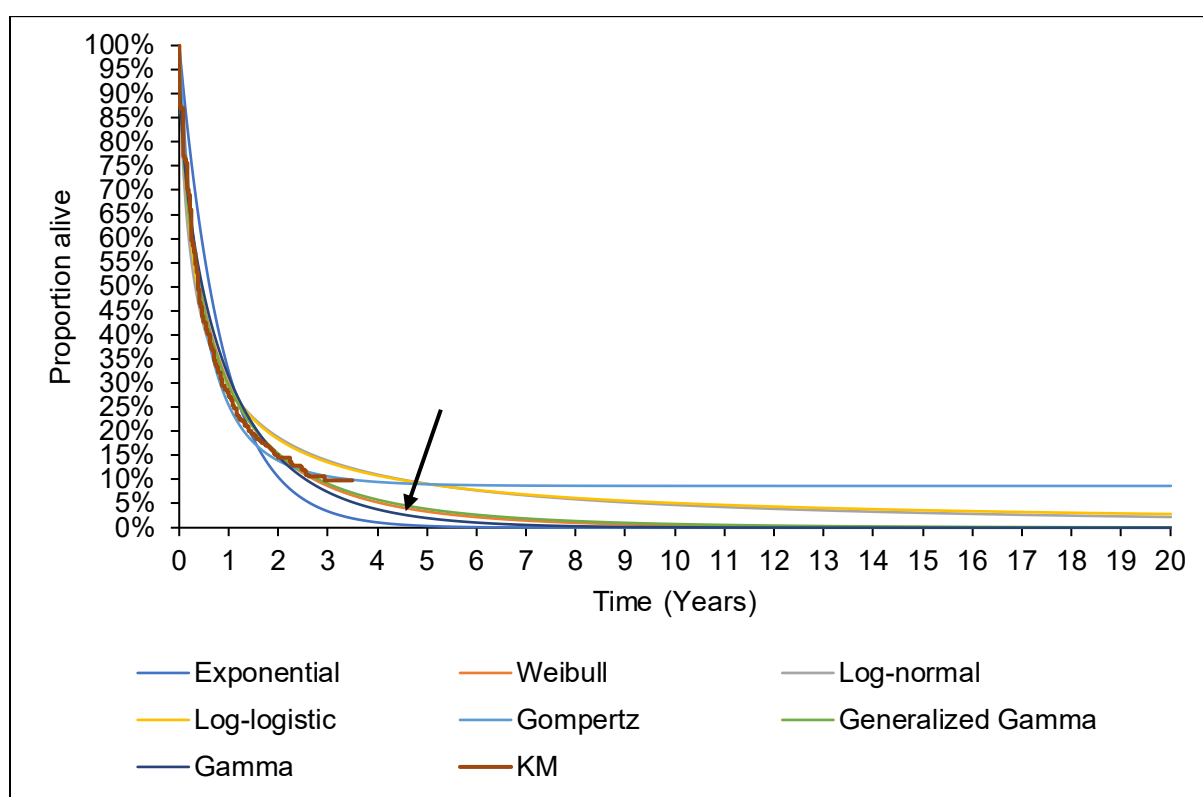


Figure 26: TTD (durvalumab only) parametric survival function extrapolations (obtained from CS Document B, Figure 49)

To the EAG, the company's TTD KM plot seemed unexpectedly "bendy" over the first six months, as though it might be influenced in some way by visit times making it rather like PFS KM plots, and it lacked 95% CIs. The EAG reconstructed the IPD underlying the KM to provide 95% CIs and compared the reconstructed KM with the KM data from the company's economic model and with the company Weibull model

(Figure 27 A and B). According to the Weibull model very few patients remained on treatment beyond about 10 years.

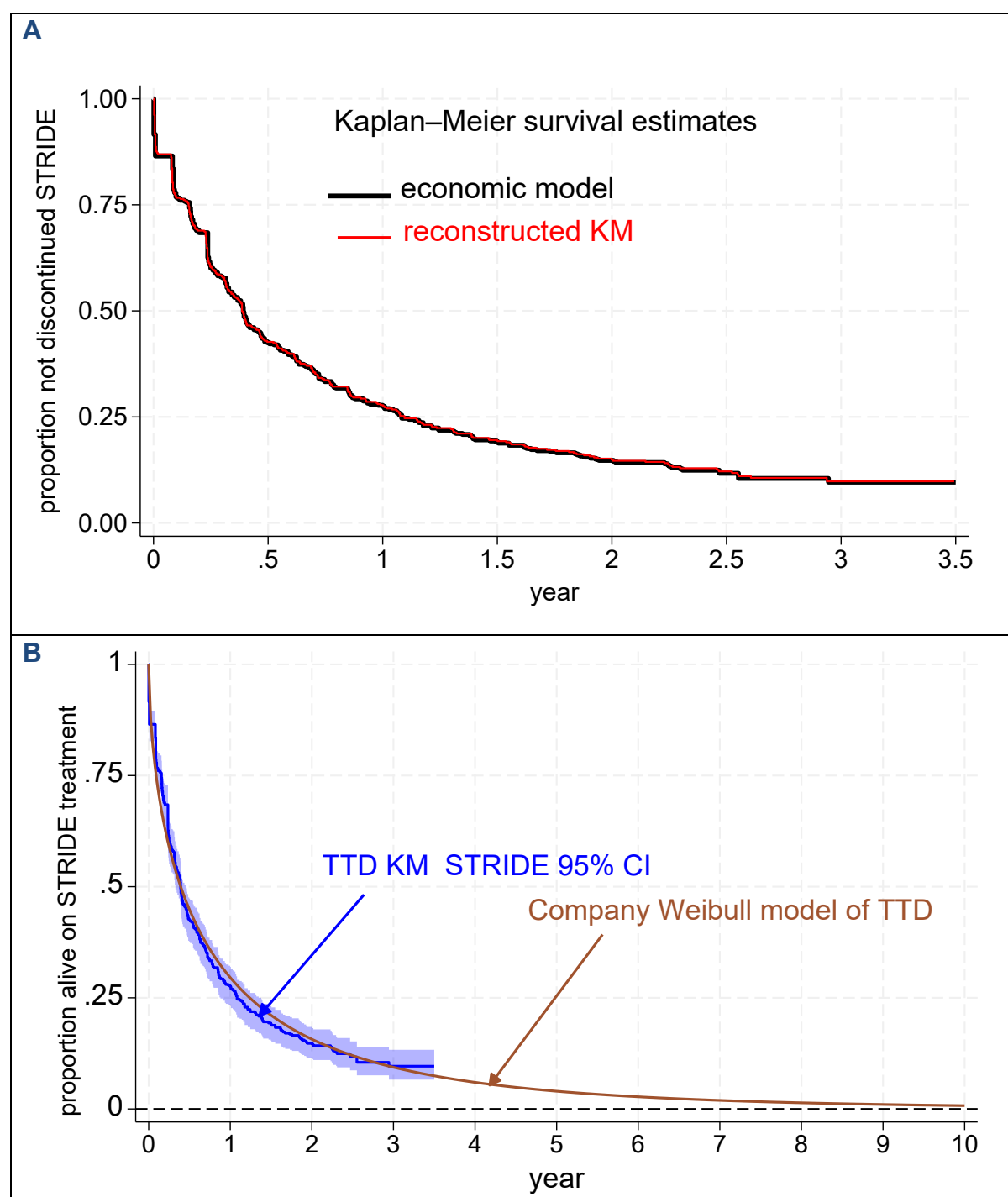


Figure 27: A) reconstructed KM for STRIDE TTD; B) company Weibull model for STRIDE TTD

The EAG explored additional models of TTD including cubic spline models since the company favoured spline models for overall survival and for PFS. Table 32 lists AIC BIC values for EAG models. On AIC BIC scores, spline models with 2 or 3 knots and

the Chen model perform better than the company's Weibull model. The 3 knot (and two knot) spline models produce better visual fit to the KM data than found with a Weibull model (Figure 28).

Table 32: AIC BIC scores for EAG models for STRIDE TTD

Model	AIC	BIC		Model	AIC	BIC
cubic spline 3knot	1570.118	1589.987		bathtub	1662.133	1674.054
cubic spline 2knot	1573.54	1589.436		lognormal	1668.036	1675.983
Chen	1595.375	1603.323		Gompertz	1668.078	1676.026
cubic spline 1knot	1602.176	1614.097		exponential	1760.764	1764.738
Weibull	1609.201	1617.149		Rayleigh 2	1762.764	1770.712
ggamma	1610.121	1622.042		Rayleigh 1	2844.636	2848.61
loglogistic	1641.017	1648.965				

However, as explained, when applied to KM plots with many bends spline models may overfit the data. Consequently, on balance, the EAG prefer the company's Weibull model.

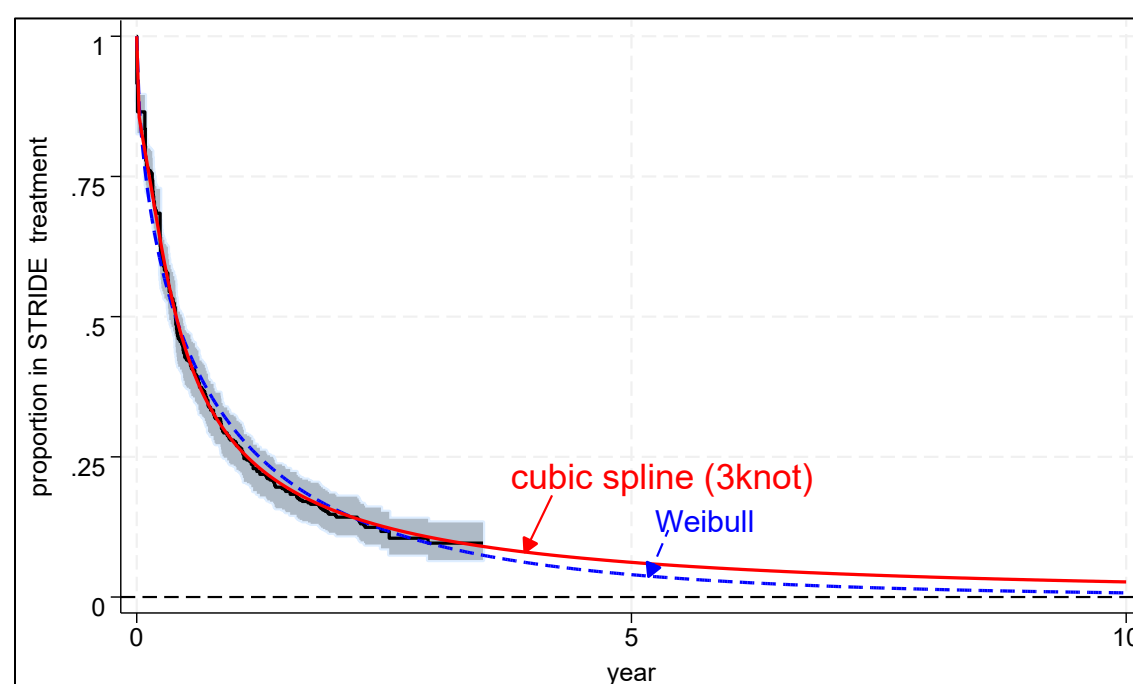


Figure 28: Weibull and cubic spline models of STRIDE TTD extrapolated to ten years

When extrapolated to the lifetime horizon the three-knot cubic spline model predicts some patients remain in treatment to about 30 years (see Figure 29).

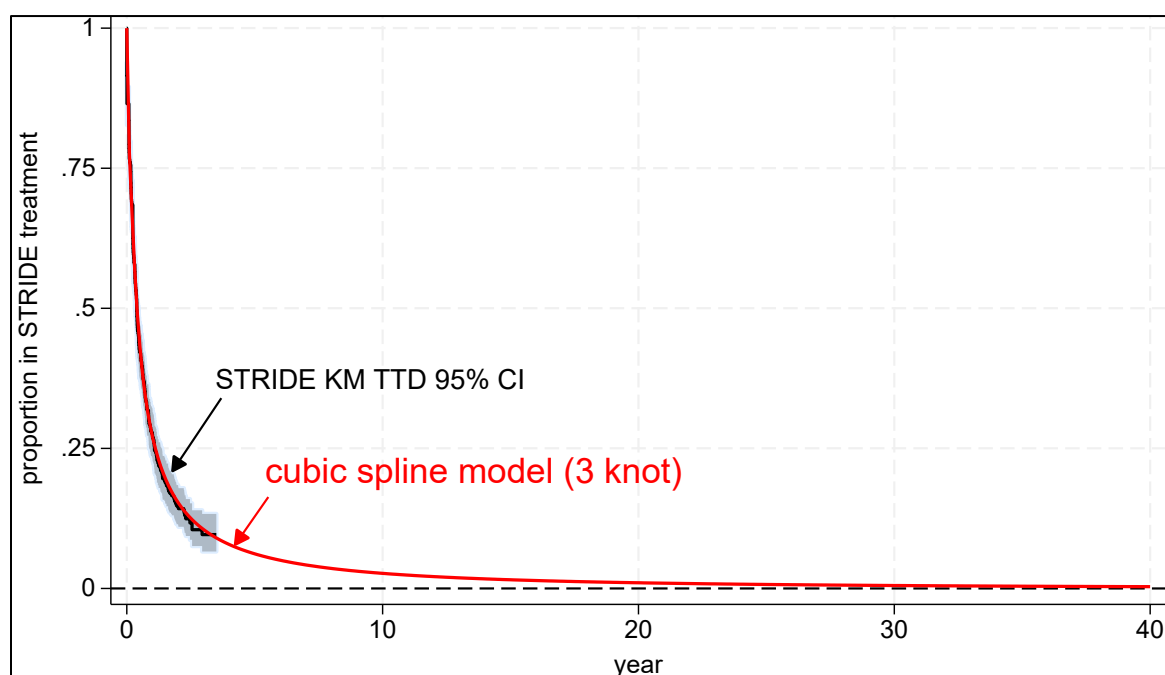


Figure 29: Cubic spline model of STRIDE TTD extrapolated to lifetime horizon

TTD sorafenib

TTD data for sorafenib was mature with the majority discontinued by end of follow up. Most models will fit well to such mature data. The company selected a lognormal model for TTD for sorafenib but did not explore spline models. The EAG reconstructed IPD for sorafenib TTD and fit standard and spline models. The best performing spline model (one knot) (Figure 30) scored less well than the lognormal model on AIC BIC values and produced a model almost indistinguishable from the company lognormal model. The EAG concluded that the company lognormal model was satisfactory.

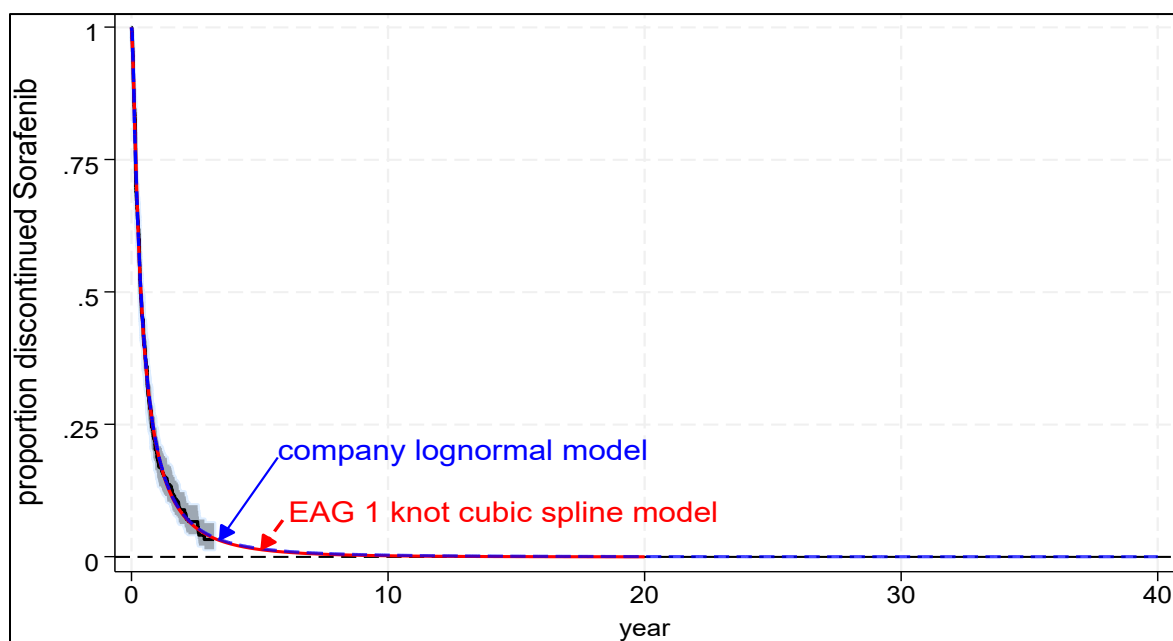


Figure 30: Spline model of sorafenib TTD extrapolated to lifetime horizon

TTD for lenvatinib and atezolizumab + bevacizumab

The company found a lack of evidence for TTD of atezolizumab + bevacizumab or lenvatinib and assumed that PFS and TTD were equivalent for these interventions.

The EAG comment:

- A. lack of evidence does not seem a sound justification for the assumption made
- B. the assertion that there is a lack of evidence for lenvatinib is incorrect
- C. Previous TAs (TA551 lenvatinib vs sorafenib, and ID1655) have modelled TTD using IPD from the relevant trials and have modelled observed TTD where possible; TA666 used PFS as a proxy for TTD where data was not available, i.e., for Lenvatinib. Committee papers indicate that their approach was acceptable to committee.

The use of PFS as a proxy for TTD of lenvatinib and for atezolizumab + bevacizumab means that the method used for STRIDE and sorafenib TTD (that is employing IPD from the HIMALAYA) differs from that used for lenvatinib and atezolizumab + bevacizumab, which the company models by applying the company's interpretation of the anchored NMA HR output to the spline model of PFS for sorafenib. This may result in a non-alignment between modelled TTD (i.e., proxy PFS) and TTD (proxy PFS) seen in the relevant RCTs from which the HRs were

extracted for input to the NMA (please see , Figure 32 and Figure 35) shown in the PFS section illustrate this mismatch).

TTD information for lenvatinib can be found in the TA551 committee papers. The EAG's report in TA551 shows TTD for lenvatinib and sorafenib based on the REFLECT RCT and is reproduced.

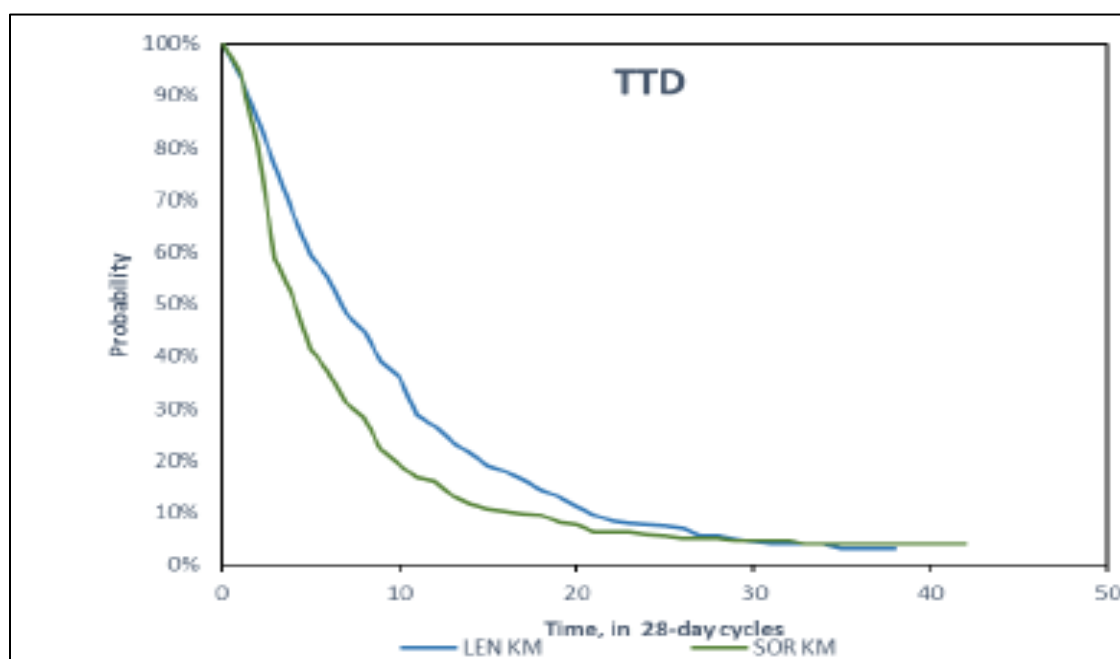


Figure 31: TTD KM plots from REFLECT (obtained from EAG report of TA551)

The EAG assumed the curve in Figure 31 represents data from all 478 patients in the lenvatinib arm, reconstructed IPD and compared TTD versus PFS (Figure 32).

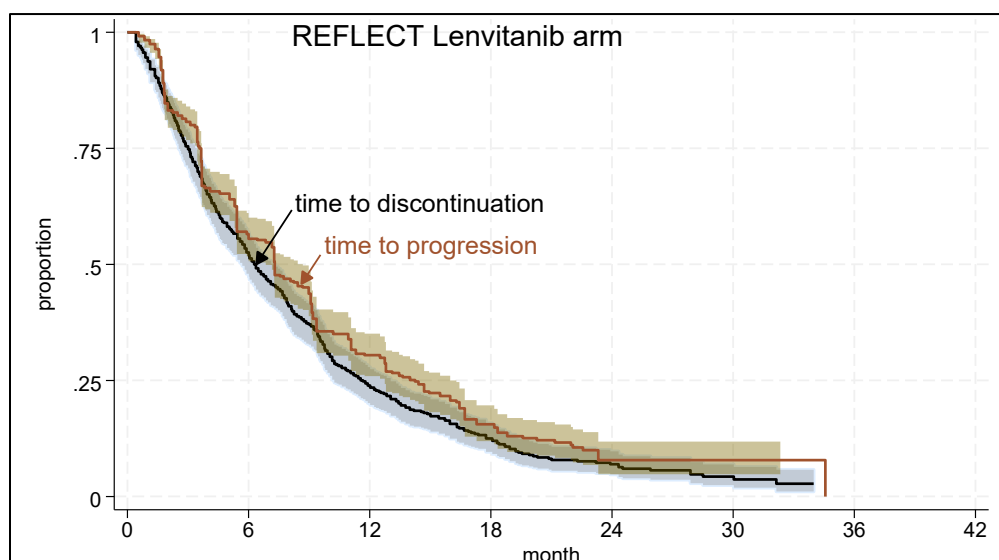


Figure 32: Lenvatinib TTD compared to PFS based on data from TA551

PFS is somewhat delayed relative to TTD. In TA551, the KM data for TTD was used in economic modelling since the data was virtually complete. The EAG notes that TTD plots from REFLECT lack the bends in trajectory seen for early times in TTD plots from HIMALAYA, likely reflecting more frequent assessment times than in HIMALAYA.

The EAG developed an exponential model of TTD for lenvatinib. The result shown in Figure 33 indicates that with this model less than 1% remain on treatment after 54 months.

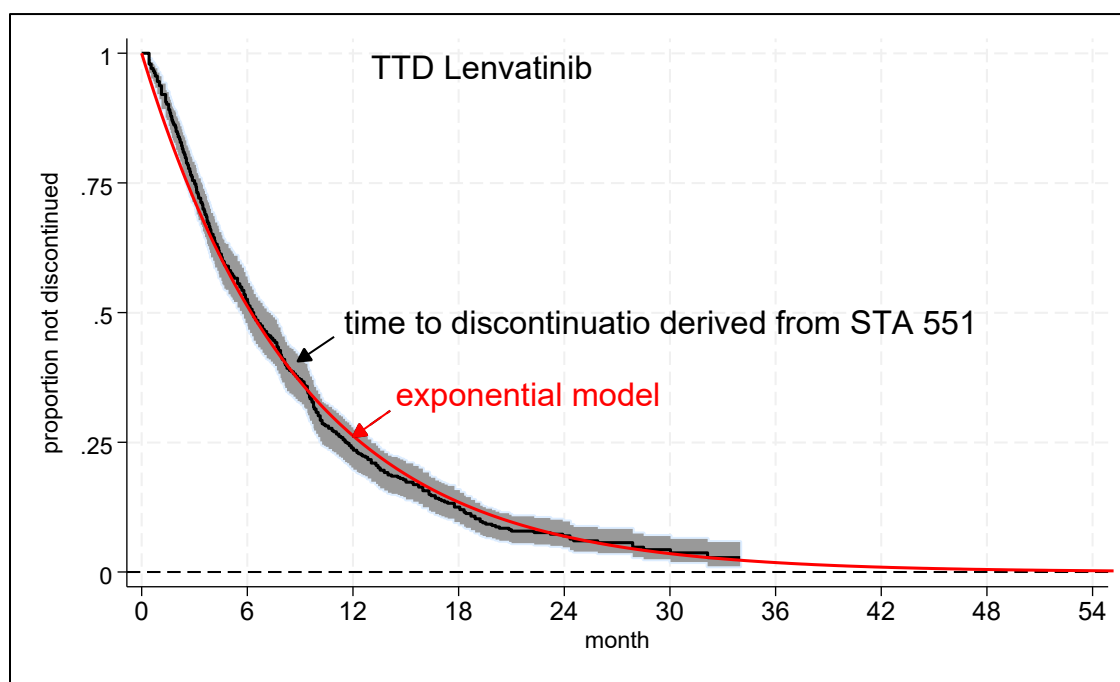


Figure 33: Exponential model fitted to lenvatinib TTD

In ID1655 (atezolizumab + bevacizumab vs. comparators) the manufacturer's submission states "*Data on time to treatment discontinuation (TTD) are available for Atezo+Bev and sorafenib in IMbrave150*". (this refers to DOC 29 AUG 2019 corresponding to the Publication by Finn et al.,)... "*As such, TTD data directly from the IMbrave150 study were used to inform treatment duration in the economic model. For bevacizumab, whilst it is administered until disease progression or unacceptable toxicity, we still consider that TTD data from the study are more accurate to estimate treatment duration, compared to PFS*".

The company used KM data for TTD followed by exponential model for extrapolation beyond the KM and the submission provides a graph for TTD but unfortunately in the committee papers available in the public domain this graph is redacted.

EAG summary: The company models based on PFS and TTD equivalence was used and accepted in TA666 where there was a lack of published evidence available to inform the lenvatinib TTD; thus, proxy PFS became a necessity, which may lead to bias particularly for STRIDE versus atezolizumab + bevacizumab and is associated with severe imprecision stemming from the wide CrIs delivered by the

NMA used to develop the PFS curves. Figure 34 compares the company's models of TTD for STRIDE and for atezolizumab + bevacizumab.

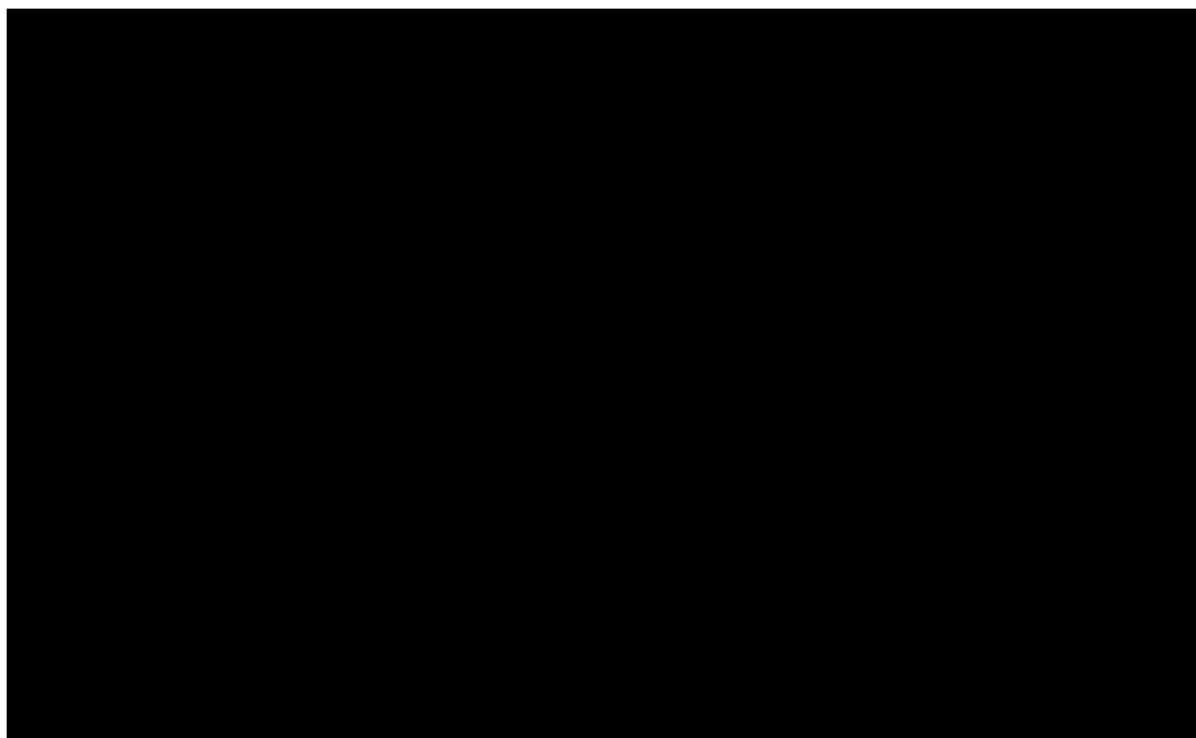


Figure 34: Company models for discontinuation of STRIDE and atezolizumab + bevacizumab treatments.

Life-years gained according to company modelling of OS, PFS and TTD

According to the company's selected spline models for OS and for PFS (Figure 35) most life year-gain occurs while patients are in the post-progression state as indicated from the area under curve (AUC) of the model plots. The company state this is clinically plausible because of long-lasting immune changes from STRIDE that exert benefit after treatment has stopped or while patients are in a post-progressed state. Post-progression benefit may be gained from second line treatments implemented after discontinuation or progression. The proportion of post-progression LYG attributable to long-lasting immune effects of STRIDE is difficult to determine.

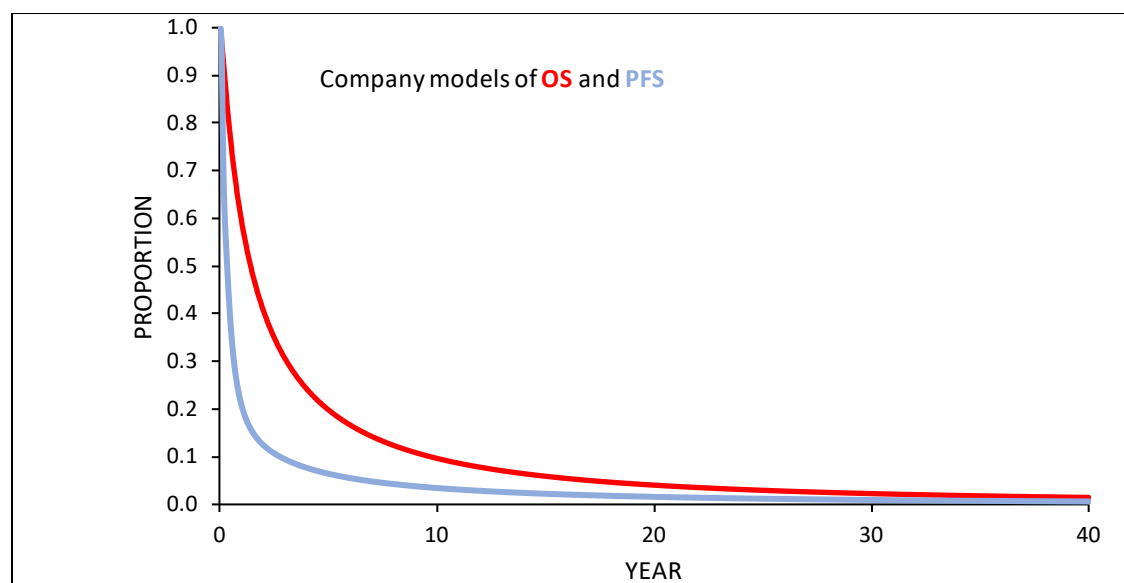


Figure 35: EAG graph of company spline models for overall survival and for PFS

Figure 36 illustrates uncertainty in LYG from the company models when the wide 95%CrIs from the NMA output are incorporated into the analysis and when STRIDE is modelled by the same method as used for comparators atezolizumab + bevacizumab and lenvatinib. According to this application of the company NMA HRs and credible 95% CIs most LYG from STRIDE occurs in the post progression state. By about 25 years very few patients remain either alive or in the post-progression state. Shaded areas representing credible 95% CIs are wide (because of the imprecision associated with credible 95% CIs in the NMA HRs) with an overlapping area where it is possible for more patients to be in unprogressed state than there are live patients. However, the model structure does not allow this to occur.

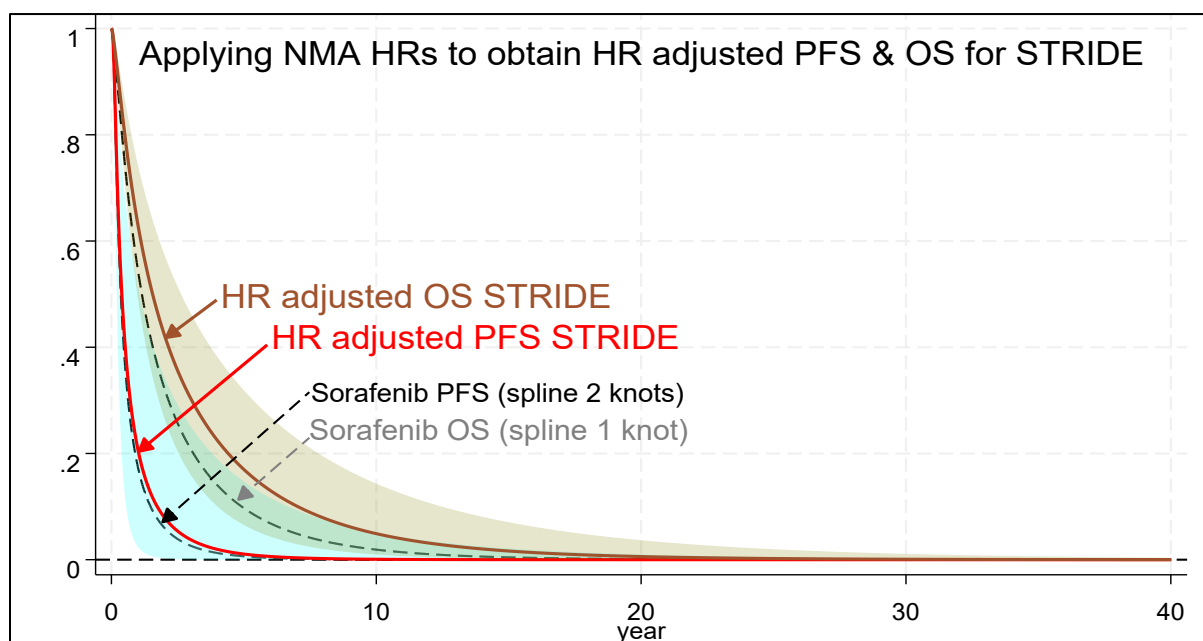


Figure 36: Models of OS and PFS for STRIDE taking account 95%CrIs

Figure 37 shows the same analysis for lenvatinib. The credible interval associated with PFS almost completely envelop that for OS, indicating that at most time points it is possible that the proportion of unprogressed individuals may be greater than the proportion alive. However, the model structure does not allow this to occur.

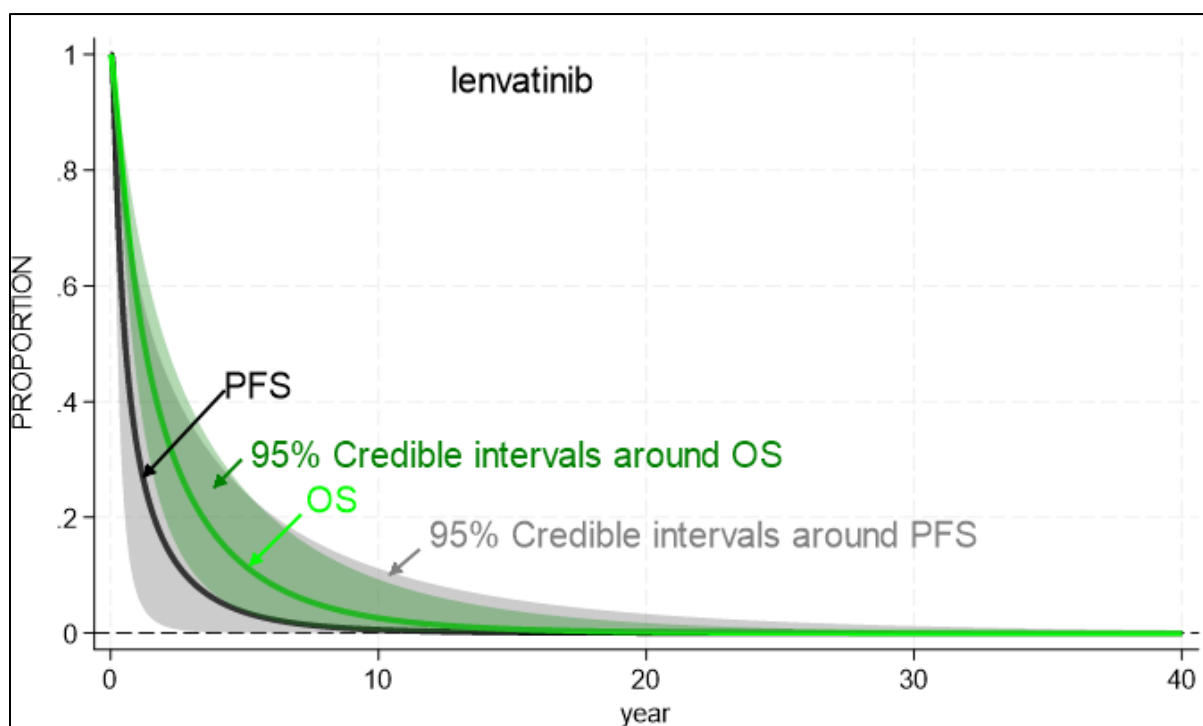


Figure 37: Company models for Lenvatinib OS and PFS taking account of 95%CrIs

A very similar result was obtained for atezolizumab + bevacizumab (see Figure 38).

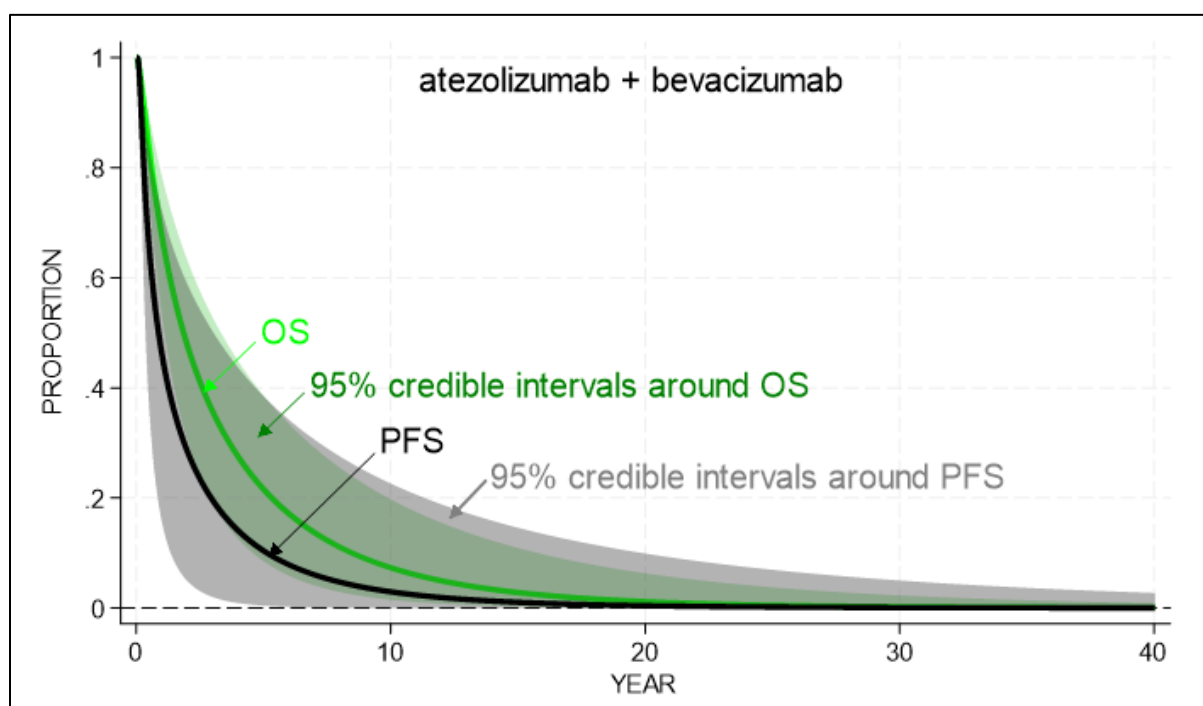


Figure 38: Company models of OS and PFS taking account of 95% CrIs

It is possible to compare the HR-adjusted STRIDE results with those derived by the company for lenvatinib and for atezolizumab + bevacizumab using the same methodology. The comparisons are shown in Figure 39 .

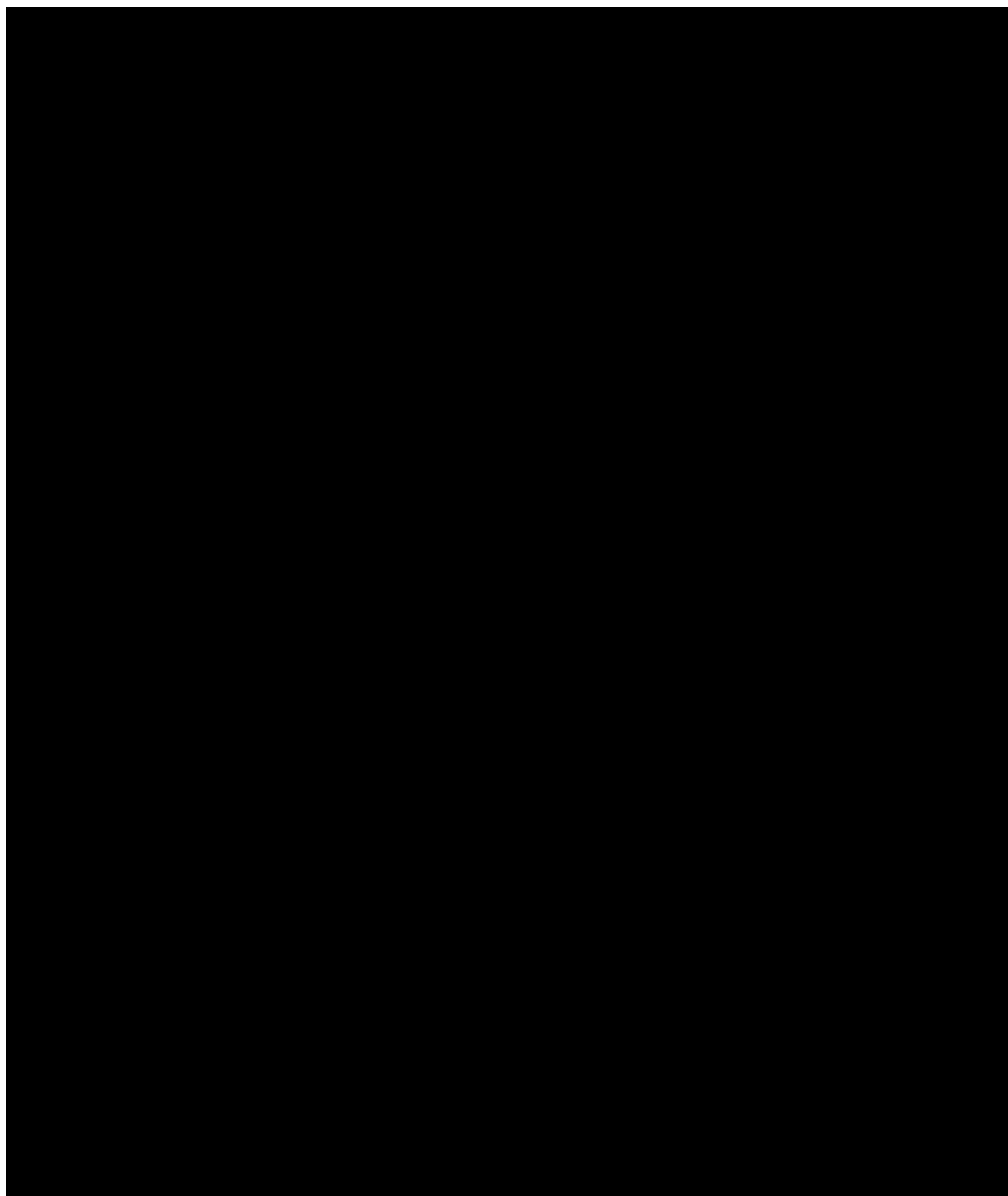


Figure 39: NMA HR-adjusted models of OS and PFS

NMA HR-adjusted models of OS and PFS for all three treatments (STRIDE, atezolizumab + bevacizumab, and lenvatinib) have negligible survivors by 24 years. In contrast STRIDE models based on IPD generate superior OS and PFS compared

to NMA_HR-adjusted STRIDE models and exhibit survivors beyond 24 years. The methodology used of generating models appears to bias in favour of STRIDE relative to lenvatinib and atezolizumab + bevacizumab.

Life-years gained (LYG) relative to time-on-treatment

The company's KM data for discontinuation of STRIDE treatment extends to 3.5 years of observation. The AUC indicates that over 3.5 years about 0.9 life years were accumulated on STRIDE treatment. Over 3.5 years of observation the company's KM plot for overall survival indicates that approximately 26% of patients remain alive, and the life years gained (estimated from AUC) over the 3.5-year time horizon was about 1.78 years. This gain was partly accumulated by patients while on STRIDE treatment and partly while alive but not on STRIDE treatment. From AUC estimates approximately 50% of the life years gained were while on STRIDE and 50% while off treatment. Thus, half of LYG seems due to a prolonged post-treatment effect of STRIDE and or secondary beneficial treatments received by patients who discontinued STRIDE. Over ten years (Figure 40) using the company's Weibull model for discontinuation the percentage LYG off treatment increases to >50%.

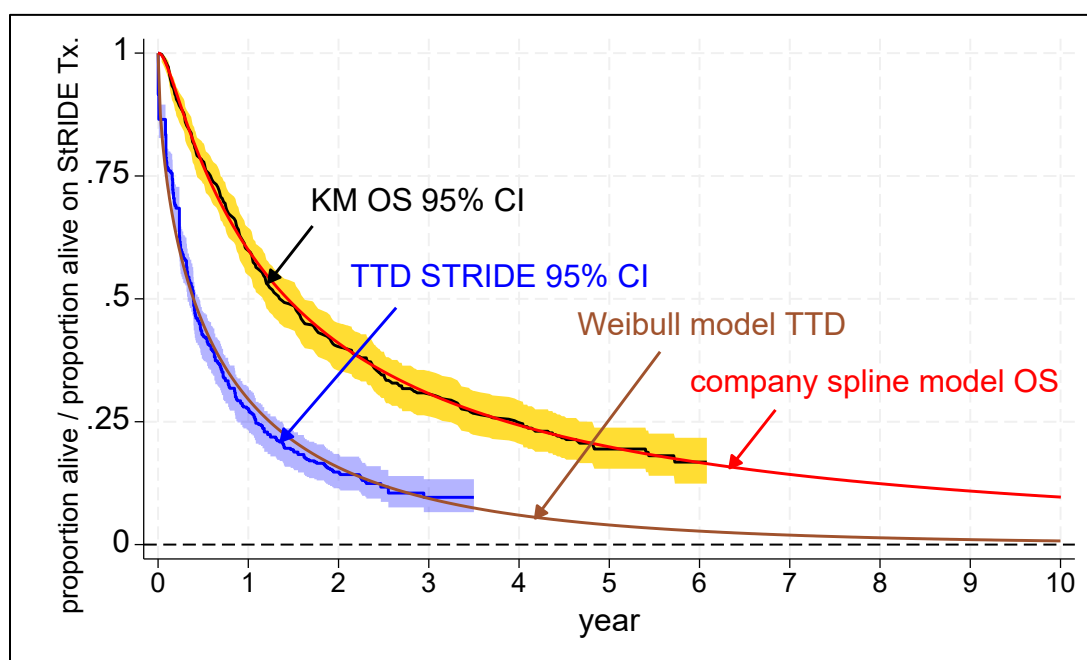


Figure 40: Company models for STRIDE OS and TTD extrapolated to ten years

EAG summary: HIMALAYA had no UK patients, the ethnic profile for the population was different to that for UK HCC patients, gender balance differs (HIMALAYA heavily weighted to males), and the age range of HCC UK patients may differ from that of HIMALAYA although median age may be similar. There is doubt that analyses of HIMALAYA can be applicable to UK HCC population.

The company used spline models for STRIDE OS and PFS, these predict a small proportion of patients unprogressed / “cured” after 40 years; the OS model seems influenced by a small subgroup of patients (14% of STRIDE population) that form a flat tail at the end of the KM plot.

The company did an anchored NMA with input for three interventions (STRIDE, atezolizumab + bevacizumab, lenvatinib) relative to sorafenib. The NMA output for these comparisons delivered wide 95% credible intervals that indicate considerable imprecision in estimates that threaten the integrity of modelled extrapolations beyond observed data to the lifetime horizon of 40 years.

The method for modelling OS and PFS of STRIDE (using IPD from HIMALAYA) differed from that for atezolizumab + bevacizumab and for lenvatinib (using NMA HR output applied to the spline model for sorafenib).

The KM plot for TTD of STRIDE appeared influenced by visit times. The company found a lack of evidence about TTD of atezolizumab + bevacizumab and of lenvatinib interventions and so assumed PFS modelling for these could be used as proxy for TTD. There is evidence about TTD for lenvatinib in the public domain but this was not recognised by the company. The assumption of equivalence for PFS and TTD is difficult to justify and limited available evidence suggests the assumption is ill-founded. The assumption of equivalence for PFS and TTD is difficult to justify, and limited available evidence suggests the assumptions although potentially ill-founded may be necessary from lack of alternative evidence. For example, although there is TTD data from TA666 this is redacted and unusable by the EAG.

It is disappointing that lack of evidence resulted in the use of PFS as a proxy for TTD. This adds an extra-layer of uncertainty in the company’s cost-effectiveness analysis. For most of the observed period to 3.5 years PFS and TTD for STRIDE do not align with each other (Figure 41). This will likely result in different treatment cost

estimations of STRIDE over 3.5 years from the two models. Modelling extrapolation beyond the observed time again adds uncertainty.

Based on information provided in committee papers it appears that time to discontinuation of treatment data exists for the trials of interest (HIMALAYA, REFLECT, and IMbrave 150). Because of CIC redactions this data seems unavailable to both EAGs and to commercial companies making submissions to NICE. As a result, PFS has been used as a proxy out of necessity rather than choice.

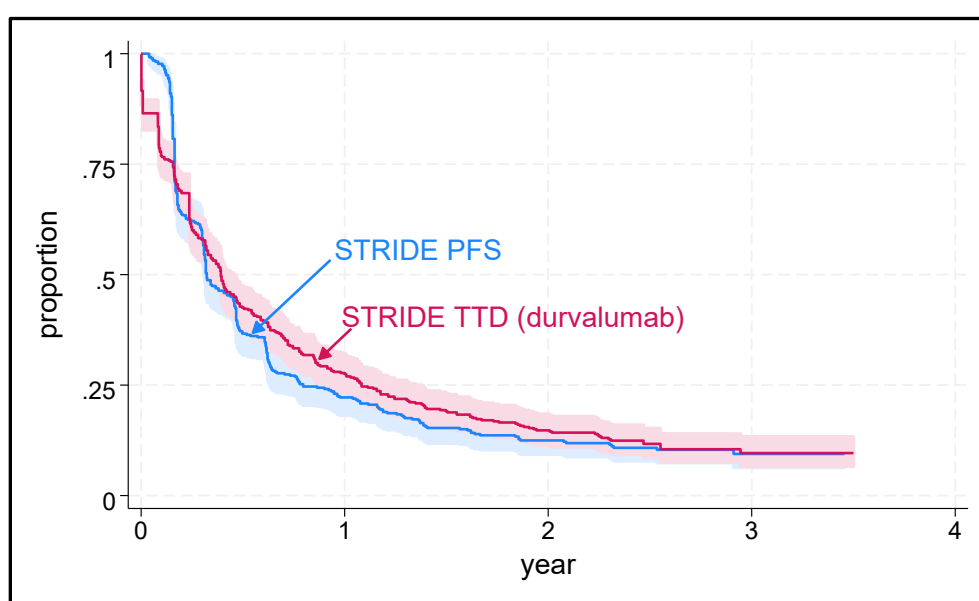


Figure 41: Reconstructed KM plots with 95%CI for STRIDE PFS and TTD (from HIMALAYA)

Modelled PFS and TTD for the other interventions (A+B and Lenvatinib) and misalignment between them is likely to be different to that for STRIDE potentially leading to skewing of the comparisons between interventions and adding uncertainty in costs. Committee papers from TA666 are heavily redacted but it seems that the EAG modelling did not employ proxy PFS for all compared treatments.

Constraints of available evidence

The EAG's economic analysis uses PFS as proxy for TTD. An advantage of this is that it allows use of network meta-analysis information and avoids naïve

comparisons. A disadvantage is that it follows previous STAs (atezolizumab + bevacizumab and of lenvatinib) since both of these appear to adopt proxy PFS out of necessity from lack of evidence. The information available in the public domain from these STAs is heavily redacted so that it is difficult to establish if there is consistency between the company and EAG approaches across these STAs and the present STA.

The constraints of available evidence that influenced the EAG decision to use proxy PFS are mainly associated with atezolizumab + bevacizumab which EAG consider to be the most important comparator to STRIDE. Both PFS and TTD graphs for atezolizumab + bevacizumab and for sorafenib were redacted in the atezolizumab + bevacizumab STA and so were not available to the EAG for analysis and use in the EAG economic model. Time limitations were judged too narrow, by NICE to request these graphs from the submitting company for the atezolizumab + bevacizumab STA. Consequently, there is a gap in available evidence about atezolizumab + bevacizumab TTD. The EAG analysed and modelled PFS from the IMbrave150 trial (see Figure 24) but have not used this in economic analysis because it would be widely regarded as an unacceptable naïve comparison versus STRIDE. The EAG judged lenvatinib a less important comparator than atezolizumab + bevacizumab since inpatient treatment pathways is considered an equivalent to sorafenib. Although limited data on TTD was presented by the assessment group for this STA the EAG have adopted the same procedure (proxy-PFS for TTD) for lenvatinib as used for other comparators. Thereby all treatments have been handled in a consistent way.

The EAG remains concerned regarding PFS information from HIMALAYA stemming from the open label design of the trial and the use of investigator decisions in preference to those of an independent assessor.

4.2.7 Treatment effectiveness and transition probabilities

Treatment effectiveness

The HIMALAYA study demonstrated that STRIDE resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) compared to sorafenib (direct treatment comparison). The primary analysis showed a median OS of [REDACTED] months for STRIDE compared to [REDACTED] months for sorafenib, with a hazard ratio (HR)

of [REDACTED] (see Table 33). Notably, exploratory long-term follow-ups at 4 years and 5-year (DCO: 1st March 2024) continued to demonstrate survival benefits, with STRIDE showing a higher survival probability at both time points. The company stated that these results provide robust evidence of the durable OS benefit associated with STRIDE.

Table 33: Summary of HIMALAYA OS results (updated analysis II; FAS) (DCO: 1st March 2024) (obtained from Table 11 CS Document B)

OS metrics	STRIDE (n=393)	Sorafenib (n=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS, mo (95% CI)	16.43 (14.16, 19.58)	13.77 (12.25, 16.13)
HR (95% CI)	0.76 (0.65, 0.89)	
Median follow-up duration in all patients (95% CI), mo ^d	62.49 (59.47, 64.79)	59.86 (58.32, 61.54)
CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; OS: overall survival; SD: standard deviation; STRIDE: Single Tremelimumab Regular Interval Durvalumab.		

The company's findings on PFS in the direct comparison between STRIDE and sorafenib revealed similar median PFS outcomes. The HIMALAYA trial showed a median PFS of 3.78 months for STRIDE and 4.07 months for sorafenib, with a hazard ratio of 0.90 (95%CI: 0.77,1.05), and no statistically significant difference between the two treatments [REDACTED] (see Table 34). The company stated that the modest PFS benefit of immune-oncology therapies like STRIDE reflects delayed treatment effects, as immune activation takes time to impact tumour growth. UK clinical experts emphasized that OS is a more important endpoint than PFS in advanced HCC, as PFS is difficult to measure accurately due to subjective assessments and continued treatment post-progression.

Table 34: Summary of HIMALAYA PFS results (primary analysis; FAS) (DCO: 27th August 2021) (obtained from CS Document B, Table 12, page 51)

PFS metrics	STRIDE (n=393)	Sorafenib (n=389)
Median PFS, months (95% CI)	3.78 (3.68, 5.32)	4.07 (3.75, 5.49)
HR	0.90	
95% CI for HR	0.77, 1.05	
2-sided p-value	[REDACTED]	
Progression-free, n (%)	[REDACTED]	[REDACTED]
CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; PFS: progression-free survival; STRIDE: Single Tremelimumab Regular Interval Durvalumab.		

In the context of indirect treatment comparisons, the company conducted a Bayesian network meta-analysis (NMA) to compare the OS of STRIDE, atezolizumab + bevacizumab, lenvatinib, and sorafenib in HCC. The analysis included data from the HIMALAYA, IMbrave150, and REFLECT trials, all linked by a common sorafenib arm. The NMA using the updated 5-year OS data from HIMALAYA indicated that when compared to sorafenib OS hazard ratios of [REDACTED] and [REDACTED] were found respectively.

[REDACTED]

[REDACTED]

[REDACTED]

The company used the same methods and similar sources as for OS to assess PFS in patients with HCC treated with STRIDE, atezolizumab + bevacizumab, lenvatinib, and sorafenib. The NMA results showed that atezolizumab + bevacizumab, lenvatinib, and STRIDE all demonstrated PFS when compared to sorafenib, [REDACTED] and [REDACTED], respectively. This shows that the random effects model

[REDACTED]

Transition probabilities

The company calculated the proportion of patients in each health state during each cycle using the following methodology: For "pre-progression (on treatment)," the minimum of PFS and TTD was applied, while "pre-progression (off treatment)" was calculated as the difference between PFS and TTD, ensuring non-negative values. For "progressed (on treatment)," the difference between TTD and PFS was used, and for "progressed (off treatment)," the OS minus the maximum of PFS and TTD was considered. Death was modelled as one minus OS.

4.2.8 Health-related quality of life

The company's methodology for assessing utility in the HIMALAYA trial utilised two patient-reported outcome (PRO) measures: EORTC QLQ-C30 and EORTC QLQ-HCC18, along with EQ-5D-5L and EQ-VAS as exploratory endpoints. Given the availability of EQ-5D data, no mapping methods were undertaken, aligning with NICE preferences. The EQ-5D-5L values from the trial were adjusted to EQ-5D-3L

using an established algorithm.⁴¹ Utility values were derived through a mixed model for repeated measures (MMRM) analysis,⁸⁶ which appropriately addressed the autocorrelation in utility scores and missing data. Treatment-dependent utility values were implemented in the model, assuming that atezolizumab + bevacizumab would have the same utility as STRIDE, while lenvatinib would align with sorafenib. This approach reflects the higher incidence of Grade 3+ or higher adverse events in patients treated with TKIs compared to those on immune checkpoint inhibitors.^{78, 87} The EQ-5D-5L values from the trial had an age-adjustment applied multiplicatively, with the multiplier starting at one and decreasing over time.⁸⁸ The model did not incorporate separate disutilities for individual adverse events in the base-case. The utility values based on the treatment model are summarised in Table 35.

Table 35: Summary of utility values for cost-effectiveness analysis (base-case) (CS, Document B, Table 50)

Treatment	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
Utility values	■	■	■	■

EAG summary: The company's approach to utility in the model includes several key features:

- **Absolute utility values:** The company has used absolute utility values for progression-free (PF) and progressed disease (PD) health states for STRIDE and the atezolizumab + bevacizumab arms.
- **Treatment-related utility:** Utility values are treatment-related, meaning they vary between treatments, even for the same health state.
- **Incorporation of adverse events:** The company confirmed, in response to a clarification, that the utility values account for all treatment-related adverse events. This means that additional AE-related disutilities are not separately included in the model.

While acknowledging the company's approach, the EAG has several critiques:

1. **Utility changes and treatment duration:** Given that treatment duration for patients with untreated advanced or unresectable hepatocellular carcinoma is often short, the EAG questions whether observable changes in utility based on health states (PF, PD) are feasible or accurately estimable. The EAG

prefers an approach similar to that used in previous STA,¹⁴ where utility values are determined based on on/off treatment time-to-death utility values.

2. **Uncertainty from using same utility for STRIDE and atezolizumab + bevacizumab treatments:** The assumption of identical utility values for STRIDE and atezolizumab + bevacizumab introduces potential uncertainties. If the company contends that utility is treatment-related and since patient experience differing adverse event (AE) profiles associated with each treatment, applying the same utility value (sourced from the HIMALAYA trial) may result in biases in the model.
3. **Utility values for primary and subsequent treatments:** If utility values reflect treatment-specific AEs, it is inappropriate to assign the same utility for patients on primary treatment (e.g., STRIDE) and those on subsequent treatments. For instance, patients who discontinue STRIDE and begin sorafenib (as subsequent treatment) should not be assumed to have the same utility as those still on STRIDE. Given that the company assigns a lower utility value for sorafenib, and that sorafenib is a common subsequent treatment, it is more reasonable to assume that the utility for patients on subsequent treatments would be at most equal to that of sorafenib. This adjustment would improve consistency and the face validity of the model.
4. **Age-adjustment for general population utilities:** While the company has incorporated age-adjustment coefficients for utilities in the model, the source of these coefficients is unclear. The EAG supports the inclusion of age-adjusted utilities but considers the company's chosen source, in comparison with TA666,¹⁴ to be more optimistic. The EAG prefers the use of the Ara & Brazier (2010)¹ coefficients, which were employed in a previous STA, as a more appropriate reference for this purpose.

4.2.9 Resources and costs

From the perspective of the NHS and PSS, the company incorporated the following cost categories in the model:

- Drug acquisition costs
- Drug administration costs

- Subsequent treatment costs
- Health state resource use costs
- Adverse events costs
- End-of-life costs

Drug acquisition and administration costs

The company considered drug acquisition and administration costs for STRIDE based on information provided by AstraZeneca. For STRIDE (durvalumab + tremelimumab), AstraZeneca supplied drug acquisition costs, while comparator costs were taken from list prices in the British National Formulary (BNF).^{89, 90} A confidential patient access scheme (PAS) was applied for durvalumab,

[REDACTED]

For the comparator treatments, including atezolizumab + bevacizumab, sorafenib, and lenvatinib, list prices were used for analysis. First-line treatment costs (both acquisition and administration) were applied in the treatment cycle during which the therapy was received.

For treatments with multiple pack sizes, the pack with the lowest cost per mg was selected. For weight-based treatments, the method of moments was used to estimate the average number of vials required per administration. Drug wastage was assumed in the base case, meaning that doses were rounded up to account for unused portions of vials. Vial sharing was considered in a scenario analysis, where costs per mg were calculated based on exact doses.

Relative dose intensity (RDI) was assumed to be 100% in the base case, with scenario analyses incorporating treatment-specific RDI values from relevant trials and evaluations. For administration costs, tremelimumab is given as a single priming dose with durvalumab on Cycle 1, Day 1, followed by durvalumab monotherapy every four weeks (Q4W), each administered separately via intravenous (IV) infusion. Initial IV administration costs were applied for the first doses of both durvalumab and tremelimumab, with subsequent administration costs for durvalumab Q4W.

Comparator drugs were administered based on their respective schedules, with IV infusions for atezolizumab + bevacizumab and oral administration for sorafenib and Lenvatinib (see Table 36 and Table 37).

Table 36: Dosing schedule of primary treatments (obtained from the company submission model)

Treatment arm	Treatment name	Dose (prescribed)	Dose per administration	Frequency	RDI
Durvalumab plus tremelimumab	Durvalumab	1500 mg	1500 mg	Q4W	100%
	Tremelimumab	300 mg	300 mg	1dose only	100%
Sorafenib	Sorafenib	400 mg	400 mg	Twice daily	100%
Lenvatinib	Lenvatinib	12 mg	12 mg	Once daily	100%
Atezolizumab plus bevacizumab	Atezolizumab	1200 mg	1200 mg	Q3W	100%
	Bevacizumab	15 mg/kg	████.mg	Q3W	100%
RDI: Relative dose intensity; Q4W: every four weeks; Q3W: every three weeks					

Table 37: Dosing schedule of primary treatments (obtained from the company submission model)

Treatment arm	Treatment name	Administration method	Cost per dose	Administration cost per dose	
				First administration	Subsequent administration
Durvalumab plus tremelimumab	Durvalumab	IV	████	£207.59	£326.46
	Tremelimumab	IV	£20,610.00	£207.59	£326.46
Sorafenib	Sorafenib	Orally	£9.86	£1.76*	£1.76*
Lenvatinib	Lenvatinib	Orally	£57.48	£6.57	£6.57
Atezolizumab plus bevacizumab	Atezolizumab	IV	£3,807.69	£207.59	£326.46
	Bevacizumab	IV	████	£207.59	£326.46
* Calculated per tablet					

Subsequent treatment costs

In Table 38, we report the total one-off costs for subsequent treatments calculated as a weighted average based on the distribution shown in Table 26, and applied as a one-time treatment cost upon discontinuation of first-line therapy. The duration of treatment was determined by the median progression-free survival reported in the most relevant clinical trial for the treatment in this specific setting (see Table 38). Costs were sourced from list prices in the BNF or eMIT (BNF).^{89, 90}

Table 38: Subsequent treatment costs (CS, Document B, Table 56, Page 143)

Subsequent treatment	Drug cost per administration	Admin cost per administration	Dose schedule	Total drug cost	Total admin cost	Duration of therapy	Total one-off cost
BSC	NA	NA	NA	£0.00	£0.00	NA	£0.00
Cabozantinib	£171.43	£6.92	60 mg QD	£27,134	£1,095	5.2 M	£28,229
Lenvatinib	£57.48	£6.92	12 mg QD	£12,947	£1,559	7.4 M	£14,505
Regorafenib	£178.29	£2.35	160 mg QD, for 21 of 28 day cycle	£13,024	£172	3.2 M	£13,195
Sorafenib	£9.86	£1.76	400 mg BID	£2,462	£440	4.1 M	£2,902
BID: twice per day; BSC: best supportive care; NA: not applicable; QD: once daily; M: months							

Health state resource use costs

The company's approach to modelling health state resource use costs involved several key categories, including physician visits, laboratory tests, radiological tests, and hospitalisations. The physician visits covered appointments with oncologists, hepatologists, gastroenterologists, clinical nurse specialists, and palliative care providers. Laboratory tests included AFP tests, liver function tests, INR, blood count, biochemistry, and endoscopy, while radiological tests involved abdominal CT and MRI scans. Hospitalisation costs encompassed inpatient stays and follow-up appointments with specialists and nurses.

The frequency and proportion of patients using each resource type by treatment and health state were provided, with the values calculated from past technology appraisals (TA666, TA551)^{14, 24} and validated with clinician input (see AstraZeneca Data on File. HIMALAYA Clinician Validation Interviews, supplied in the CS reference pack). Costs were obtained from NHS Reference Costs (2021/2022) and PSSRU Unit Costs (2022/2023).^{91, 92} For patients treated with atezolizumab + bevacizumab, costs were slightly higher in the progression-free state due to number of laboratory tests required and the need for initial endoscopy. Patients who received sorafenib in first-line therapy had higher costs in the progressed disease state due to the need for more monitoring and hospitalisation. Table 39 provides total resource use costs per health state per cycle for different treatments.

Table 39: Total resource use costs per health state per cycle (Obtained from CS, Document B, Table 61, Page 151)

Health state	Cost			
	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
PF (first cycle)	████	████	████	████
PF (subsequent cycles)	████	████	████	████
PD	████	████	████	████
PD, progressed disease; PF, progression-free				

Adverse event costs

The probabilities of individual AEs for each intervention were derived from safety data reported in the respective clinical trials (Including HIMALAYA, IMbrave150, and REFLECT trials). Grade 3 or higher AEs occurring in 5% or more of patients in the relevant treatment arms of the HIMALAYA, IMbrave150, and REFLECT trials were included.^{36, 93, 94} The incidences of these AEs are shown in Table 40.

Table 40: Incidence of Grade 3+ adverse events for STRIDE and relevant comparators (Obtained from CS, Document B, Table 49, page 137)

Adverse event; n (%)	STRIDE (HIMALAYA) N=388	Atezolizumab + bevacizumab (IMbrave150) N=329	Sorafenib (HIMALAYA) N=374	Lenvatinib (REFLECT) N=476
Aspartate aminotransferase increased	20 (5.2)	14 (4.3)	12 (3.2)	24 (5.0)
Blood bilirubin increased	3 (0.8)	2 (0.6)	8 (2.1)	31 (6.5)
Gamma-glutamyl transferase increased	8 (2.1)	4 (1.2)	7 (1.9)	26 (5.5)
Hypertension	7 (1.8)	34 (10.3)	23 (6.2)	111 (23.3)
Lipase increased	24 (6.2)	0 (0.0)	11 (2.9)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	0 (0.0)	0 (0.0)	34 (9.1)	14 (2.9)
Platelet count decreased	████	8 (2.4)	████	26 (5.5)
Proteinuria	████	9 (2.7)	████	<u>27 (5.7)</u>
Weight decreased	████	0 (0.0)	████	36 (7.6)

The costs for treating AEs by treatment are presented in Table 41. The total AE costs for each treatment were calculated by multiplying the AE incidence rates by the cost per event, and these total costs were applied in each treatment cycle.

Table 41: Adverse event costs, costs per treatment arm (Obtained from CS, Document B, Table 63, Page 152)

Adverse events	Costs per treatment arm			
	STRIDE	Atezolizumab + bevacizumab	Sorafenib	Lenvatinib
Aspartate aminotransferase increased	████	£55.28	████	£85.04
Blood bilirubin increased	████	£11.42	████	£158.76
Gamma-glutamyl transferase increased	████	£15.79	████	£92.12
Hypertension	████	£180.59	████	£529.02
Lipase increased	████	£0.00	████	£0.00
Palmar-plantar erythrodysesthesia syndrome	████	£0.00	████	£29.83
Platelet count decreased	████	£31.59	████	£92.12
Proteinuria	████	£45.36	████	£122.11
Weight decreased	████	£0.00	████	£133.29
Total	████	£189.28	████	£340.03

End-of-life costs

The model incorporates a cost for end-of-life care, applied at the time of death. In line with the TA666 and TA551 appraisals and the findings from Georgiou and Bardsley (2014), this cost was updated to current prices and estimated to be £8,249.15 for individuals with advanced or unresectable HCC.^{14, 24, 95}

EAG summary: There are several issues regarding the company's approach to resources and costs: The company has not fully accounted for the costs of some medications, such as opioids, ondansetron, and metoclopramide, for patients receiving BSC as second-line treatment, whether as monotherapy or in combination with other treatments. According to the company's response to the EAG's clarification questions, these drug costs were not included in BSC. While the EAG acknowledges that the majority of resource use costs are covered in the current model, it still considers the BSC costs to be underestimated.

The use of third-line treatment, as confirmed by the company and at clarification, was emphasised to affect only a small proportion of patients. However, the company

has not provided sufficient detail about the costs associated with third-line treatment, despite EAG's request for more information. Although the proportion of patients receiving third-line treatment may be small, the EAG argues that the associated costs are higher than those of BSC and should be better reflected in the model.

The company's approach to applying the half-cycle correction appears to inflate the drug cost of tremelimumab. By allocating the full cost (£20,610) in the first week (CS, Model, worksheet Engine (1), cell BC41) and half the cost (£10,305) in the second week (CS, Model, worksheet Engine (1), cell BC42), the company overestimates the total cost as £30,915, which exceeds the cost of tremelimumab (CS, Model, worksheet Drug Costs, cell E75). An appropriate method would be to apply half of the cost at the start of the cycle and the other half at the end, maintaining the total cost at £20,610. The current approach inaccurately inflates costs, and revision is needed to align with standard health economic methods for applying a half-cycle correction.

In addition, the company uses a similar method for calculating the administration costs of tremelimumab. The total drug cost per administration is listed as £207.59 (CS, Model, Drug Costs worksheet, cell H75). However, by using a time-to-discontinuation (TTD) value of 1 for the first cycle and 0.5 for the second (to account for the half-cycle correction), the cost is increased to £370.82. The appropriate approach is to divide the cost evenly between the start and end of the cycle, ensuring the total cost remains £207.59 (CS, Model, Engine (1) worksheet, cell BN14).

4.2.10 Severity modifier

The company notes that survival for patients with advanced or unresectable HCC is critically low, with an average life expectancy under two years.⁶⁴ Patients experience significant symptoms that severely affect their HRQoL,⁹⁶ reporting lower wellbeing compared to the general population and those with other cancers.⁹⁷

To quantify this impact, the company utilised a severity modifier tool developed by SchAAR and Lumanity, employing the Measurement of Valuation of Health (MVH)

value set and the Health Survey for England (HSE) 2014 Adjusted Limited Dependent Variable Mixture Model (ALDVMM).⁹⁸ The QALY shortfall analysis revealed a proportional QALY shortfall that met the criteria for applying a severity modifier of x1.2 to incremental QALYs when comparing treatments against lenvatinib and sorafenib. Key features of the analysis included a starting age of [REDACTED] years and a sex distribution of [REDACTED] male patients.

The model predicts a median OS of approximately 22 months for atezolizumab + bevacizumab and around 13 months for sorafenib and lenvatinib, with some patients potentially facing even lower survival rates (see Table 42).

Table 42: Summary of QALY shortfall analysis (CS, Document B, Table 65)

Expected total QALYs for the general population	Current treatment	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute shortfall	Proportional shortfall	QALY weight
[REDACTED]	Atezolizumab + bevacizumab	2.42	[REDACTED]	[REDACTED]	x1.0
	Sorafenib	1.48	[REDACTED]	[REDACTED]	x1.2
	Lenvatinib	1.48	[REDACTED]	[REDACTED]	x1.2
QALY, quality adjusted life years					

EAG summary: The company applied a QALY weight of 1.2 in its model, which is based on sorafenib. However, to accurately calculate the severity modifier, it is essential to use the QALYs associated with the established treatments currently available within NHS practice in the UK.⁹⁹ Presently, patients with untreated advanced or unresectable HCC have access to atezolizumab + bevacizumab treatment through the NHS.¹⁴ As indicated in Table 42, if the total QALYs expected for patients receiving atezolizumab + bevacizumab treatment is considered, the QALY weight for this technology appraisal should be adjusted to 1, when comparing STRIDE against all comparators.

4.2.11 Overview of model assumptions and EAG critique

In Table 43, we present the company's modelling assumptions with comments from the EAG.

Table 43: Model assumptions with EAG's comments

Category	Assumption	Justification	EAG's comments
Time horizon	A time horizon of 40 years is considered sufficient to capture the relevant consequences of first-line HCC treatment in terms of costs and QALYs.	7% of patients remain alive in the intervention arm after a 20-year period and hence a longer timeframe was required	As noted in section 4.2.5, the EAG views the company's 40-year time horizon as overly optimistic, as it exceeds the typical 14 to 20 years used in similar STAs. With only 1.1% of patients projected to survive beyond 20 years, a 20-year horizon is more appropriate for capturing costs and benefits, aligning with NICE guidelines and previous STAs.
Time to treatment discontinuation	For atezolizumab + bevacizumab and lenvatinib TTD is assumed equal to PFS.	This is a conservative assumption as both treatments are recommended until loss of clinical benefit and as such, treatment may continue beyond progression in clinical practice.	As mentioned in section 4.2.6 and 4.2.2, the EAG finds the assumption that TTD equals PFS only for atezolizumab + bevacizumab and lenvatinib problematic, as it can lead to biases. The EAG uses the assumption that the TTD curve is equal to the PFS curve for all comparators.
Subsequent treatments	Within the model, patients will not receive the same treatment again in later lines.	As the model only considers the patient's first and second line of therapy, it is assumed that they will not continue their first treatment as a subsequent therapy.	The EAG is satisfied with this assumption.
	A one-off cost for subsequent therapies (drug costs plus administration costs) is applied upon treatment discontinuation.	Simplifying assumption to avoid undue complexity through introducing multiple treatment lines in the model.	The EAG is satisfied with this assumption.
Utilities	A general population utility multiplier is applied in the model base case.	To account for age and sex related decline in health-related quality of life.	As mentioned in section 4.2.8, the EAG supports age-adjusted utilities but finds the

Category	Assumption	Justification	EAG's comments
			company's source unclear and overly optimistic, preferring the Ara & Brazier (2010) coefficients for accuracy.
	In the base case it is assumed that HRQoL (utilities) is treatment-dependent.	This approach was selected as it was considered to be the most robust way of capturing the impact of adverse events due to TKIs on patients.	As mentioned in section 4.2.8, the EAG finds the assumption of using the same utility value for different conditions unsupported by clinical advisor and inconsistent with previous STAs, such as TA666. Additionally, the application of different utilities for the same health state across comparators does not align with NICE reference case guidelines.
Costs	No vial sharing is allowed.	This assumption reflects clinical practice and NHS guidelines.	The EAG is satisfied with this assumption.

5 COST-EFFECTIVENESS RESULTS

The company reported deterministic, sensitivity and scenario analysis results for the comparison between durvalumab + tremelimumab versus atezolizumab + bevacizumab, sorafenib and lenvatinib. Main outcomes are reported in terms of costs, life-years and QALYs, with the overall results reported in the form of an ICER expressed as cost per life-year gained and cost per QALY. The company reported pairwise comparisons as well as fully incrementally analyses. We present results for the fully incremental analyses.

In the company submission, results have been reported based on list prices for all comparators and applying the PAS price for durvalumab + tremelimumab.

5.1 Company's cost effectiveness results

5.1.1 Company's deterministic base-case results

The results in Table 44 shows that treatment

Table 44: Company deterministic base-case results

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Sorafenib	£36,798.68	1.92	1.48	-	-	-	-
Lenvatinib	£48,444.96	1.92	1.48	-	-	-	
STRIDE							
Atezolizumab + bevacizumab	£244,087.04	3.02	2.42	-	-	-	
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality adjusted life years gained							

5.1.2 Company's sensitivity analyses

5.1.2.1 Company's probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was undertaken for the outcome cost per QALY. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. Probability distributions were applied to key model input parameters. The PSA results were reported in tabular form (see Table 45), and iterations presented on scatterplots (Figure 42 through to Figure 44) and their corresponding cost-effectiveness acceptability curves (CEACs) (Figure 45). The PSA results show that the ranking of the technologies remained the same as the deterministic results, but

.

Table 45: Company probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Sorafenib	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-
Lenvatinib	£49,648.43	1.92	1.47	-	-	-	[REDACTED]
STRIDE	£103,904.23	3.09	2.44	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Atezolizumab + bevacizumab	£249,036.81	3.10	2.47	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality adjusted life years gained							

Figure 42 shows the company's PSA results for the pairwise comparison between STRIDE versus sorafenib.



Figure 42: Incremental cost-effectiveness scatterplot for the comparison between STRIDE versus sorafenib

Figure 43 shows the company's PSA results for the pairwise comparison between STRIDE versus lenvatinib.



[REDACTED]

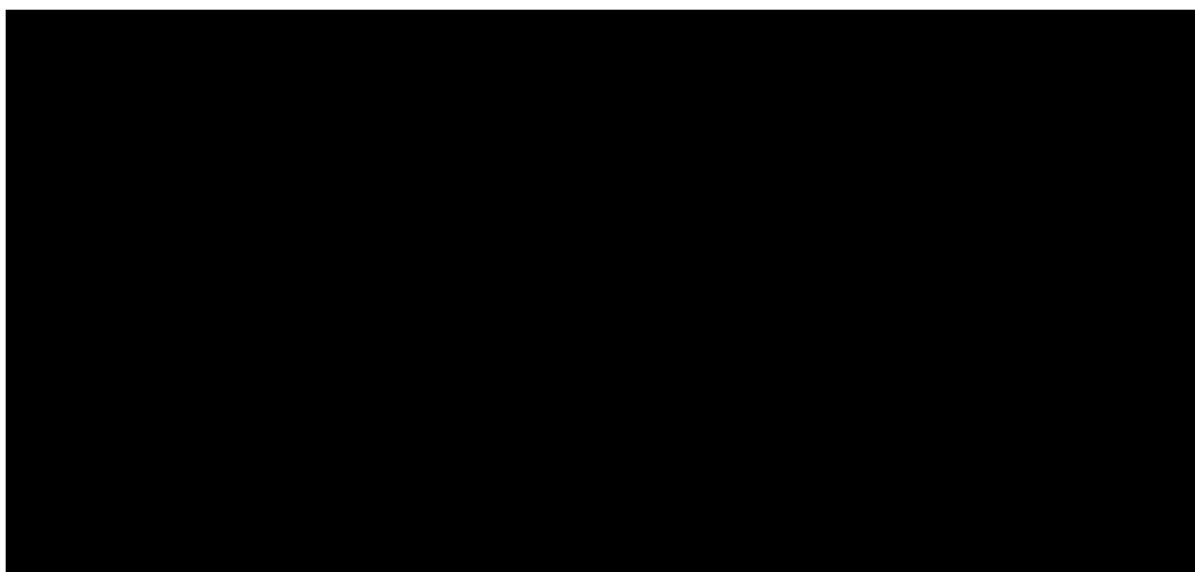


Figure 43: Incremental cost-effectiveness scatterplot for the comparison between STRIDE and lenvatinib

Figure 44 shows the company's PSA results for the pairwise comparison between STRIDE versus atezolizumab + bevacizumab.

[REDACTED]

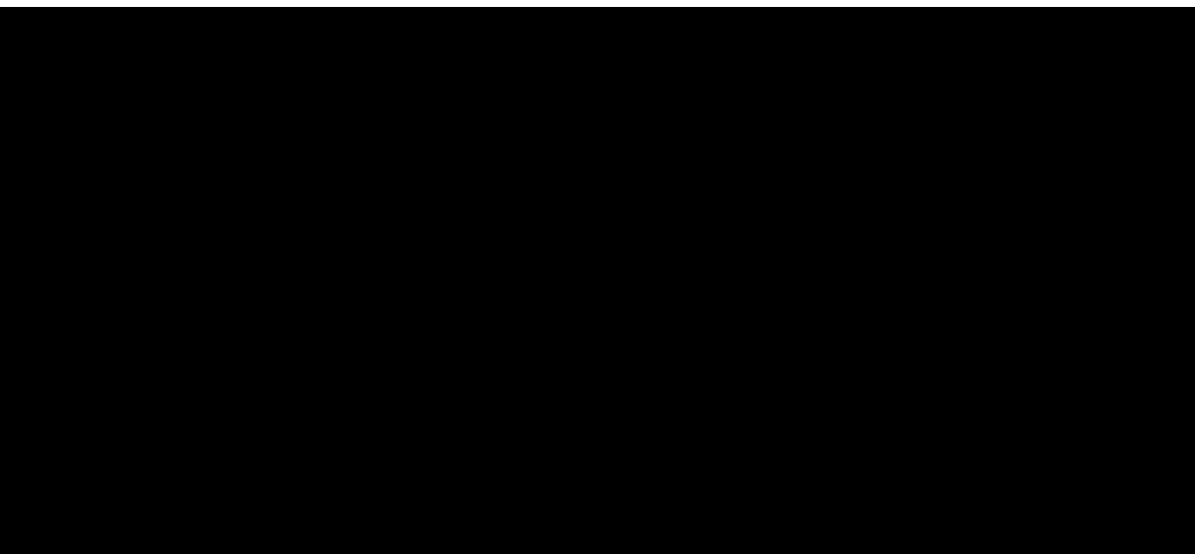


Figure 44: Incremental cost-effectiveness scatterplot for the comparison between STRIDE and atezolizumab + bevacizumab

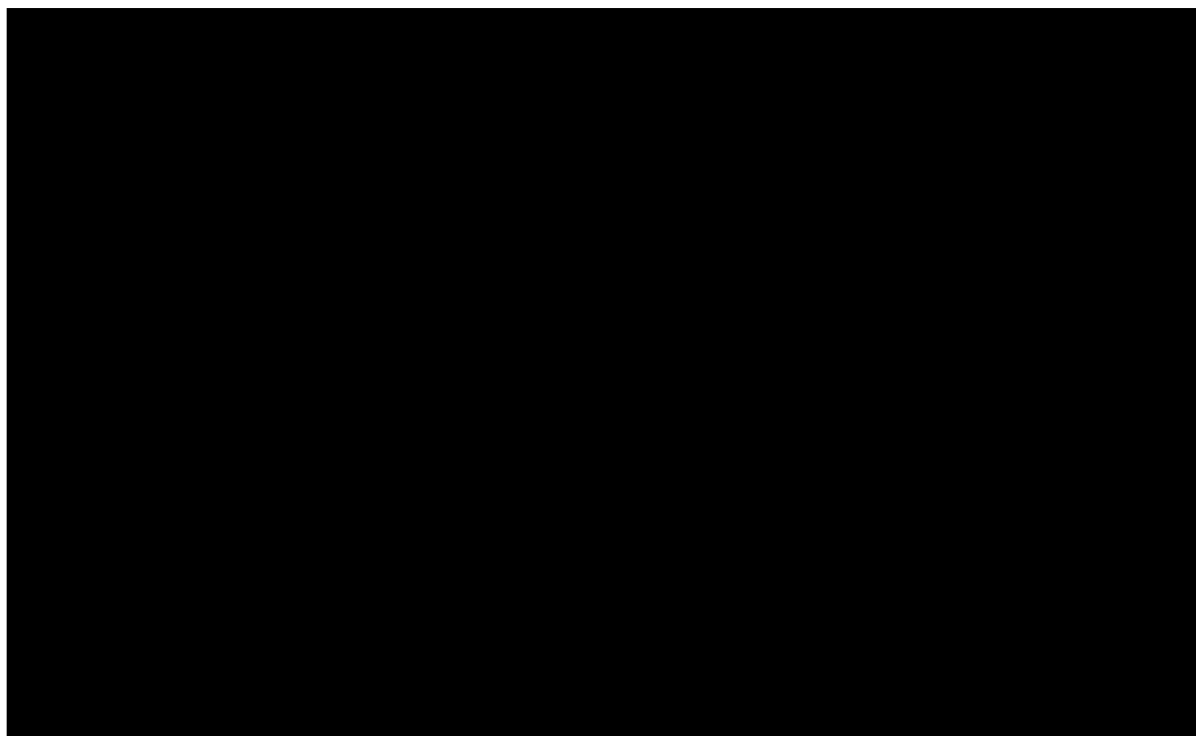


Figure 45: Cost-effectiveness acceptability curve

5.1.2.2 Cost minimisation analysis (STRIDE versus atezolizumab + bevacizumab)

The company undertook a cost comparison analysis between STRIDE and atezolizumab + bevacizumab because the deterministic and PSA results showed that the incremental QALYs were close to zero, indicating that there is likely equivalence between the two interventions. For this analysis, the company set the incremental QALYs to zero, then assessed the differences between the incremental costs. Assuming equal efficacy,

[Redacted text block]

5.1.2.3 Deterministic sensitivity analysis

The company undertook one-way sensitivity analysis for the comparisons between STRIDE versus sorafenib, versus lenvatinib and versus atezolizumab + bevacizumab by varying key model input parameters, and the results were reported in the form of tornado diagrams for the outcome incremental net health benefit assuming a willingness-to-pay threshold of £30,000.

The results of the OWSA are presented in Figure 46 through to Figure 48. In Figure 46, the company stated that these results show that the base-case results were robust to the changes for the comparison between STRIDE versus sorafenib. In Figure 47, the hazard ratio for PFS, which informed the duration of treatment for lenvatinib, and the drug costs explains the influence of this parameter. In Figure 48, these results showed that for the comparison between STRIDE versus atezolizumab + bevacizumab, the PFS hazard ratio was the most influential model input.

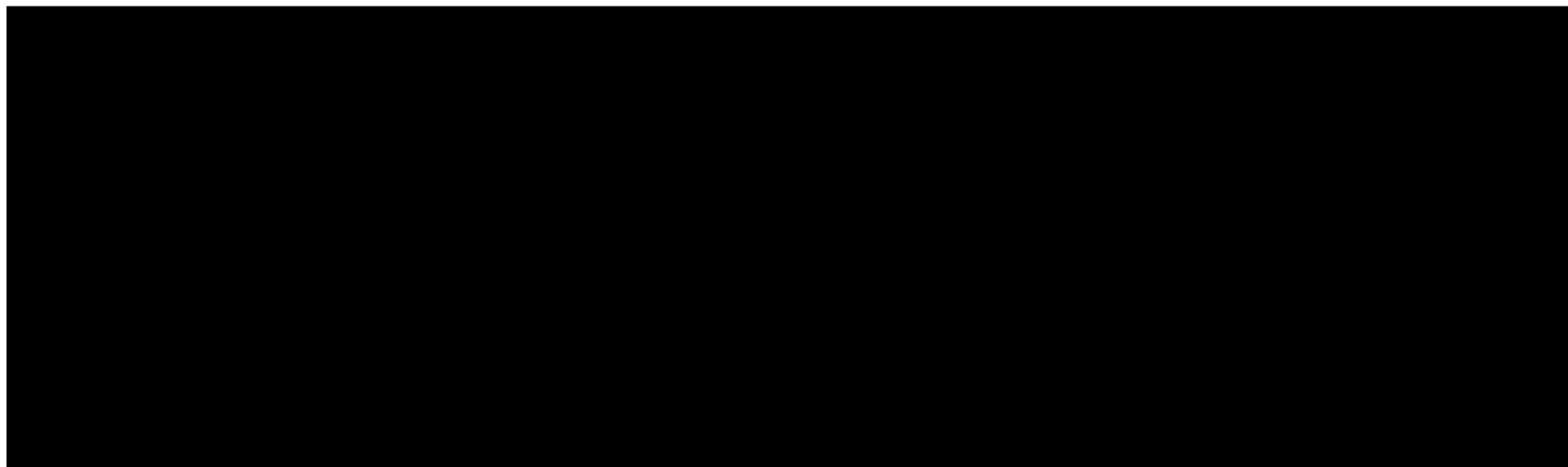


Figure 46: Company tornado diagram for the comparison between STRIDE versus sorafenib

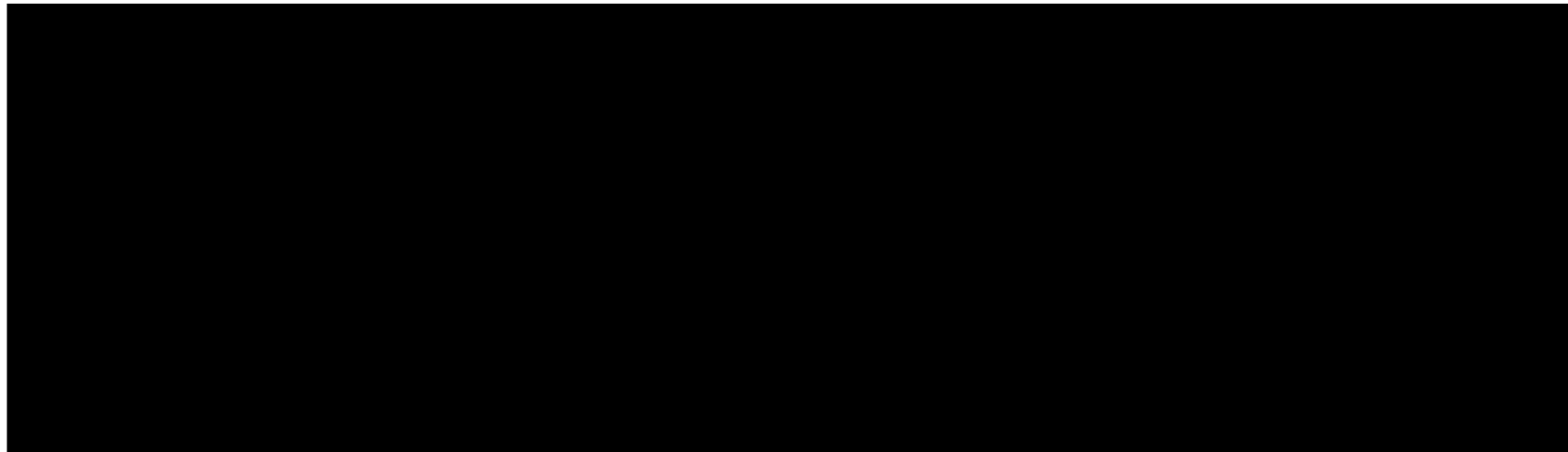


Figure 47: Company tornado diagram for the comparison between STRIDE versus lenvatinib

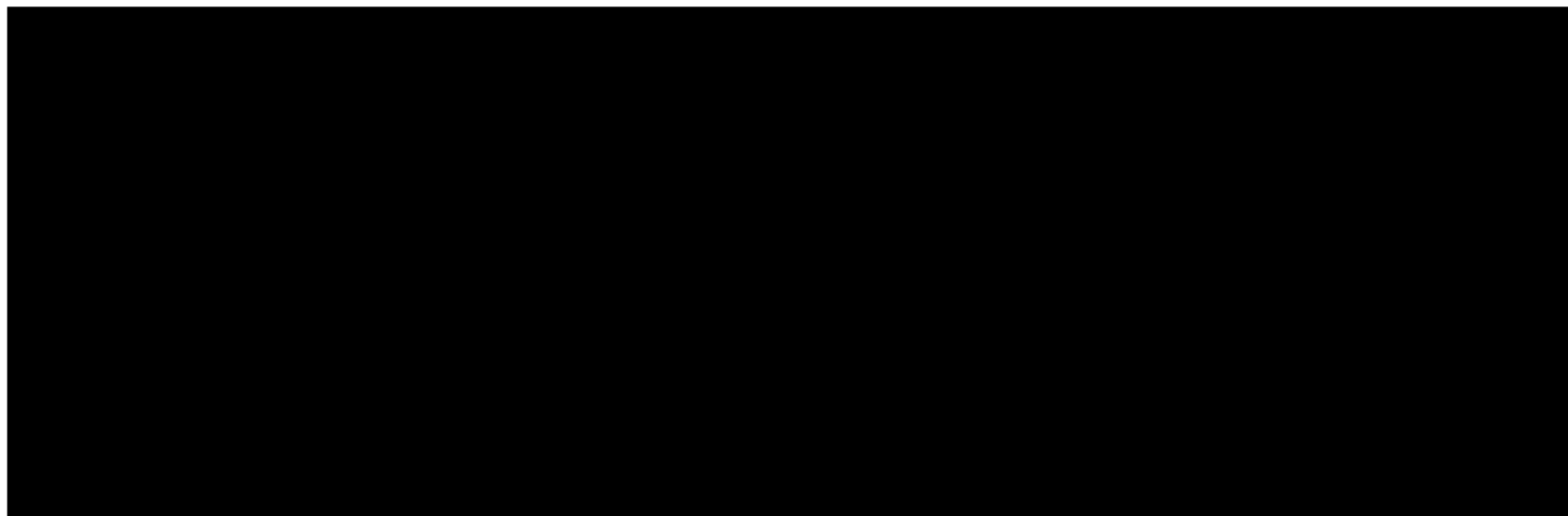


Figure 48: Company tornado diagram for the comparison between STRIDE versus atezolizumab + bevacizumab

5.1.2.4 Scenario analysis results

The company undertook several scenario analyses to further understand the robustness of the results to making changes to key assumptions and alternative inputs. In Table 47, we present the company's scenario analysis results. Results are reported for the pairwise comparisons between STRIDE versus all comparators for the outcome cost per QALY.

At clarification stage, the company provided rationale for their approach to using treatment dependent utility values as well as functionality to explore other approaches, time-to-death utility. Time-to-death utility values used in scenario analysis are reported in Table 46, with the results reported in Table 47.

Table 46: Summary of marginal mean utility values for time-to-death analysis

Treatment	<=5 weeks before death	5-15 weeks before death	15-30 weeks before death	>30 weeks before death
Utility values				

Table 47: Company scenario analysis results for STRIDE versus all comparators

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Base case		██████	██	██████	██████	██	██████	██████	██	██████
1	20-year time horizon	██████	██	██████	██████	██	██████	██████	██	██████
2	Inclusion of vial sharing	██████	██	██████	██████	██	██████	██████	██	██████
3	Treatment-specific RDIs	██████	██	██████	██████	██	██████	██████	██	██████
4	OS extrapolation choice for STRIDE: generalised gamma	██████	██	██████	██████	██	██████	██████	██	██████
5	OS extrapolation choice for sorafenib: generalised gamma	██████	██	██████	██████	██	██████	██████	██	██████
6	PFS extrapolation choice for STRIDE: generalised gamma	██████	██	██████	██████	██	██████	██████	██	██████
7	PFS extrapolation choice for sorafenib: log-normal	██████	██	██████	██████	██	██████	██████	██	██████
8	TTD extrapolation choice for STRIDE: generalised gamma	██████	██	██████	██████	██	██████	██████	██	██████
9	TTD extrapolation choice for sorafenib: log-logistic	██████	██	██████	██████	██	██████	██████	██	██████
10	Mean utility values for time-to-death analysis	██████	***	██████	██████	***	*****	██████	***	██████

Scenario	STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)

5.1.3 Critique of company's analyses

The EAG considers that the results presented in the company's economic model is accurately reflected in the company main submission documents. In the company's reporting of their PSA, in the fully incremental analysis, it was reported that for the

[REDACTED]

[REDACTED]

[REDACTED]

5.1.4 Model validation and face validity check

The company used several quality control and technical validation methods for model validation, following guidelines from Drummond et al. (2015), Philips et al. (2004), and TECH-VER.¹⁰⁰⁻¹⁰² The company stated that this included a manual review of programming in Microsoft Excel and Visual Basic for Applications (VBA) to confirm that mathematical calculations align with specifications. Patient flow sheets and sensitivity analysis functionalities were reviewed, along with validity checks to ensure clinical trial data corresponds with model outcomes. Extreme value testing was performed to evaluate the model's responses to parameter changes, alongside editorial checks on text and graphical outputs.

Additionally, the company stated that external validation included clinical feedback on treatment pathways and long-term survival extrapolations, with a focus on UK sources to ensure outputs reflect NHS practices. The company stated that this approach aims to ensure the model's accuracy and relevance to clinical settings.

5.2 Conclusion of company cost-effectiveness sections

The EAG assessed the company's model and identified several key issues affecting its credibility and effectiveness. While the model logically depicts treatment pathways, it oversimplifies the structure, leading to potential biases. Additionally, the 40-year time horizon proposed by the company is unusually long compared to the typical 14-20 years for similar STAs. The inconsistent application of individual patient data and hazard ratios across treatments has resulted in unrealistic overall survival projections, particularly for STRIDE (see Section 4.2.6). Furthermore, the utility values derived from health states may not accurately reflect the short treatment durations typical for patients with advanced disease. The unclear source of age-adjustment coefficients for utilities appears overly optimistic, which could skew the model results. Moreover, the company's half-cycle correction for tremelimumab costs misallocates expenses, leading to inflated figures beyond the actual drug cost and diverging from accepted health economic practices. Finally, regarding the severity modifier, the weight should reflect established treatments like atezolizumab + bevacizumab currently available within NHS practice. The cost-effectiveness issues are outlined in Table 48.

Table 48: Issues identified and EAG recommendations

Row no.	ID2725	Summary of issues	Report section	EAG recommendation
1	Generalisability of the HIMALAYA trial	Limitations in the generalisability of the HIMALAYA trial population outcomes to NHS clinical settings	Section 3.2	Conducting additional analyses is not possible
2	Model inconsistently assumes PFS equals TTD, oversimplifying treatment subgroups.	The model structure oversimplifies by collapsing the "on treatment" and "off treatment" subgroups in health states and inconsistently assumes that PFS equates to TTD for atezolizumab + bevacizumab and lenvatinib, introducing bias across treatments.	Section 4.2.2	See solutions for issue 5

Row no.	ID2725	Summary of issues	Report section	EAG recommendation
3	Modelling of OS and PFS	The method used for modelling OS and PFS for STRIDE (using IPD from HIMALAYA possibly at different DCO for OS and PFS) is different to that used for comparators (atezolizumab + bevacizumab and lenvatinib) where NMA HRs associated with very substantial uncertainty are employed. There is a lack of equity in the handling of STRIDE versus atezolizumab + bevacizumab and lenvatinib.	Section 4.2.6	Base-case: Using the constant HRs (vs. sorafenib) from the selected NMA for all treatments.
4	Company assumed that TTD for atezolizumab + bevacizumab and Lenvatinib is equivalent to PFS	The company states that an absence of TTD information for atezolizumab + bevacizumab and for lenvatinib they have assumed TTD for these is equivalent to the PFS the company developed. However, the PFS models (employing NMA output HRs) are associated with severe imprecision and in the case of atezolizumab + bevacizumab bear little resemblance to what is seen in the IMbrave150 trial used for NMA input. The EAG is unconvinced that equivalence of TTD and PFS only for atezolizumab + bevacizumab and Lenvatinib, is a sensible assumption for modelling.	Section 4.2.6	Base-case: The TTD curve was assumed to be equal to the PFS curve for all comparators. Scenario analysis: Using the company's approach
5	Company's NMA	Appropriateness of methods used to do an NMA	Sections 3.2.8.1 and 3.2.9.1	Base-case: Using the most appropriate NMA chosen through a quality assessment of available NMAs. Scenario analysis: Using the constant HRs to estimate the OS and PFS of different treatments, based on the company's NMA.
6	Time horizon	Previous evaluations of comparable treatments	Section 4.2.5	Base-case: using the 20-year time horizon

Row no.	ID2725	Summary of issues	Report section	EAG recommendation
		generally employed a time horizon of 14 to 20 years, whereas the company's proposed 40-year horizon is viewed as overly optimistic by the EAG clinical advisors. The EAG deemed the company's rationale for the varying time horizons unpersuasive and advocates for a 20-year horizon, which sufficiently reflects treatment costs and benefits. Importantly, only a small fraction of patients is expected to survive beyond 20 years.		Scenario analysis: Using different time horizons of 10 and 40 years.
7	Using the same utility for different conditions and different utilities for the same health state between two different treatments	The company has used the same utility value for different conditions or health states of the treatment. For example, the same utility value was applied for both progression-free and progressed disease states, as well as for the "on treatment" and "off treatment" conditions. The EAG considers this approach unsupported by one of the EAG clinical advisors and inconsistent with a previous STA (TA666). On the other hand, the company used treatment-related utility values, meaning different utility values were applied for the same health states across different comparators. The EAG considers this method to be inconsistent with the previous STA (TA666) and not in line with the NICE reference case.	Section 4.2.8	Base-case: The EAG determined that the most appropriate approach is to utilize health state-based utility values in the base case analysis. However, two primary limitations hinder the use of available health state-based utility values: first, there is the unavailability of a suitable source for these utility values, and second, there is insufficient data regarding the disutilities associated with adverse effects and other patient conditions under various treatments. Given these limitations, the EAG considers the next best alternative to be the use of time-to-death utility values. This approach assigns a consistent utility value for a defined period based on time to death across different treatments, aligning more closely with NICE's reference case by applying the same utility value for identical health states among

Row no.	ID2725	Summary of issues	Report section	EAG recommendation
				various treatments. The time-to-death utility values were provided in the company's response to the EAG's clarification questions and were subsequently used for the base case analysis. Scenario analysis: first, In EAG scenario analyses, we have used on treatment time-to-death utility values from TA666. Second, using the company's approach. Third, using the sorafenib utility as off-treatment utility in the company approach. Fourth, using the utility values from Su et al.,² 0.76 and 0.68 are assigned as the proxy of utility values for PFD and PD, respectively.
8	Unclear sources of age-adjustment coefficients for utilities.	The source of age-adjustment coefficients for utilities is unclear and appear overly optimistic	Section 4.2.8	Base-case: using Ara & Brazier (2010)¹ coefficients. Scenario analysis: Using the company approach
9	Half-cycle correction	The company's half-cycle correction method for tremelimumab costs overestimates total expenses by misallocating costs, and inflating figures beyond the actual drug cost.	Sections 4.2.9 and 5.2	Base-case: using the appropriate approach to half-cycle correction.
10	Severity modifier	The company's use of a QALY weight of 1.2, based on sorafenib, is inappropriate; the QALY weight should reflect established treatments like atezolizumab + bevacizumab, which have higher QALY gains and currently available in NHS practice for all treatments.	Sections 4.2.10	Base-case: using the total QALYs expected for individuals receiving atezolizumab + bevacizumab treatment as input for calculating the QALY weight.

Row no.	ID2725	Summary of issues	Report section	EAG recommendation
	EAG, evidence assessment group; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time-to-treatment discontinuation			

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 EAG's changes made to the company's base-case model

Table 49 presents the company data utilised in the company's base-case for some parameters, along with new values derived from the EAG issues outlined in Table 48. For further details and justifications, please refer to the associated issues listed in Table 48 and their corresponding sections discussing the company's perspectives and the EAG's critiques. In Table 49, we present the EAG's preferred assumptions which will be used in the forthcoming sections.

Table 49: EAG's changes made to the company's base-case model

Variable	Company's Value	EAG's value	Reference to related issue in Table 48
Controls			
Time horizon	40	20	Row 6
Efficacy inputs			
Overall survival			
Approach – STRIDE	Splines and knots: Normal - 1 knot	Constant HR: HR vs sorafenib=0.7816 (95% CrI: 0.66, 0.93)	Row 3, and 5
Approach – Sorafenib	Splines and knots: Hazard - 1 knot	Generalized Gamma model (based on HIMALAYA trial)	Row 3, and 5
HR vs. sorafenib – Lenvatinib	1.00	Constant HR: HR vs sorafenib= 0.92 (95% CrI: 0.78, 1.08)	Row 5
HR vs. sorafenib - atezolizumab + bevacizumab		Constant HR: HR vs sorafenib= 0.68 (CrI: 0.42, 1.10)	Row 5
PFS			
Approach – STRIDE	Splines and knots: Hazard - 3 knots	Constant HR: HR vs sorafenib=0.9041 (CrI: 0.62, 1.35)	Row 3, and 5
Approach – Sorafenib	Splines and knots:	Company's approach accepted	Row 3, and 5

Variable	Company's Value	EAG's value	Reference to related issue in Table 48
	Hazard - 2 knots		
HR vs. sorafenib – Lenvatinib	■	Constant HR: HR vs sorafenib= 0.6535 (CrI: 0.44, 1)	Row 5
HR vs. sorafenib - atezolizumab + bevacizumab	■	Constant HR: HR vs sorafenib= 0.66 (CrI: 0.27, 1.59)	Row 5
TTD			
Approach – STRIDE	One piece (Separately fitted): Weibull	Equivalent to STRIDE PFS	Row 4
Approach – Sorafenib	One piece (Separately fitted): Log-normal	Equivalent to sorafenib PFS	Row 4
Approach – Lenvatinib	Constant HR (1.00) vs. PFS	Equivalent to lenvatinib PFS	Row 4
Approach - Atezolizumab + bevacizumab	Constant HR (1.00) vs. PFS	Equivalent to EAG model of atezolizumab + bevacizumab's PFS	Row 4
Primary treatment Utilities			
Treatment: sorafenib, lenvatinib	■	Parameter Estimate ≤ 5 weeks from death ■ 5-15 weeks from death ■ 15-30 weeks from death ■ >30 weeks from death ■	Row 7
Treatment: STRIDE, Atezolizumab plus bevacizumab	■		
Severity modifier			
QALY weight	1.2	1	Row 10
Age-adjustment coefficients for utilities			
The source of age-adjustment coefficients for utilities	Unclear	Using Ara & Brazier (2010) ¹	Row 8
Half-cycle correction method of tremelimumab drug costs			
Drug cost of tremelimumab including acquisition and administration costs	Allocating the full cost in the first week, and half the cost in the second week	Using the appropriate coefficients (0.5 for the first and second cycles) leads to allocating half of the costs in the first cycle and the other half in the second one.	Row 9

6.2 Impact of EAG changes on the company's base-case results

In Table 50, we report the pairwise results for the comparison between STRIDE versus comparators and the impact of these suggested changes outlined in Table 48. The impact is reported based on the outcome cost per QALY only.

Table 50 indicates that

Table 50: Results of EAG's exploratory analysis for the comparison between STRIDE and comparators

EAG's preferred assumption based on issues		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company's base case										
1	20-year time horizon									
2	Using the generalized Gamma model (based on HIMALAYA trial) for Sorafenib's OS									
3	Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the OS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib.									
4	Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the PFS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib.									
5	Using PFS as a proxy of TTD in all treatments.									
6	Using the time-to-death utility value (data from the HIMALAYA trial)									
7	Using the QALY weight calculated from Atezolizumab plus bevacizumab as the standard treatment in the UK for all comparators.									
8	Using the utility values from Su et al., 0.76 and 0.68 are assigned as the proxy of utility values for PFD and PD, respectively.									
9	Using Ara and Brazier (2010) as the source of age-adjustment coefficients for utilities									
10	Amendment of the formula for calculating the half-cycle correction for the drug cost of tremelimumab									

6.3 Results of EAG base-case analysis

6.3.1 EAG cost-effectiveness results

The EAG's base-case analysis compares STRIDE versus all comparators, using the PAS agreement in place for STRIDE and list or eMIT prices for the comparators (see Appendix 9.7 for list of analyses applying confidential prices when in place for comparator treatments and their source of prices) (results presented in a separate confidential appendix document). The EAG's preferred base-case includes making the following changes simultaneously:

- 20-year time horizon.
- Using the generalized Gamma model (based on HIMALAYA trial) for Sorafenib's OS.
- Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the OS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib.
- Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the PFS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib.
- Using PFS as a proxy of TTD in all treatments.
- Using the time-to-death utility value (data from the HIMALAYA trial).
- Using the QALY weight calculated from atezolizumab plus bevacizumab as the standard treatment in the UK for all comparators.
- Using Ara and Brazier (2010) as the source of age-adjustment coefficients for utilities.
- Amendment of the formula for calculating the half-cycle correction for the drug cost of tremelimumab.

In Table 49 and Table 59, we provide details of the changes made in the spreadsheets used to amend the company's economic model, which formed the basis of the EAG model.

6.3.1.1 Deterministic base-case results

In Table 51 we present the EAG pairwise analysis results for STRIDE versus each comparator. These results show that treatment

Table 51: EAG deterministic results (pairwise analysis-STRIDE vs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INMB	
								WTP1: £20000	WTP2: £30000
STRIDE									
Sorafenib									
Lenvatinib									
Atezolizumab plus bevacizumab									
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; STRIDE, Single Tremelimumab Regular Interval Durvalumab; WTP, willingness to pay; INMB, Incremental Net Monetary Benefit.									

Table 52 presents a fully incremental analysis comparing four treatment options.

Table 52: EAG deterministic base-case results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (cost per QALY)
Sorafenib							
Lenvatinib							
STRIDE							
Atezolizumab + bevacizumab							

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; STRIDE, Single Tremelimumab Regular Interval Durvalumab

6.3.1.2 Probabilistic sensitivity analysis (PSA) results

Table 53 presents the probabilistic cost-effectiveness analysis of various treatments compared to STRIDE. These pairwise results show that treatment with

[REDACTED]

Table 53: EAG probabilistic sensitivity analysis results (pairwise analysis-STRIDE vs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	INMB	
								WTP1: £20000	WTP1: £20000
STRIDE	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sorafenib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Lenvatinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Atezolizumab + bevacizumab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; WTP, willingness to pay; INMB, Incremental Net Monetary Benefit.									

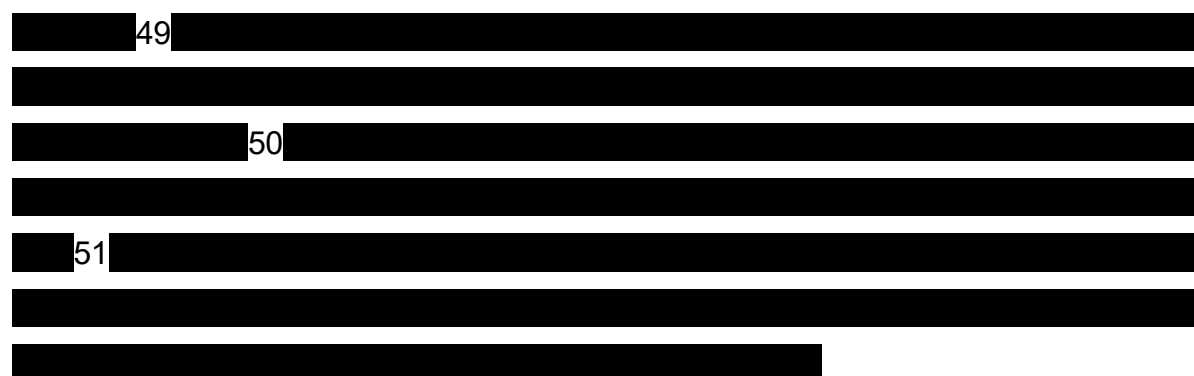
Table 54 provides the PSA results presented as a fully incremental analysis. These results show that the comparison between

[REDACTED]

Table 54: EAG probabilistic sensitivity analysis results (fully incremental analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER
Sorafenib	████	██	██	█	█	█	█
Lenvatinib	████	██	██	████	██	██	██████
STRIDE	████	██	██	████	██	██	████
Atezolizumab + bevacizumab	████	██	██	████	██	██	████
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab							

The upcoming figures present the results of the PSA in the form of scatter plots illustrating the cost-effectiveness comparisons between STRIDE and three other treatments: sorafenib, lenvatinib, and atezolizumab + bevacizumab.



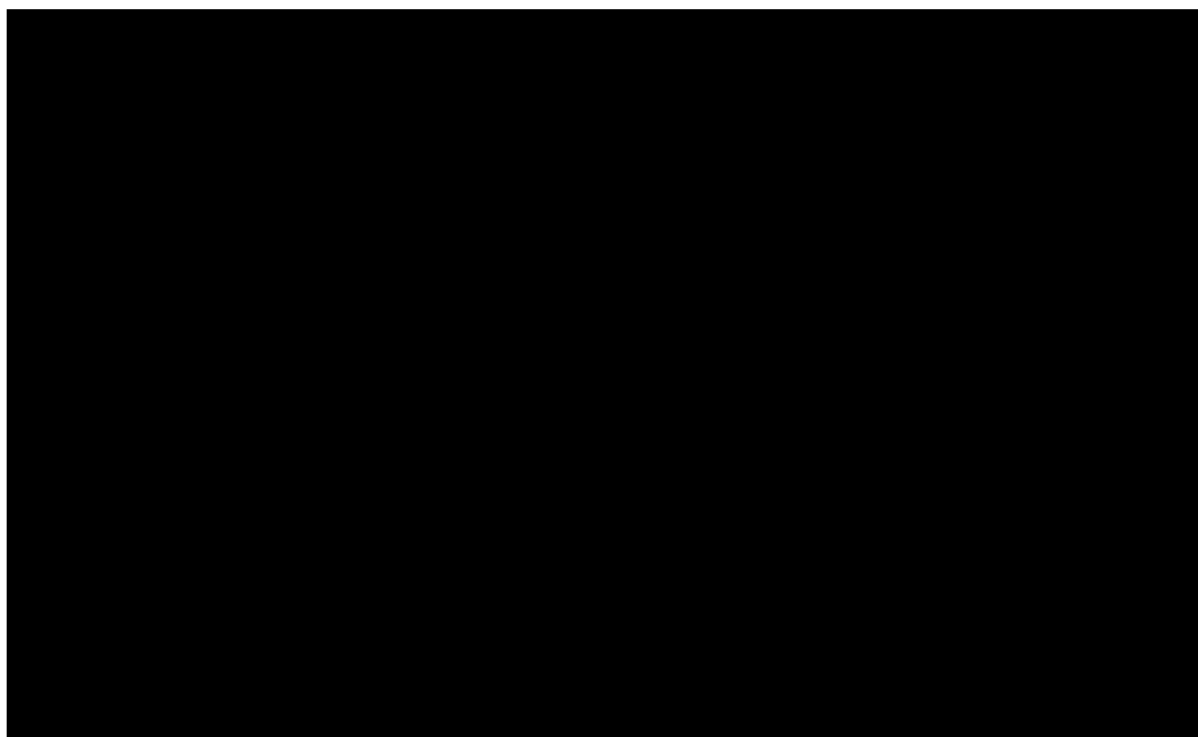


Figure 49: EAG incremental cost-effectiveness scatterplot for the comparison between STRIDE versus sorafenib

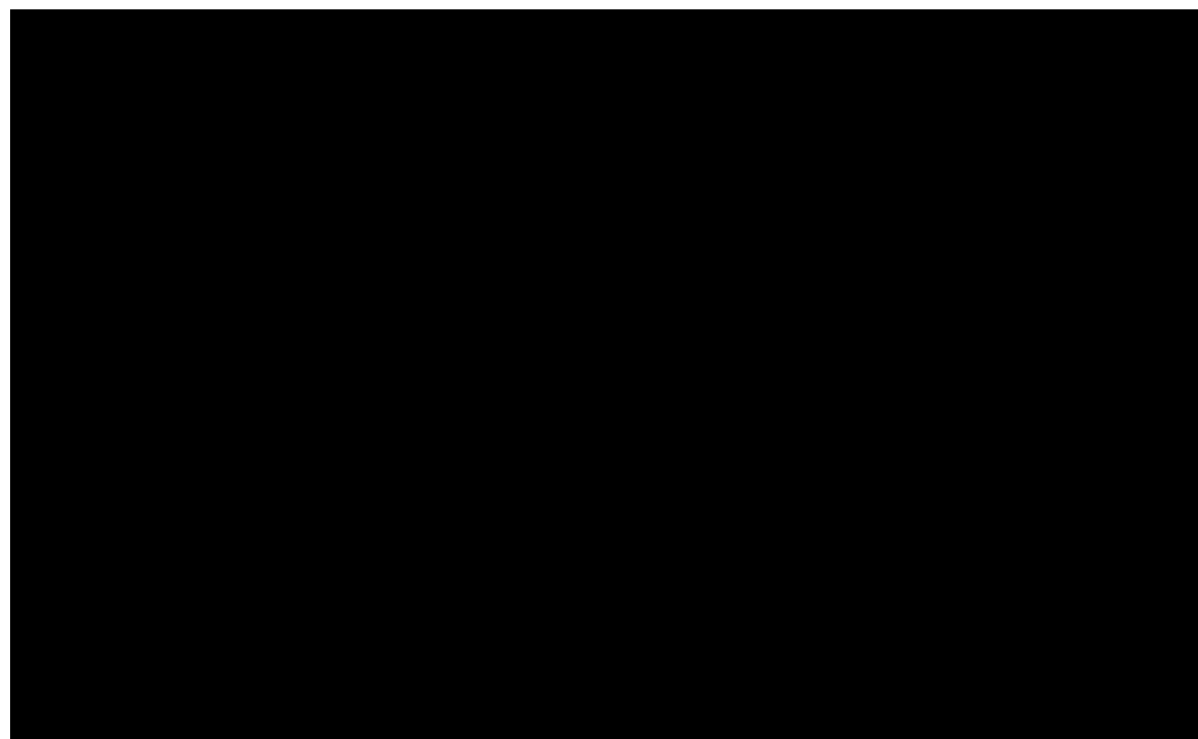


Figure 50: EAG incremental cost-effectiveness scatterplot for the comparison between STRIDE and Lenvatinib

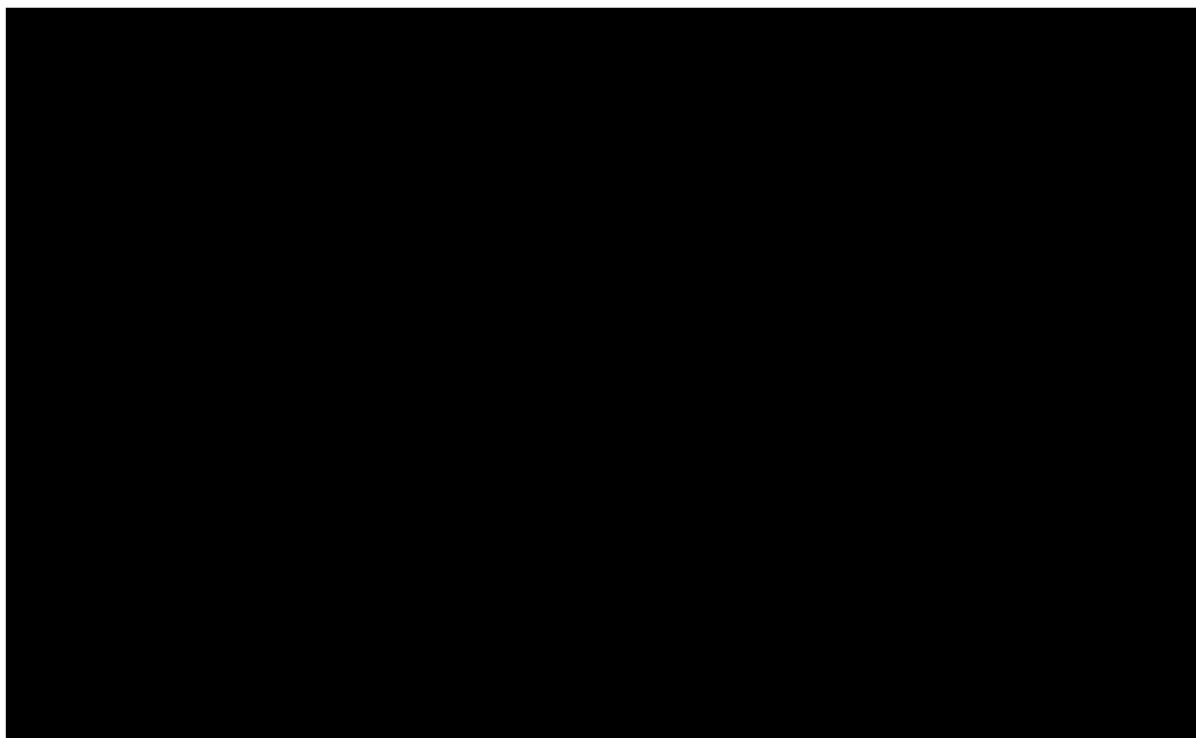


Figure 51: EAG incremental cost-effectiveness scatterplot for the comparison between STRIDE and atezolizumab + bevacizumab

Figure 52 shows the corresponding results plotted on a cost-effectiveness acceptability curve (CEAC) indicating the probability of being cost-effective at different willingness-to-pay (WTP) thresholds. At a WTP threshold of £30,000 per QALY, STRIDE has a [REDACTED] probability of being cost-effective, while atezolizumab plus bevacizumab has a [REDACTED].

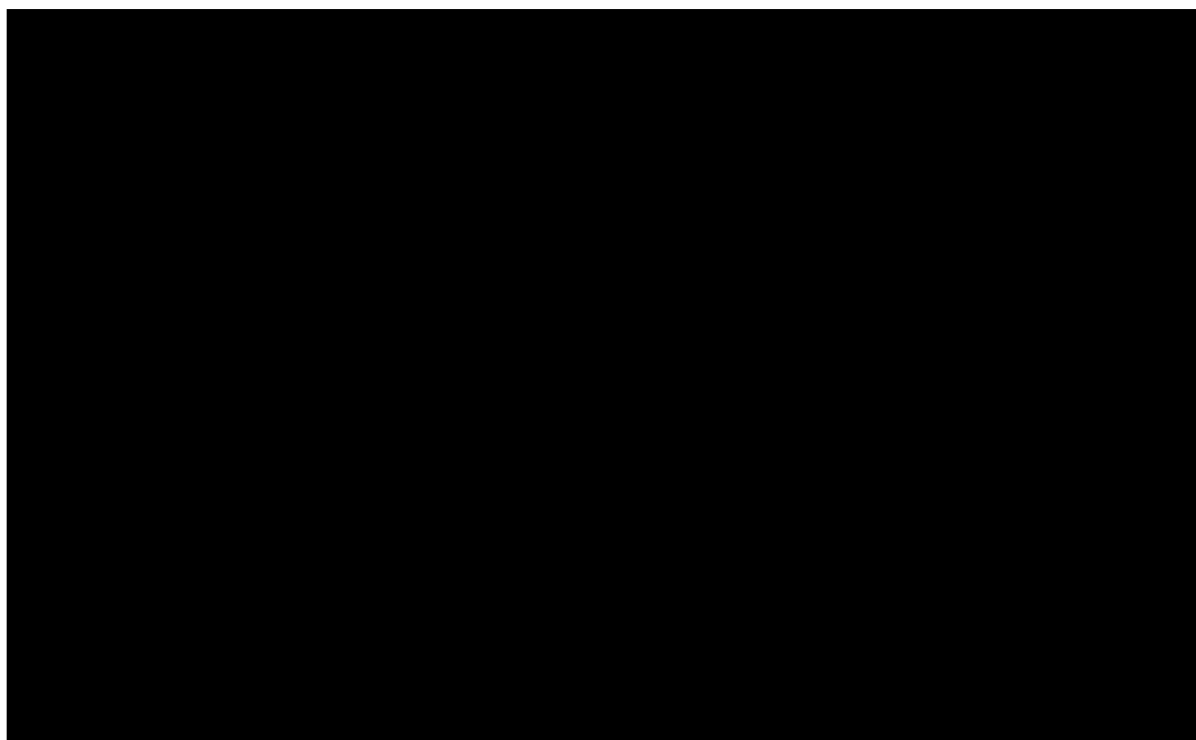


Figure 52: EAG cost-effectiveness acceptability curves

6.3.1.3 One-way sensitivity analysis results

In Figure 53 through to Figure 55, we present one-way sensitivity analysis (OWSA) results highlighting the 10 most influential parameters impacting the cost-effectiveness results of STRIDE compared to sorafenib, lenvatinib and atezolizumab + bevacizumab, respectively.

For the comparison between STRIDE versus sorafenib (see Figure 53),

[REDACTED]

[REDACTED] For the comparison of STRIDE versus lenvatinib (see Figure 54),

[REDACTED]

[REDACTED] For STRIDE versus atezolizumab plus bevacizumab (see

Figure 55),

[REDACTED]

[REDACTED]

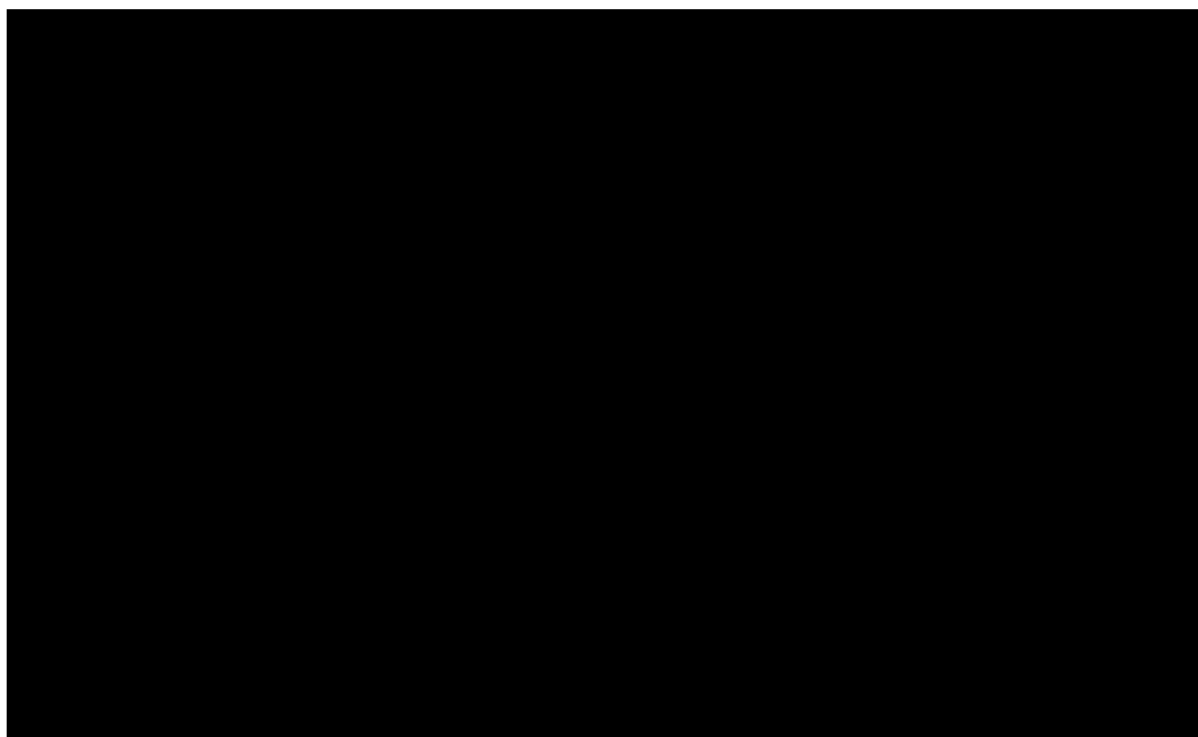


Figure 53: EAG tornado diagram for the comparison between STRIDE versus sorafenib

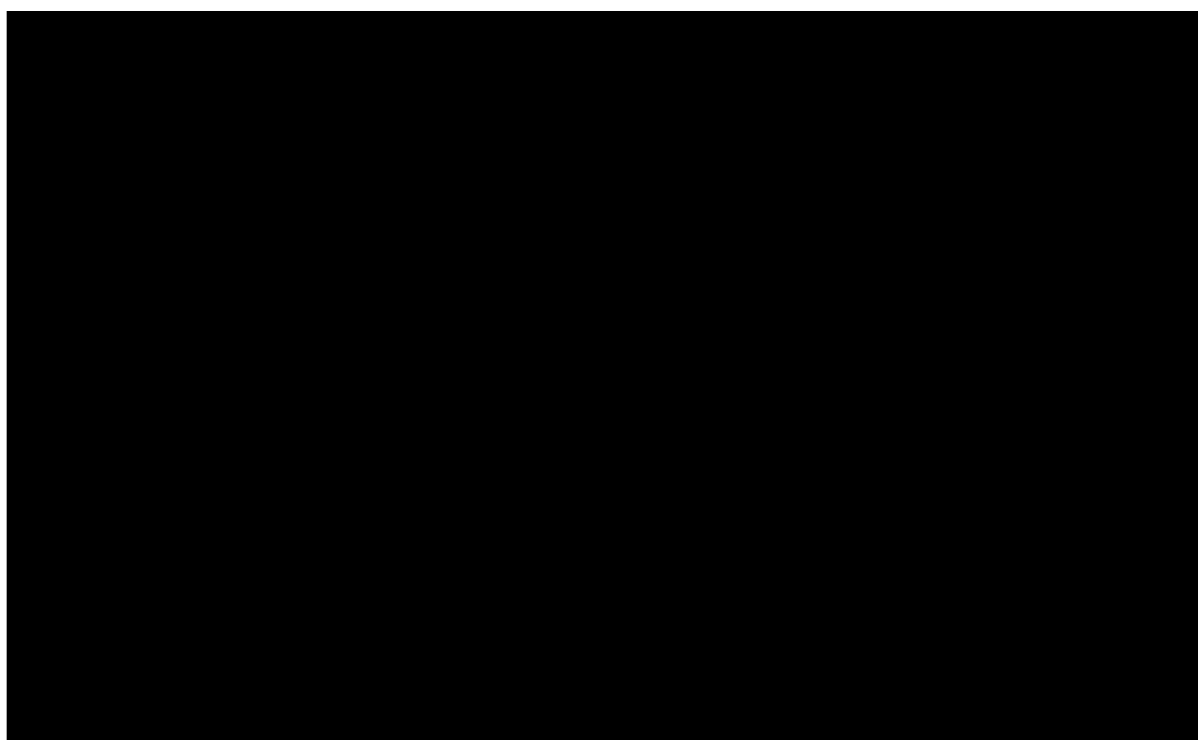


Figure 54: EAG tornado diagram for the comparison between STRIDE versus Lenvatinib

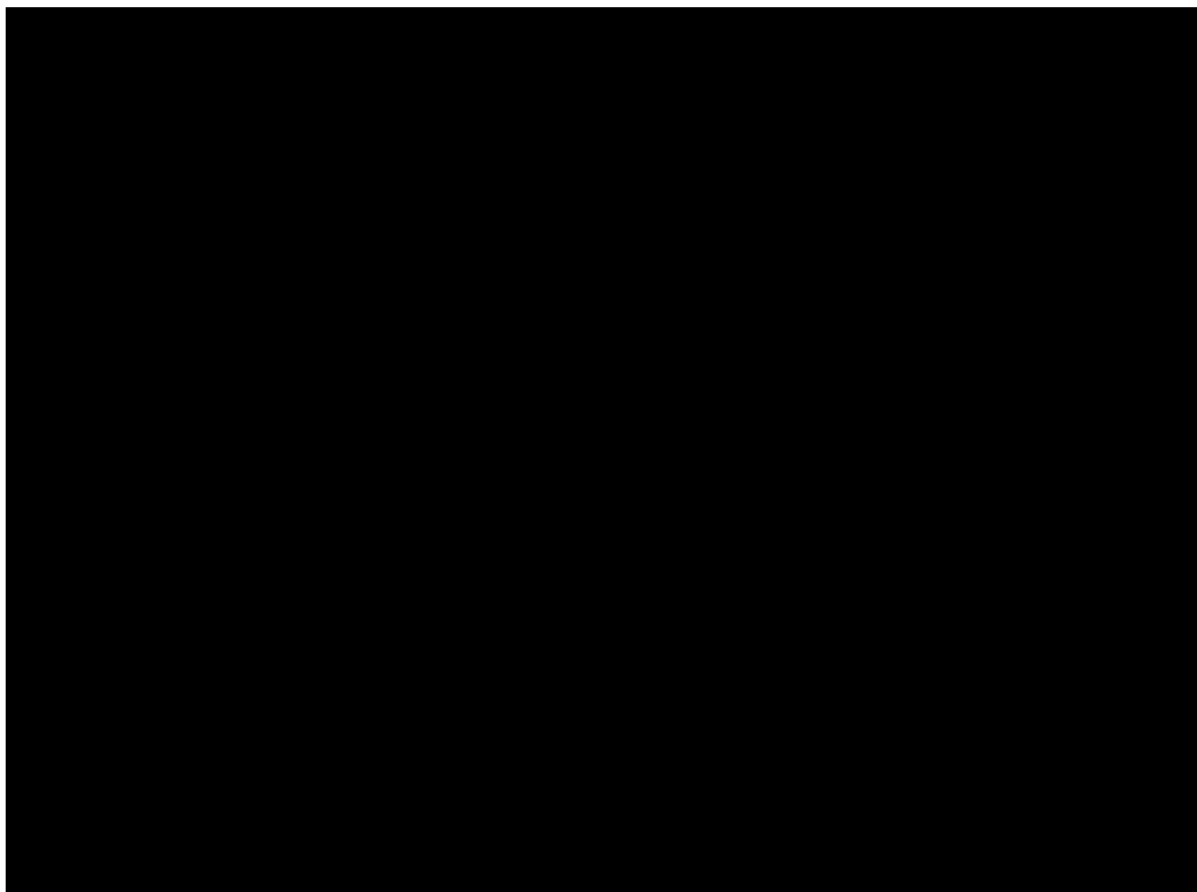


Figure 55: EAG tornado diagram for the comparison between STRIDE versus atezolizumab + bevacizumab

6.3.1.4 Scenario analysis results

Table 48 presents a scenario analysis of EAG's results for STRIDE compared with relevant comparators, using a deterministic approach. For STRIDE versus atezolizumab + bevacizumab,

Table 55: Scenario analysis EAG's results for STRIDE vs relevant comparators (deterministic)

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
EAG's Base-case										
1	Using the company's approach for TTD (Company assumed									

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	that TTD for atezolizumab + bevacizumab and Lenvatinib is equivalent to PFS)									
2	Using the constant HRs to estimate the OS and PFS of different treatments, based on the company's NMA									
3	40-year time horizon									
4	10-year time horizon									
5	Using on-treatment time-to-death utility values from TA666									
6	Using the company's approach									
7	Using the sorafenib utility as off-treatment utility in the company approach									
8	Using the utility values from Su et al., 0.76 and 0.68 are assigned as the proxy of utility values for PFD and PD, respectively.									
9	Using the company approach of age-									

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	adjustment coefficients for utilities									
10	Inclusion of vial sharing									
11	PFS extrapolation choice for STRIDE: Splines and knots									
12	PFS extrapolation choice for sorafenib: log-normal									
13	Treatment-specific RDIs									
14	Using the company's approach (splines and knots: normal, 1 knot) for overall survival in STRIDE, sorafenib, and 40-year time horizon									
15	Using the overall survival HR of 0.76 from the company's NMA for STRIDE vs sorafenib, and 40-year time horizon									
16	Using the company's NMA OS hazard ratios (Atezolizumab + bevacizumab vs STRIDE and lenvatinib)									

Scenario		STRIDE vs atezolizumab + bevacizumab			STRIDE vs sorafenib			STRIDE vs lenvatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	vs STRIDE) applied to the company's spline model for STRIDE to obtain models for atezolizumab + bevacizumab and lenvatinib for sorafenib. Splines and knots is used for sorafenib (see Appendix 9.6)									
17	Using the company's approach for incorporating the severity modifier (1.2 for sorafenib and lenvatinib, and 1.0 for atezolizumab + bevacizumab)	■■■■■	■■■	■■■■■	■■■■■	■■■	■■■■■	■■■■■	■■■	■■■■■
18	Using the severity modifier of 1.2 for all comparisons	■■■■■	■■■	■■■■■	■■■■■	■■■	■■■■■	■■■■■	■■■	■■■■■
ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; STRIDE: Single Tremelimumab Regular Interval Durvalumab; TTD: time to treatment discontinuation										

6.4 EAG's model validation

EAG implemented a comprehensive approach to model validation, employing multiple quality control and technical validation methods in alignment with guidelines from Philips et al. (2004).¹⁰¹ To maintain accuracy, any changes to the model were rechecked by an additional health economist. Validation efforts included comparing results from the company's model with those generated independently by the EAG, tracking processes to ensure consistency.

Model assumptions—such as OS and PFS curves, time horizons, and assumptions around TTD—were reviewed by EAG's clinical advisors and cross-referenced with related single technology appraisals (notably, TA666). External validation incorporated clinical feedback on treatment pathways and long-term survival projections, drawing on UK sources to align model outputs with NHS practices, thereby enhancing relevance to clinical settings.

To verify robustness, EAG reviewed probabilistic and deterministic base-case results, along with sensitivity analysis functionalities, discussing any differences with clinical team members. The observed discrepancies between PSA and deterministic base-case results were further investigated, ensuring the data and processes aligned with intended model outcomes. Additional validation efforts included extreme value testing to assess model responses to parameter changes, as well as editorial checks on textual and graphical outputs. This multifaceted approach reinforces the model's accuracy, relevance, and dependability in clinical decision-making.

7 Overall conclusion

The evidence of clinical effectiveness for durvalumab with tremelimumab in people with advanced, unresectable untreated hepatocellular carcinoma comes from the HIMALAYA trial that compared durvalumab with tremelimumab versus sorafenib. For overall survival the HIMALAYA trial documents a strongly favourable effect for durvalumab with tremelimumab over sorafenib. For progression-free survival there was little difference between the two treatments particularly up to when more than 75% in both arms had already progressed. The EAG's major concerns centred on the lack of UK patients recruited in HIMALAYA and the questionable generalisability of clinical effectiveness findings from the trial population to the UK HCC population stemming from demographic differences between the two populations. The EAG has

concerns about the company's network meta-analysis that aimed to compare clinical effectiveness of durvalumab with tremelimumab versus alternative first line therapies. Concerns centred on a lack of clarity about the company's analysis, the lack of a specific search strategy to find suitable studies for the analysis, the sparsity of data input for the analysis, and the failure of the company to place their analysis in the context of published analyses on the same subject. Compared to other published analyses the company's network analysis seems biased for the comparison of progression free survival from durvalumab with tremelimumab versus that from atezolizumab with bevacizumab.

The company's economic analysis was based on a partitioned survival model programmed in Microsoft Excel. The EAG considered the choice of the model to be appropriate to capture the long-term costs and benefits associated with treating people with advanced, unresectable untreated hepatocellular carcinoma. The comparators included in the economic analysis were narrower than the NICE scope, but the EAG considered this approach appropriate. All comparators were in keeping within their marketing authorisation and licensed dosing schedule.

The company employed clinical evidence from the HIMALAYA trial of durvalumab with tremelimumab versus sorafenib and results from its network meta-analysis to identify information to populate its economic model. The EAG focussed on uncertainty associated with company's modelling of major outcomes (overall survival, progression-free survival, and time to treatment discontinuation) for compared treatments. The EAG considered extrapolation of observed data from six years to the company's life-time horizon of forty years to be excessive, and the modelling that resulted in some survivors to the forty-year time horizon unrealistic for the UK population. The company's network meta-analysis output lacked precision and the use the output in modelling compared treatments resulted in imprecision affecting all outcomes for durvalumab with tremelimumab versus atezolizumab with bevacizumab, and for durvalumab with tremelimumab versus Lenvatinib.

Under the company's assumptions, and using a PAS price for durvalumab and tremelimumab and list prices for all other comparators, the company's fully incremental results showed that

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The EAG made amendments to the company's economic model inputs, which formed the basis for the EAG's base-case model. These changes resulted in differences between the company's base-case results and the EAG's base-case results. The company's results were presented based on using the commercial agreement in place for durvalumab with tremelimumab and list prices for all comparators, and this was the approach to the EAG's analysis.

The EAG's amendments:

- 20-year time horizon.
- Using the generalized Gamma model (based on HIMALAYA trial) for Sorafenib's OS.
- Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the OS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib.
- Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the PFS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib.
- Using PFS as a proxy of TTD in all treatments.
- Using the time-to-death utility value (data from the HIMALAYA trial).
- Using the QALY weight calculated from atezolizumab plus bevacizumab as the standard treatment in the UK for all comparators.
- Using Ara and Brazier (2010) as the source of age-adjustment coefficients for utilities.
- Amendment of the formula for calculating the half-cycle correction for the drug cost of tremelimumab.

Considering the EAG's preferred assumptions, all being made simultaneously, resulted in an

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9 APPENDICES

9.1 Critique of search strategy

Searches in a relevant set of bibliographic databases were undertaken on 31st August 2020, updated on 26th October 2021, and updated again on 10th April 2024. Suitable search terms for the comparators in the CS scope and others are used, but some important search terms were missing in the original SLR searches (e.g. terms for the intervention and synonyms for hepatocellular carcinoma), which is a concern in terms of potentially missing earlier publications. The searches for both updates are better, using a variety of suitable terms (including free-text synonyms for HCC, a broader thesaurus terms for the population, and terms for durvalumab and tremelimumab); this gives the EAG more confidence that the searches were sensitive enough to retrieve relevant studies added to sources after 31st August 2020 and before 10th April 2024. All searches were limited to English language and study type using search filters (RCTs in the original SLR and clinical trials more broadly in the updates). The original search of MEDLINE and Embase was limited to records of articles published in or after 2016 up to the search date (31st August 2020). Update searches were limited by date (since the date of the previous search for the first update and including or since the publication year that the previous search was run in for the second update, the latter of which isn't best practice but with a nearly 10-month overlap is less of a concern than if this had been for a shorter period). Update searches are also limited to remove animal only studies and some publication types (case study, case reports, letters, editorials, letters and notes), which is reasonable. In addition to database searches, the CS states that searches of three clinical trials registries, abstracts from five relevant conferences (from 2015 to Aug 2020 (via database searching, followed by manual checking), and 2021-2024 (via manual searching)) were undertaken. Details are not given for how the manual conference searching was undertaken in the original SR. No searches of HTA sources are reported. The CS does state that 'bibliography searches' were also carried out on all relevant SLRs and NMAs; a list of these was provided in response to clarification question A2. The EAG notes that this is an important supplementary search approach, which if undertaken thoroughly on a comprehensive set of reviews would have helped to mitigate the effects of the less sensitive original database searches. However, The EAG are concerned that a sensitive search for these study

types has not been conducted. The CS states that these SLRs and NMAs were identified during all three SLR iterations, yet the MEDLINE and Embase searches were limited to RCTs / clinical trials only. Also, the only review-specific database searched in addition to these was the Cochrane Database of Systematic Reviews (CDSR), which only contains Cochrane reviews, and no sources of HTAs were reported. While the RCT and clinical trial terms in MEDLINE and Embase will have picked up some reviews, other relevant SLRs and NMAs may have been missed.

9.2 EAG assessment of risks of bias of the CS systematic review about the scope of the appraisal (modified ROBIS)

Table 56: EAG ROBIS evaluation of the company's SLR

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	The review's objectives were initially well-defined but later amended. The eligibility criteria, detailed in CS Appendix D (Table 14), were broader than the NICE final scope. Modified SLR criteria were used for the NMA, aligning closely with the NICE scope. The NMA focused only on Overall Survival (OS) and Progression-Free Survival (PFS), excluding other previously included outcomes.
1.2 Were the eligibility criteria appropriate for the review question?	Probably no	The initial eligibility criteria were broad, leading to the inclusion of irrelevant studies. The exclusion criteria are not specified.
1.3 Were eligibility criteria unambiguous?	Probably no	There were ambiguities regarding the rationale for including certain interventions and comparators, population, and exclusion criteria (e.g. CS, Appendix D.1.4, Table 16). No exclusion criteria and justifications for such were reported.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably no	Restrictions to RCTs were appropriate. However, the company's justification in B.2.9.2 for restricting studies to Phase III RCTs reporting OS and PFS for the STRIDE population lacks sufficient information to determine the

ROBIS domain, and signalling questions	EAG's rating	Reasoning
		appropriateness of these restrictions.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably no	In CS, Appendix D.1.4, Table 16, study number 6 ⁶⁴ is deprioritised and excluded, although its data has been incorporated into the NMA results. This study reports the updated results of the IMbrave150 trial.
Concerns regarding specification of study eligibility criteria	High concern	The EAG has some concerns about the restrictions in eligibility criteria and the rationale and justification behind inclusion/exclusions.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	Searches for both the original systematic literature review (SLR) and the 2 updates were conducted using a suitable range of databases.
2.2 Were methods additional to database searching used to identify relevant reports?	Probably no	Checking reference lists of included studies, and contacting experts were not conducted. No searches of Health Technology Assessment (HTA) sources are reported. Manual searching of abstracts from five relevant conferences is reported. The CS also mentions that 'bibliography searches' were carried out on SRs and network meta-analyses (NMAs) and a list of these was supplied (clarification A2). However, it is unclear where these were sourced from, and the list is not comprehensive (the EAG's search found other relevant NMAs not listed).
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no	The original SR searches used suitable terms for comparators in the CS scope but missed important synonyms for hepatocellular carcinoma, potentially overlooking earlier publications before 31 st August 2020. The updated searches were improved by incorporating a variety of suitable terms, including free-text synonyms for hepatocellular carcinoma, broader thesaurus terms for the population, and specific terms for durvalumab and tremelimumab. MEDLINE and Embase searches were limited to

ROBIS domain, and signalling questions	EAG's rating	Reasoning
		RCTs / clinical trials only, using appropriate search terms, but no terms for SRs / NMAs were included. Although some SRs and NMAs would still have been found, this restriction is likely to have missed other relevant SRs and NMAs, which are a useful alternative source of trials.
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably yes	Databases were searched from 2016. Studies not in the English Language were excluded but justified. Database searches were limited to study types using search filters (RCTs in the original SR and clinical trials more broadly in the updates). Update searches were also limited to animal-only studies; some publication types (case studies, case reports, letters, editorials, letters, and notes) were removed, which is reasonable.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Two independent reviewers with consensus or a third reviewer screened abstracts and full papers for any discrepancies.
Concerns regarding methods used to identify and/or select studies	Unclear concern	Some potential for studies to have been missed from the SR
3: Data collection and study appraisal sections		
3.1 Were efforts made to minimise error in data collection?	Yes	Data were extracted by a single reviewer and checked by a second reviewer.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Sufficient study characteristics for all studies including studies in the SLR were reported in Tables 20 – 23 in CS Appendix D.
3.3 Were all relevant study results collected for use in the synthesis?	Yes	Relevant study results were reported in Figures 4-9 in CS Appendix D.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes	The company has specified that the RoB tool used in Table 28 of Appendix D is provided in the NICE STA template and the guidance by the CRD at the University of York. ³¹
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	Two reviewers undertook the risk of bias assessment (clarification response A1)
Concerns regarding methods used to collect	Low risk of bias	

ROBIS domain, and signalling questions	EAG's rating	Reasoning
data and appraise studies		
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	No	The company's inclusion/exclusion criteria for the NMA lacks detail, so it is difficult to determine whether a particular study should have been included or not when applying the company's criteria. The company's vague inclusion/exclusion criteria for the NMA led to limited data input, resulting in wide credible confidence intervals and no statistically significant comparisons for OS.
4.2 Were all predefined analyses followed or departures explained?	Unclear	No discussion of predefined analyses was reported.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	No	The synthesis only utilised three studies and restricted these to two interventions per study. This neglected some information available from one included study from the synthesis. Other authors tackling the same or very similar decision problem have included many more studies and interventions in their synthesis. In the opinion of the EAG the company synthesis neglected to use and to formally discuss additional evidence to that used and in so doing have generated synthesis outputs that are associated with severe imprecision that are poorly suited to the purpose of modelling extrapolation beyond the observed data.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Probably no	While the EAG acknowledges the discussion of heterogeneity issues, no steps were taken to address these problems in the synthesis. This suggests that between-studies variation was not adequately addressed.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No	The EAG indicates the absence of funnel plots and limited sensitivity analyses. It also points out the lack of robustness in the NMA results due to large CRD intervals, indicating low precision. This suggests that the findings are not robust.

ROBIS domain, and signalling questions	EAG's rating	Reasoning
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably no	Sensitivity analyses or adjustment approaches were not employed. There were methodological inadequacies.
Concerns regarding the synthesis and findings	High risk of bias	More than one ROBIS question has no or probably no response.
Risk of bias	High risk of bias	The limitations have not been addressed or justified. Only one domain had a low risk of bias.

9.3 Risk of bias for HIMALAYA trial

The EAG used Cochrane's risk of bias tool (RoB2) to assess the HIMALAYA trial.

Table 57: HIMALAYA trial RoB2 assessment

Domain	Signalling question	Response	Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Yes	A blocked randomisation was generated. Patients were randomized using IWRS in a 1:1:1:1 ratio to (Arm A), (Arm B), (Arm C), or (Arm D) in a stratified manner accordingly.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Probably yes	The company claims that the baselines are well-balanced. However, the EAG points out that factors such as gender, [REDACTED] and Child-Pugh scores are slightly skewed in favour of STRIDE, although these differences are not statistically significant. These characteristics can impact patient prognosis and treatment outcomes. ¹⁰³⁻¹⁰⁵ The cumulative effect of these small differences favours STRIDE's outcomes over sorafenib.
	Risk of bias judgement	Some concerns	Although the baseline characteristics do not show significant imbalances between treatments, several key prognostic factors favour STRIDE, and their

Domain	Signalling question	Response	Comments
			cumulative impact raises concerns for EAG.
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Yes	It is an open-label trial in which both trial personnel and participants are unblinded.
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Probably yes	Measurement of outcomes by unblinded assessors raises concerns. Patient-reported outcomes (PRO), PFS, TTD, and ORR could have been impacted, affecting the reliability of secondary outcomes. The blinded central independent review (BICR) evaluated the exploratory analysis and outcomes, but no data or further information on BICR was reported in the CS. Therefore, the extent and direction of bias cannot be determined, and the outcomes are likely affected.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Probably yes	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Unclear	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	ITT has been used.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable	
	Risk of bias judgement	Moderate to high risk of bias	High risk of bias in part 1 questions because of the open-label design.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes	The data has been reported for the ITT population including all randomised patients. <i>"All efficacy analyses were carried out on</i>

Domain	Signalling question	Response	Comments
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable	<i>the full analysis set (FAS).</i> " (CS Document B, section B.2.3.5)
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable	
	Risk of bias judgement	Low risk of bias	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No	Data for the durvalumab group was not presented.
	4.3 Were outcome assessors aware of the intervention received by study participants?	Yes	It was an open-label study.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes	Knowledge of the assigned intervention could influence participant-reported outcomes as well as secondary outcomes such as TTD, PFS, and ORR.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Yes	<i>"In general, the assessment was carried out by the trial investigator, and tumour status was assessed according to RECIST 1.1"</i> (CS Document B, section B.2.3.5). The company does not report any data measured by Blinded Independent Central Review (BICR) in the submission. Although the protocol mentions measurements by a BICR, these results were not reported in the CS. Therefore, knowledge of the intervention by investigators and participants could affect

Domain	Signalling question	Response	Comments
			PRO and the secondary outcomes.
	Risk of bias judgement	High risk of bias	Assessment of the outcome was likely influenced by knowledge of the intervention received.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Probably yes	The EAG compared the analyses that were defined in the protocol with the published results. No changes to analysis plans were detected.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes	The tabulated form of all safety and adverse event data for the 5-year DCO was requested by the EAG and the response was not clear and did not report requested results (clarification question A15). The outcomes and analysis from BICR compared to investigators' assessments are also not reported. The multiplicity adjustments for the risk of Type I errors were not considered and controlled.
	5.3 ... multiple eligible analyses of the data?	Probably no	
	Risk of bias judgement	Some concerns	Some concerns are available due to not reporting all measured outcomes.
	Overall bias	Risk of bias judgement	Moderate to high risk of bias
BICR, blinded independent central review; EAG, Evidence assessment group; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RoB, risk of bias:			

9.4 Record of targeted search for EAG's NMA selection

Epistemonikos

Search date: 24/09/2024

Advanced Search

title:(((hepatocellular OR "hepatic cell" OR "liver cell") AND (cancer OR cancers OR cancerous OR tumor OR tumors OR tumour OR tumours OR neoplasm OR neoplasms OR neoplastic OR carcinoma)))

AND

(title:(advanced OR metastasis OR metastatic OR metastases OR recurrent OR recurrence OR recurrences OR unresectable OR inoperable) OR abstract:(advanced OR metastasis OR metastatic OR metastases OR recurrent OR recurrence OR recurrences OR unresectable OR inoperable))

AND

(title:("network meta analysis" OR "network meta-analysis" OR NMA OR "indirect treatment comparison") OR abstract:("network meta analysis" OR "network meta-analysis" OR NMA OR "indirect treatment comparison"))

AND

(title:((durvalumab AND tremelimumab) OR STRIDE OR lenvatinib OR sorafenib OR (atezolizumab AND bevacizumab)) OR abstract:((durvalumab AND tremelimumab) OR STRIDE OR lenvatinib OR sorafenib OR (atezolizumab AND bevacizumab)))

Filtered by publication type: Systematic Review

Total: 52

Information specialist exported the 52 records to EndNote and used Endnote's Find Full Text feature to add PDFs.

Information specialist filtered results ((consulting each article's abstract, plus the full text if the abstract was unclear) to put the records into the following groups:

- NMAs including at least durvalumab and lenvatinib and atezolizumab and sorafenib
- Other NMAs including at least lenvatinib and atezolizumab and sorafenib
- Other NMAs

Sent groups to reviewer for final check and selection.

9.5 EAG's selected NMA

Table 58: EAG assessment of risk of bias for EAG's selected NMA

ROBIS Domain and Signalling Questions	Celsa-2024⁶⁶	Vogel-2023⁷⁵	Wang-2024⁷⁶	Comments
1: Study eligibility criteria				
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes	Yes	Yes	All studies adhered to their pre-defined objectives and eligibility criteria.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	Yes	Yes	Eligibility criteria were appropriate for the review questions in all studies.
1.3 Were eligibility criteria unambiguous?	Yes	Yes	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably Yes	Yes	Probably Yes	Both Wang's 2024 and Celsa's 2024 studies have limited their studies to only phase III trials. They have not missed the data sources of interest.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably yes	Yes	Probably yes	English Language-only publications for Celsa and Wang 2024 were included. However, the reported studies match the data sources of interest.

Concerns regarding specification of study eligibility criteria	Low	Low	Low	All studies had clear and appropriate eligibility criteria.
2: Identification and selection of studies				
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes	Yes	Yes	
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	Yes	Probably no	No additional searches other than of 2 conferences were conducted for Wang 2024.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably Yes	Yes	Probably Yes	The search strings for each database for Celsa (2024) are not provided and it is unclear how Boolean operators are used in relation to the reported search terms. The Embase search for Wang (2024) is unclear. The numbers for database searches in both PRISMA flow diagrams suggest the searches were structured appropriately. Search strategies for Vogel (2024) were well-

				structured and sensitive.
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	Yes	Yes	Restrictions were appropriate and justified.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Yes	Yes	Efforts were made to minimize errors in study selection.
Concerns regarding methods used to identify and/or select studies	Low	Low	Low	Wang (2024) did not conduct additional searches; however, the EAG did not identify any missing studies related to this concern. Therefore, all relevant studies have been captured.
3: Data collection and study appraisal sections				
3.1 Were efforts made to minimise error in data collection?	Yes	Yes	Yes	Standardized methods were used to minimize errors.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Yes	Yes	Detailed study characteristics were provided.
3.3 Were all relevant study results collected for use in the synthesis?	Yes	Yes	Yes	All relevant results were collected and used.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	Probably yes	Yes	Vogel 2023 has used the Centre for Reviews and Dissemination (CRD risk of bias). ³¹

3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	Yes	Yes	Multiple reviewers independently assessed the risk of bias.
Concerns regarding methods used to collect data and appraise studies	Low	Low	Low	
4: Synthesis and findings				
4.1 Did the synthesis include all studies that it should?	Yes	Yes	Yes	All relevant studies were included in the synthesis.
4.2 Were all predefined analyses followed or departures explained?	Yes	Yes	Yes	Predefined analyses were followed, and departures were explained.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes	Yes	Yes	The synthesis was appropriate and accounted for study similarities.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	Yes	Yes	Heterogeneity was addressed using appropriate methods.
4.5 Were the findings robust, e.g., as demonstrated through funnel plot or sensitivity analyses?	Yes	Yes	Yes	The findings were robust and supported by sensitivity analyses.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes	Probably yes	Yes	Necessary assessments have been properly taken to minimize the risk of bias.

Concerns regarding the synthesis and findings	Low	Low	Low	The synthesis and findings were robust and appropriately addressed biases.
Risk of bias	Low	Low	Low	Overall, all studies demonstrated a low risk of bias.

9.6 EAG changes to model

In Table 59, we present the technical details of the changes made to the company model that formed the basis of the EAG analyses.

Table 59: EAG changes to the company model

EAG's preferred assumption based on issues	Technical report of changes in the company's model
20-year time horizon	"Controls" worksheet, Cell E19, has changed to "20"
Using the generalized Gamma model (based on HIMALAYA trial) for Sorafenib's OS	"Controls" worksheet, Cell C84: choice has changed to "One piece (Separately fitted)" (Generalized Gamma)
Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the OS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib	"Controls" worksheet, Cell C83: choice has changed to "Constant hazard ratio (HR)" "NMA Data" worksheet, Cell C14, has changed to: 0.7816 (95% CrI: 0.66, 0.93) "NMA Data" worksheet, Cell C16, has changed to: 0.92 (95% CrI: 0.78, 1.08) "NMA Data" worksheet, Cell C17, has changed to: 0.68 (CrI: 0.42, 1.10)
Using the constant HR (vs. sorafenib) from Vogel et al.'s NMA for the PFS of STRIDE, Atezolizumab + bevacizumab, and lenvatinib	"Controls" worksheet, Cell C102: choice has changed to "Constant hazard ratio (HR)" "NMA Data" worksheet, Cell C27, has changed to: 0.9041 (CrI: 0.62, 1.35) "NMA Data" worksheet, Cell C29, has changed to: 0.6535 (CrI: 0.44, 1) "NMA Data" worksheet, Cell C30, has changed to: 0.66 (CrI: 0.27, 1.59)
Using PFS as a proxy of TTD in all treatments.	"Controls" worksheet, Cell D122 and D123: choice has changed to "Constant hazard ratio (HR) vs. PFS"
Using the time-to-death utility value (data from the HIMALAYA trial)	"Controls" worksheet, Cell I43: choice has changed to "Yes"
Using the QALY weight calculated from Atezolizumab plus bevacizumab as the standard treatment in the UK for all comparators	"Deterministic Results" worksheet, Cell D178: choice has changed to "No"
Using Ara and Brazier (2010) as the source of age-adjustment coefficients for utilities	"Life Tables" worksheet, put the Age-adjustment coefficients for general population utilities table in the AQ17:AU26 area At Cell BE41: BE2128 in "Engine (1), (2),(3), and (4))" worksheets, is put this formula: CHOOSE(\$H\$12,AAA_intercept+(AAA_Sex_male*control_PopMale)+(AAA_AGE*H41)+(AAA_Age_power2*(H41^2)),1) At Cell BF41: BF2128 in "Engine (1), (2),(3), and (4))" worksheets, the previous formula is replaced with this formula: BE41/\$BE\$41
Half cycle correction	Engine (1), Cell Z41: Formula has changed to: IF(P41="NA","",CHOOSE(\$H\$10,IF(\$B41=0,P41/2,(P41+P40)/2),P41))

For the scenario analysis, using the company's NMA OS hazard ratios (Atezolizumab + bevacizumab vs STRIDE and lenvatinib vs STRIDE) applied to the

company's spline model for STRIDE to obtain models for atezolizumab + bevacizumab and lenvatinib for sorafenib. Splines and knots is used for sorafenib.

This contrasts with the company base-case in which NMA HRs are applied to the sorafenib spline model.

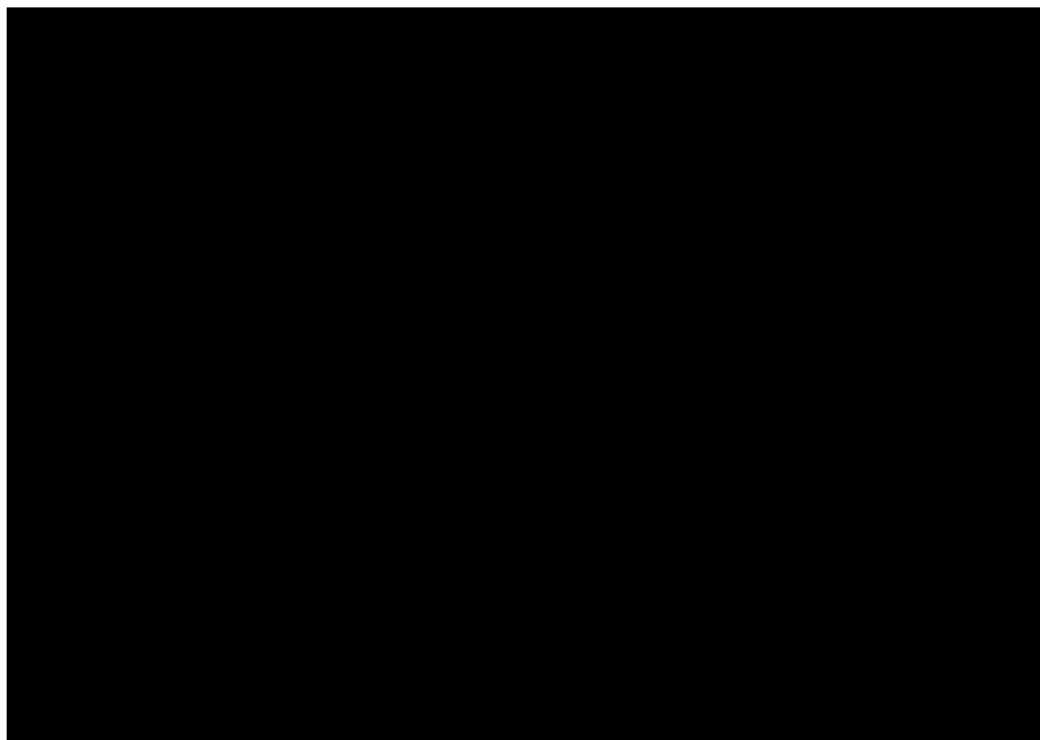


Figure 56: Applying company's NMA-derived OS HRs applied to STRIDE for atezolizumab + bevacizumab and lenvatinib

Using Vogel NMA HRs instead of the company's, generated similar results (i.e., improved overall survival for Lenvatinib and atezolizumab + bevacizumab relative to the company's base-case OS model).

9.7 List of company and EAG cost-effectiveness analyses (applying confidential prices) and source of prices

The EAG re-ran the company's base-case analysis and conducted its own base-case analysis to compare STRIDE versus all comparators, using the available PAS discounts and MPSC prices for treatments. This report is provided separately in the document titled "EAG Confidential Appendix." In Table 60, we present the sources of the prices used in the analyses in the EAG Confidential Appendix document.

The EAG confidential appendix report includes the following analyses:

- Company's cost-effectiveness results applying confidential prices for comparator treatments
 - Deterministic base-case results, using the highest MPSC prices (pairwise and fully incremental analysis)
 - Deterministic base-case results, using the lowest MPSC prices
 - Deterministic base-case results, using the mid-point MPSC prices
 - Probabilistic sensitivity analysis results, using the mid-point MPSC prices
 - Scenario analysis results, using the mid-point MPSC prices
 - Scenario analysis using a mixed modifier approach based on the mid-point MPSC prices
- EAG cost-effectiveness results applying confidential prices for comparator treatments
 - Deterministic base-case results, using the highest MPSC prices (pairwise and fully incremental analysis)
 - Deterministic base-case results, using the lowest MPSC prices
 - Deterministic base-case results, using the mid-point MPSC prices
 - Probabilistic sensitivity analysis results, using the mid-point MPSC prices
 - Scenario analysis results, using the mid-point MPSC prices

Table 60: Sources of prices used in EAG confidential appendix (provided separately)

Treatment	Available form	Pack size	Total mg per pack	Source used
Durvalumab	50 mg/ml; 2.4 ml (vial)	1	120 mg	PAS discount
Durvalumab	50 mg/ml; 10 ml (vial)	1	500 mg	PAS discount
Tremelimumab	20 mg/ml; 15 ml (vial)	1	300 mg	List price-BNF
Sorafenib	200 mg (per tablet)	112	22400 mg	List price-eMIT
Lenvatinib	10 mg (per capsule)	30	300 mg	PAS discount
Atezolizumab	60 mg/ml; 20 ml (vial)	1	1200 mg	PAS discount
Bevacizumab	25 mg/ml; 4 ml (vial)	1	100 mg	Low, high and mid-point MPSC
Bevacizumab	25 mg/ml; 16 ml (vial)	1	400 mg	Low, high and mid-point MPSC
Regorafenib	40 mg (per tablet)	84	3360 mg	List price-BNF
Cabozantinib	20 mg (per tablet)	30	600 mg	List price-BNF
Cabozantinib	40 mg (per tablet)	30	1200 mg	List price-BNF
Cabozantinib	60 mg (per tablet)	30	1800 mg	List price-BNF
eMIT, Drugs and pharmaceutical electronic market information tool; BNF, British National Formulary; MPSC, Medicines procurement supply chain; PAS, Patient access scheme				

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 11 November 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Generalisability of HIMALAYA baseline patient characteristics to UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50: Age at diagnosis (HIMALAYA recruited some adults diagnosed with HCC at age ≥ 18 years whereas guidelines from the British Society of Gastroenterology¹ (see Figure 1) indicate that diagnosis in the UK at age < 30 years is very rare; median age at diagnosis in HIMALAYA is lower than in the UK);	Page 50: Age at diagnosis (HIMALAYA recruited some adults diagnosed with HCC at age ≥ 18 years whereas guidelines from the British Society of Gastroenterology¹ (see Figure 1) indicate that diagnosis in the UK at age < 30 years is very rare; median age at diagnosis in HIMALAYA is 65 years).	The EAG report refers to BSG guidelines and does not provide an exact figure for the median age at diagnosis in the UK, which is misleading the reader as to the extent of the difference. Median age of diagnosis reported from a comparable time period is 68-69 years,^{2,3} which is broadly aligned to the median age in HIMALAYA (65 years. The majority of the patients (50.4%) in the STRIDE arm were older than 65 years (Clinical Study Report Table 14.1.4), and including patients aged ≥ 18 years is in line with standard clinical trial methodology.	There is no factual error. The company refers here to alternative sources of information (i.e. Beecroft et al., and Childs et al.,) The amendment suggests HIMALAYA median of 65 years. Table 9 of the submission states medians of 65 and 64 years (maybe with rounding up or down) for STRIDE and Sorafenib. Suddle et al., do not report a median value but provide a distribution and state: <i>The incidence of liver cancer incidence rises from the age of 40 to 44, this rise is steep in men and steady in women. The peak age incidence is in people over 80 years.</i> The submission refers to Suddle et al., several times but makes no reference to Suddle's age and gender distributions. The company do not present the age

			distribution for HIMALAYA only ranges, median, mean. It is clear according Suddle et al., that HIMALAYA likely differs from UK in both age (being younger) and gender (being heavily weighted with males) distributions. In HIMALAYA the ratio of males to females was 5.66:1, whereas Suddle et al., indicate an approximate 2.3:1. Ratio. Should the response to treatments differ between genders (as somewhat implied by the company's subgroup analysis), this would skew outcomes from HIMALAYA relative to UK HCC population. Suddle et al., comment: <i>there are approximately 2100 new cases of liver cancer in women every year and there are approximately 4100 new cases of liver cancer in men every year.</i>
Page 50: The EAG notes that a recent real-world study of UK HCC that included 2160 patients suggests that more than half of	Page 50: ~~The EAG notes that a recent real-world study of UK HCC that included 2160~~	It is misleading to highlight that 50% of patients with HCC in the UK do not receive treatment, whilst not accounting for the disease stage and status of these	The EAG acknowledges that the patient mix of those that receive or do not receive treatment is not known.

the patients receive no specific cancer therapy. Page 69 However, the EAG notes that a recent study estimated that more than 50% of HCC cases in England receive no cancer-specific treatment at all.² In the HIMALAYA trial, virtually all participants receive treatment; so there is a much broader mismatch between the RCT and real-world treatment in the UK.	~~patients suggests that more than half of the patients receive no specific cancer therapy~~ Page 69 ~~However, the EAG notes that a recent study estimated that more than 50% of HCC cases in England receive no cancer-specific treatment at all.² In the HIMALAYA trial, virtually all participants receive treatment; so there is a much broader mismatch between the RCT and real-world treatment in the UK.~~	patients, a lot of which may have very advanced liver disease/ not eligible for any treatment options/awaiting transplant. The 50% figure is irrelevant to the appraisal scope which includes patients specifically with advanced/unresectable HCC ineligible for locoregional therapy which forms only a proportion of the population from the real-world study the EAG is quoting. In the HIMALAYA trial all patients receive treatment due to the trial setting of the study.	EAG has modified the text on page 69 to: <i>The EAG note that a recent study estimated that $\geq 50\%$ of HCC cases in England receive no cancer-specific treatment at all.² Patient mix of treatment receivers and treatment non-receivers is unknown. In the HIMALAYA trial, virtually all participants receive treatment due to trial setting of the study.</i>
Page 55 The audit also shows that UK patients have a more severe disease status profile. The audit lacks data on ethnicity, BCLC stage, and other factors. These differences threaten the validity of applying the trial results to the UK population.	Page 55 ~~The audit also shows that UK patients have a more severe disease status profile. The audit lacks data on ethnicity, BCLC stage, and other factors. These differences threaten the validity of applying the trial results to the UK population.~~	The multicentre audit study is a UK RWE-based study³, while HIMALAYA is a global trial. Some of the audit population is out of scope, for example it included patients with PS =2, and cholangiocarcinoma, which were excluded from HIMALAYA. The audit study³ referenced in the CS provides a general overview of population trends and it is misleading to suggest a not exact match of population characteristics threatens the validity of the HIMALAYA trial results, due to the different settings of the studies.	The EAG considers this a divergence of opinion rather than factual error. The submission states: <i>Furthermore, despite not having UK centres in this trial, the trial participant characteristics closely align with an advanced HCC patient audit in the UK, ensuring the trial is generalisable to patients in the UK.</i> The EAG do not agree.

Page 56 The EAG's clinical expert noted that the HIMALAYA trial population is unlikely to fully represent the UK. Regional variations in the UK include older, predominantly white, overweight (BMI >30), and a lower prevalence of viral aetiology. Based on some studies found by the EAG, almost 55% of the UK population with HCC are over 69 years old. [REDACTED] [REDACTED]⁴⁰⁻⁴²	Page 56 The EAG's clinical expert noted that the HIMALAYA trial population is unlikely to fully represent the UK. Regional variations in the UK include older, predominantly white, overweight (BMI >30), and a lower prevalence of viral aetiology. Based on some studies found by the EAG, almost 55% of the UK population with HCC are over 69 years old. [REDACTED]⁴⁰⁻⁴² This is commonly observed in global clinical trials in liver cancer (eg IMBbrave150) due to the higher incidence of HCC in Asian countries.	While the company acknowledges the numerical differences in the certain population characteristics vs the audit study, the clinical experts the company interviewed consisting of 6 UK medical oncologists and 1 UK hepatologist considered the baseline characteristics patients enrolled in HIMALAYA trial are representative of the population with first-line unresectable or advanced HCC in UK clinical practice.⁴ They noted the differences in viral aetiology, however, do not expect these to influence generalisability; other factors such as age, race or BMI were not flagged. The company considers it important to consult both oncologists and hepatologists to assess the generalisability of the characteristics, not only based on the epidemiological presentation, but also from the perspective of the influence on the generalisability of the efficacy results of the treatment. In this regard, the perspective of a prescribing oncologist is crucial.	The EAG does not consider that a factual error occurs.

Page 86 The mean age of participants in the trial is 63.1 years, whereas UK clinical experts indicate that the average age of HCC patients in practice is closer to 70 years. This age discrepancy raises concerns about the generalisability of the results to the UK population. Further details on other characteristics of differences between the HIMALAYA trial and UK population are outlined in Section 3.2.3. This presents challenges in generalising the findings of the HIMALAYA trial, including its economic evaluation, to the UK context.	Page 86 The mean age of participants in the trial is 63.1 years, <u>aligned with the 63.3 years reported as mean age of HCC patients in England in the reference used by the EAG.</u>⁵ ~~whereas UK clinical experts indicate that the average age of HCC patients in practice is closer to 70 years. This age discrepancy raises concerns about the generalisability of the results to the UK population.~~ Further details on other characteristics of differences between the HIMALAYA trial and UK population are outlined in Section 3.2.3. This presents challenges in generalising the findings of the HIMALAYA trial, including its economic evaluation, to the UK context.	The mean age of participants in HIMALAYA is 63.1, aligned with the 63.3 years reported as mean age of HCC patients in England in the reference used by the EAG.⁵ The mean age of participants in HIMALAYA is also comparable to the mean age of patients from the IMBrave150 study (63.4), which was seen as broadly generalisable of UK clinical practice by NICE in TA666 and not inappropriate for economic evaluation.⁶ The same trend is observed for median age, 65 in both the HIMALAYA and IMBrave150 studies. It is therefore inconsistent to raise the mean and median ages of HIMALAYA patients as a key concern. The EAG notes the statement was informed by clinical experts but does not provide information on their expertise. The company consulted 6 UK medical oncologists and 1 UK hepatologist which considered the baseline characteristics patients enrolled in HIMALAYA trial including age to be representative of the population with first-line unresectable or advanced HCC in UK clinical practice.	This text is from the EAG Cost effectiveness section and refers to CS Table 33. EAG have modified the text “The mean age of participants in the trial is 63.1 years” to: The mean age of the modelled participants is 63.1 years,

Issue 2 Errors relating to other data from the HIMALAYA trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57 Additionally, not all PROs (including PGIC and PRO-CTCAE) Page 59 the EAG found no data on the PGIC or PRO-CTCAE questionnaires in the CS.	Page 57 Additionally, not all PROs (including PGIC and PRO-CTCAE) ...PROs (including PGIC and PRO-CTCAE) were provided as part of the CS reference pack. Page 59 the EAG found no data on the PGIC or PRO-CTCAE questionnaires in the CS, this data was provided as part of the CS reference pack.	Data on PGIC and PRO-CTCAE can be found in the Clinical Study Report Section 14 – Tables and Figures provided as part of the reference pack. This has not been requested by the EAG.	We have removed this text from the report.
Page 58 The median PFS for STRIDE was 3.78 (95%CI:3.68, 5.32) months and for sorafenib was 4.07 (95%CI:3.19, 3.75)	Page 58 The median PFS for STRIDE was 3.78 (95%CI:3.68, 5.32) months and for sorafenib was 4.07 (95%CI:3.75-5.49)	This statement is factually incorrect - the CI interval for sorafenib is 3.75 - 5.49 (CS Table 12).	We have now included the 95%CI for sorafenib.

Pg 99 "In CS Document B, the EAG could not find PFS results for a later DCO."	~~"In CS Document B, the EAG could not find PFS results for a later DCO."~~	The wording proposed by EAG misleads the reader that PFS analysis was pre-planned beyond the study final analysis. As per the HIMALAYA trial protocol, PFS was a secondary endpoint. The primary study analysis (DCO: 27th August 2021) includes analysis of PFS as of the official final analysis for the study. Further analysis of PFS was not conducted as part of the 4- and 5-year OS exploratory analyses as those served to inform long-term survival and safety outcomes.	We have deleted the text as suggested.

Issue 3 Inaccuracies in adverse effects reporting commentary

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57 The tabulation of all safety and adverse event data for the 5-year data cut-off (DCO) was requested by the EAG, but no helpful response was elicited.	Page 57 The tabulation of all safety and adverse event data for the 5-year data cut-off (DCO) was requested by the EAG, in response to which the company presented the numbers of serious TRAEs and AEs that were not treatment-related from updated analysis II (1st March 2024).	The company presented numbers of serious TRAEs and AEs that were not treatment-related from updated analysis II (1st March 2024) in Figure 1 of the CQ document, question A8. Therefore, it is factually incorrect to state no helpful response was elicited.	The EAG acknowledges the frequencies that the company has provided, although uncertainties remain. The EAG has made changes as follows: The EAG requested the tabulation of all safety and adverse event data for the 5-year data cut-off (DCO) and beyond. In response, the company presented only an overview of serious TRAEs and AEs that were not treatment-related from updated analysis II (1st March 2024). However, no further information on delayed treatment-related events

			after five years or beyond was provided. The EAG finds the overview with general results and frequencies inadequate and insufficient. Concerns about long-term TRAEs remain.
Page 60 169 patients (43.6%) receiving durvalumab had dose delays. The EAG considers that this is a relatively high proportion. Delays in 117 patients (30.2%) were due to AEs. The EAG finds the proportion of AEs that led to discontinuation and the proportion of durvalumab dose delays concerning.	Page 60 169 patients (43.6%) receiving durvalumab had dose delays. ~~The EAG considers that this is a relatively high proportion.~~ Delays in 117 patients (30.2%) were due to AEs. ~~Other causes of dose delays are [REDACTED] and [REDACTED]~~ The proportion of AEs leading to discontinuation of study treatment possibly related to the treatment was [REDACTED]% in the STRIDE arm.⁷ This proportion is lower to the observed in the IMbrave150 trial with 15.5% of AEs leading to the discontinuation of study treatment in the atezolizumab+bevacizumab arm.⁸ ~~The EAG finds the proportion of AEs that led to discontinuation and the proportion of durvalumab dose delays concerning.~~	To prevent potential misinterpretation and accurately assess the real impact of dose delays, it is necessary to contextualize with other reimbursed treatments in the same setting (e.g atezolizumab+ bevacizumab) and evaluate dose delays in terms of proportion of patients with delays, and the number of delays as well as associated reasons. Most of the patients in the STRIDE arm (56.4%) did not experience any dose or cycle delay. Dose delays due to non-AEs reasons are expected to be lower in clinical practice [REDACTED] The inclusion of a statement regarding the proportion of AEs that led to discontinuation without providing the percentage could be misleading. The proportion of AEs that led to discontinuation of study treatment in the STRIDE arm was [REDACTED] being	The EAG doesn't consider this an incorrect statement as the EAG has only reported the proportions the company has provided. The EAG disagrees with the company's suggestion. The EAG has only reported the number of delays and discontinuations provided by the company. To avoid any ambiguities, the EAG has revised the text based on the company's explanations as follows: In the CS, document B, section B.2.10.2, the company states that durvalumab-related dose delays in the STRIDE treatment arm affected [REDACTED]. In the CS, document B, section B.2.10.3, the company reports that [REDACTED] discontinuations due to any adverse event leading to the discontinuation of study treatment. The company only considers [REDACTED] of these cases as possibly related to the treatment, which the EAG finds not justified. The reported proportions are calculated and captured by investigators who were not blinded,

		possibly related to treatment in [REDACTED] of the patients as shown in Table 27 of CS. The proportion of AEs leading to withdrawal from any study treatment in the atezolizumab+bevacizumab arm of the IMBrave150 trial was 15.5% according to CS Table 22 of TA666⁶	making the results prone to bias. Therefore, the EAG cannot fully agree that all of these AEs leading to discontinuation are possibly treatment-related.
Page 61 In Table 28 of CS Document B, section B.2.10.3, the company summarises treatment-related adverse effects (TRAEs) for the HIMALAYA trial, categorising them as “TRAEs of any cause” and “TRAEs”. The EAG requested definitions and lists of AEs in these categories for clarification (A7). The company provided a brief explanation of how AEs were interpreted by the investigators, however, details anticipated by the EAG were not provided. The CS reports that patients in the STRIDE arm suffered a higher incidence of adverse events in both categories of TRAE compared to sorafenib, although the Abou-Alfa et al paper⁹ based on much shorter maximum follow-up reported that Grade 3/4 treatment-emergent adverse events occurred for 50.5%	Page 61 In Table 28 of CS Document B, section B.2.10.3, the company summarises treatment-related adverse effects (TRAEs) for the HIMALAYA trial, categorising them as “TRAEs of any cause” and “TRAEs”. The EAG requested definitions and lists of AEs in these categories for clarification (A7). The company provided a brief explanation of how AEs were interpreted by the investigators, however, details anticipated by the EAG were not provided. The CS reports that patients in the STRIDE arm suffered a higher incidence of <u>treatment-emergent TRAE</u> compared to sorafenib, <u>although the Abou-Alfa et al paper⁹ based on much shorter maximum follow-up reported that</u> Grade 3/4 treatment-emergent adverse events	As part of CQ A7, the company provided an amended version of CS Table 28, clarifying that the two categories of AEs covered in the table are “Treatment-emergent AEs of any cause” and “Treatment-related AEs”. Therefore, only the second category of AEs captures TRAEs, the first category captures AEs that were treatment-emergent, with no established causal relationship with a therapy under investigation. The table is sourced from Table 3 in the Abou Alfa paper¹⁰ where the same classification and data cut-off is used, therefore a comparison between CS Table 28/CQ Table 2, and Abou Alfa Table 3 is irrelevant, as it is equivalent data. In the light of this, the company proposes wording changes to reflect the difference	In response to the clarification question A7, even though the company has changed “TRAE of any cause” to “Treatment-emergent AEs of any cause”, this has not been reported in CS document B, Table 8. Therefore, the EAG finds the company’s suggestions contradictory to document B, which they have provided a second time after the clarification responses were delivered. Additionally, the EAG notes that based on the definition provided by the company in response to clarification question A7, a treatment-emergent AE is defined as starting “after dosing or prior to dosing and worsening following exposure to the treatment.” The AE exacerbations or worsening occurred as the treatment started, and as the caption of Table 8 indicates, the reported AEs are

of patients with STRIDE, and 52.4% with sorafenib. Relative to sorafenib, STRIDE exhibited higher rates of serious TRAEs, immune-mediated TRAEs requiring high-dose steroids, and grade 3 or 4 immune-mediated TRAEs, raising the EAG's concerns. Immune-mediated TRAEs leading to death were observed in STRIDE but not in sorafenib. STRIDE also had a higher incidence of grade 3 or 4 hepatic TRAEs.	occurred for 50.5% of patients with STRIDE, and 52.4% with sorafenib. Relative to sorafenib, STRIDE exhibited <u>lower rates of any TRAEs</u>, higher rates of serious TRAEs, <u>immune-mediated TRAEs requiring high-dose steroids</u>, and grade 3 or 4 immune-mediated TRAEs, raising the EAG's concerns. Immune-mediated TRAEs leading to death were observed in STRIDE but not in sorafenib. STRIDE also had a higher incidence of grade 3 or 4 hepatic TRAEs.		experienced by patients. The investigators who evaluated and reported these AEs were working for the company unblinded, therefore, the EAG considers them biased. Concerning the company's wording suggestions, the EAG cannot accept that almost 50% of Grade 3/4 treatment-emergent adverse events are low and not of concern.
Page 61 However, Table 20, Appendix I of the clarification responses, lacks results for common non-treatment-related serious adverse events (SAEs) from the HIMALAYA trial.	Page 61 <u>However, Table 20, Appendix I of the clarification responses, lacks results for common non-treatment-related serious adverse events (SAEs) from the HIMALAYA trial.</u>	Table 20 in Appendix I of CQs covers Not treatment-related serious AEs observed, no reasonable possibility the AE is casually related to durvalumab/tremelimumab/sorafenib (primary analysis, SAS) (DCO: 27th August 2021) (>1% frequency). Therefore, the table covers common non-treatment-related SAEs from the HIMALAYA trial. The statement suggesting this is lacking is inaccurate.	The company is not referring to a factual inaccuracy. The EAG disagrees with the company's suggestion to remove this statement as it clearly refers to the company's provided response. The company has only reported the list of SAEs without any distinction between sorafenib, tremelimumab, and durvalumab (durvalumab arm and STRIDE). The reported SAEs in this table concern the EAG, and we cannot refer to the company's caption that these do not have a reasonable possibility of being treatment-related. Simply classifying them without reason as non-treatment-related, while they are life-threatening, is not sufficient. The

			company has not discussed this further, and as part of the FAC comment, the unclear justification for this table remains. The EAG does not accept the company's comment in this regard.
Page 61 Reported AEs in order of frequency include pneumonia, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, sepsis, death, anaemia, abdominal pain, and ascites	Page 61 ~~Reported AEs in order of frequency include pneumonia, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, sepsis, death, anaemia, abdominal pain, and ascites~~	This is factually incorrect. These data were specifically requested by EAG and are non-treatment related significant AEs, not just any AEs. The AEs flagged by the EAG in this statement refer to the non-treatment related AEs listed in Table 20 of the CQ document. It is misleading to refer to them as simply AEs. These were provided at the EAG request.	This comment is not factually incorrect. As discussed previously, these serious adverse effects, although considered irrelevant to the treatment, lack a proper justification for the company's decision to find them irrelevant to the treatment (clarification question A6). The EAG's concerns regarding these SAEs remain. However, for better understanding, the EAG has modified it to:

			
Page 61-62 The company reported serious TRAEs and non-treatment-related AEs after five years (Clarification responses A15, Figure 1), showing an increase in non-treatment-related SAEs. EAG's concerns about STRIDE's safety persist.	Page 61-62 The company reported serious TRAEs and non-treatment-related AEs after five years (Clarification responses A15, Figure 1), showing an increase in non-treatment-related SAEs <u>in both STRIDE and sorafenib arms. EAG's concerns about STRIDE's safety persist.</u>	It is incorrect to highlight an increase in non-treatment related SAEs without highlighting what this is compared to, and the fact that this was observed in both arms of the trial. The company also propose a deletion of the final sentence, as it is factually incorrect to state that there could be safety concerns when relating to non-treatment related SAEs (which are typically related to the underlying disease). The MHRA and EMA did not conclude this in regards to non treatment related AEs when assessing the risk-benefit profile of this medicine.^{11, 12} The HIMALAYA updated analysis II represents the longest follow up period in Phase III studies in advanced or unresectable HCC, providing robust efficacy and safety evidence, with a reduced level of uncertainty, compared to other treatments such as atezolizumab plus bevacizumab.	The EAG disagrees with the company's assertion to delete the last sentence. The EAG has considered opinions from the MHRA, EMA, FDA, clinical experts, and other pieces of evidence to report an independent critique of the company's results. The EAG cannot verify the safety of STRIDE, and this should be evaluated further, considering the company has not provided a good justification for several clarification questions that the EAG has asked merely about the treatment's safety profile and to elucidate the concerns. Additionally, the EAG cannot note the safety comparison of atezolizumab plus bevacizumab compared to the STRIDE because the HIMALAYA trial did not have this comparator. Please find the modified text, including the sorafenib and comparison, below. "The company reported serious TRAEs and non-treatment-related AEs after five years (Clarification

			responses A15, Figure 1), showing an increase in non-treatment-related SAEs in both STRIDE and sorafenib arms. EAG's concerns about STRIDE's safety persist.”

Issue 4 Inaccuracies in long-term immune-related adverse effects reporting

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62 The EAG evaluations indicate that immunotherapy treatments, particularly immune checkpoint inhibitors like nivolumab (Opdivo) and pembrolizumab (Keytruda) (like durvalumab and tremelimumab), can cause irAEs, potentially leading to autoimmune diseases even years after treatment	Page 62 The EAG evaluations indicate that immunotherapy treatments, particularly immune checkpoint inhibitors like nivolumab (Opdivo) and pembrolizumab (Keytruda) (like durvalumab and tremelimumab), can cause irAEs, potentially leading to autoimmune diseases even years after treatment in a very small proportion of patients	It is factually incorrect to conduct naïve comparison of regimens such a nivolumab and pembrolizumab to STRIDE, due to STRIDE's distinct mechanism of action. It cannot be suggested the pattern of imAEs with these regimens is comparable without direct H2H studies, despite being in the immune checkpoint inhibitor family. The differences in disease aetiologies have not been accounted for, further impacting the accuracy of the statement.	The EAG has clearly asked about the possibility of irAE in the long term as clarification question A15. In response, the company has listed the names of tables and figures that they have reported about the safety profile of treatments, which has not directly and clearly answered the EAG's concerns. At the end, very briefly, the company said, “<i>Although imAEs with</i>

		To evaluate the long-term impact of immunotherapy treatments, especially in terms of irAEs that may cause autoimmune diseases, it is necessary to incorporate the perspective of the HCP responsible for treating these patients and prescribing and monitoring these drugs (the oncologist). Providing only the perspective of a hepatologist, whose role is focused on liver cancer function and who does not act as a prescriber of IO treatments or comparators does not accurately support this statement.	<i>STRIDE could occur at any time,”</i> and then discussed that although it is possible, they hope that these won’t happen in the long term. Considering the company’s argument, the EAG has not compared STRIDE to nivolumab and pembrolizumab. These have only been mentioned as examples and referenced accordingly. The EAG has not conducted a head-to-head comparison, as the company claims. As part of the justification for the amendment, the company does not deny the possibility of irAE in the long term. Then, the company claims that there has been a head-to-head comparison, which has not happened, and the company’s claim is not correct. Later, the company indirectly states that it might be possible, but we cannot determine the impact due to various reasons (similar to the A15 clarification question), and it is for the oncologist to decide and determine. The company’s justification is

			contradictory. It appears to the EAG that the company addresses the issue the EAG has raised and then implies that this should not be included or relevant to the EAG to discuss it. The EAG disagrees, and it is a concern for patient safety.
Page 62 The company's response to A15 indicates that irAEs from STRIDE can occur anytime, mainly within the first 3 months, but does not address long-term TRAE and irAE concerns. While most irAEs manifest during or shortly after treatment, some autoimmune complications, such as colitis, hepatitis, pneumonitis, and endocrine disorders, may arise a year or more later Therefore, patients treated with immune checkpoint inhibitors may develop autoimmune conditions even five years post-treatment	Page 62 The company's response to A15 indicates that irAEs from STRIDE can occur anytime, mainly within the first 3 months ~~but does not address long-term TRAE and irAE concerns.~~ While most irAEs manifest during or shortly after treatment, some autoimmune complications, such as colitis, hepatitis, pneumonitis, and endocrine disorders, may arise a year or more later in a very small proportion of patients Therefore, a very small proportion of patients treated with immune checkpoint inhibitors may develop autoimmune conditions even five years post-treatment	This is factually incorrect. The company has addressed long-term TRAE and irAE concerns. In addition to an overview of TRAEs from the 5-year exploratory analysis, the company has also provided detailed analysis of temporal patterns of imAEs with STRIDE from the 3-year analysis, highlighting the majority of imAEs were observed within the first three months after treatment initiation (Clarification question A15). It is therefore misleading to highlight irAEs may arise after several years without clarifying this occurs in a very small number of patients. AstraZeneca, as marketing authorisation holder, are continuing to undertake the required pharmacovigilance activities and interventions detailed part of Routine Risk Minimisation Measures of the RMP of tremelimumab.¹³	In the clarification question, the EAG has asked for the January 23, 2023, and March 1, 2024 data cutoffs safety profile. The company has only reported the January 23, 2023 data cutoff results and refused to report details of irAE results for 5 years or later to address the EAG's concerns. The fact that most irAEs were experienced in the first 3 months does not resolve the EAG's long-term concerns about the possibility that irAEs might occur. Considering their severity and life-threatening nature, the EAG remains

		The time to the presentation of irAEs observed in HIMALAYA is similar to pharmacovigilance data with other ICIs, where the first 2 months can be considered as the 'critical pharmacovigilance window'.¹⁴ Variable onsets have been described for the different toxicities, ranging from early occurrence (first week) to delayed events (up to 26 weeks). The HIMALAYA follow-up not only covers this monitoring period but extends it up to 3 years, significantly reducing the level of uncertainty in terms of safety. The safety data including irAE data provided as part of the submission package is no less detailed than the safety data submitted to NICE in prior appraisals of ICIs. In the TA666 appraisal of atezolizumab plus bevacizumab, a 16-month follow-up was considered sufficient.⁶	concerned about the long-term safety of irAEs. Additionally, the EAG has modified the following text to clarify: "The company's response to A15 indicates that irAEs from STRIDE can occur anytime, mainly within the first 3 months, but does not address long-term TRAE and irAE concerns for the latest data cutoff (5 years). The company has only reported serious AE after 4 years in the CS, appendix F, table 32. While most irAEs manifest during or shortly after treatment, some autoimmune complications, such as colitis, hepatitis, pneumonitis, and endocrine disorders, may arise a year or more later Therefore, patients treated with immune checkpoint inhibitors may develop autoimmune conditions even after five years post-treatment.

.Page 64 Adverse events have been tracked by the company only up to 90 days post-treatment or until subsequent therapy begins, which may not capture all irAEs or those overlapping with new treatments. The company's responses to the EAG's safety concerns were not adequate	Page 64 Adverse events have been tracked by the company only up to 90 days post-treatment or until subsequent therapy begins, which may not capture all irAEs or those overlapping with new treatments. ~~The company's responses to the EAG's safety concerns were not adequate~~	It is inaccurate to state that the company responses with regards to safety concerns are not adequate. The company supplied the EAG with a detailed overview of AEs, TRAEs and imAEs from the HIMALAYA primary analysis (median follow-up 33.18 months for STRIDE) and TRAEs from the 5-year exploratory OS analysis (median follow-up 62.5 months). These follow-ups are substantially longer than the follow-up of the dataset from the IMBrave150 trial assessed in TA666 (16 months maximum follow-up),⁶ and represent the longest follow-up to date in Phase III trials of an IO combination regimen in the advanced/unresectable HCC setting assessed by NICE, providing robust evidence base on safety and effectiveness.	The company believes that their responses and listing of the tables they have reported, or an overview of safety results, would be sufficient. The EAG has asked the company to provide details of safety issues as part of clarification questions A6-8, and A15. In all questions, the company neglected to report some part of safety results and has considered most life-threatening AEs as not treatment-related (A6), with no justification reported or reported an overview instead of details (A15) or not reported long-term safety issues (A8 and A15). The company has not been clear about the long-term safety concerns that the EAG has raised as part of the clarification questions. The company has indicated that irAE can occur at any time (A15). The company has refused to report safety concerns for 5 years regarding STRIDE. Therefore, the EAG doesn't consider this inaccurate,

			and no changes are required.

Issue 5 Durvalumab monotherapy is not relevant to the appraisal scope

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 51 The EAG notes that published meta-analyses and network meta-analyses aimed at comparing first-line treatments for HCC include durvalumab as a first-line option, in EAG's opinion, the company's handling of comparators reflects an over-narrow interpretation of the submission's remit.... Page 52 Both submissions lacked analysis of durvalumab, considered by EAG to be an omission of data.	Page 51 The EAG notes that published meta-analyses and network meta-analyses aimed at comparing first-line treatments for HCC include durvalumab as a first-line option, ~~in EAG's opinion, the company's handling of comparators reflects an over-narrow interpretation of the submission's remit....~~ Page 52 ~~Both submissions lacked analysis of durvalumab, considered by EAG to be an omission of data.~~	The Company believes it is incorrect to state our interpretation of the submission remit is narrow, as the appraisal scope covers STRIDE's marketing authorisation (durvalumab + tremelimumab), and does not include durvalumab monotherapy. Discussions on these data are irrelevant to this appraisal's scope and decision problem.	This is a divergence of opinion rather than factual error. The company's view / opinion on treatment options is shown in CS Figure 2. The figure represents an amalgam of information selected from various sources (Suddle, A. et al. (2024)³ ; NICE TA666 (2020).¹⁰ NICE TA474 (2017).⁹ NICE TA551 (2018).) The EAG notes that Figure 5 in Suddle et al., itemises durvalumab as an option for first line therapy.

Issue 6 The median length of follow-up from March 2024 DCO is 60 months, it is incorrect to refer to 72 months for maximum follow-up

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 52 The company's first submission (dated 13th August 2024) presented a CIC analysis of overall survival using the latest cutoff (March 1, 2024) encompassing 6 years (approximately 72 months) maximum follow-up Page 54, Table 11 18, 24, 36, 48, 72 months	Page 52 The company's first submission (dated 13th August 2024) presented a CIC analysis of overall survival using the latest cutoff (March 1, 2024) encompassing <u>5</u> years (approximately <u>60</u> months) maximum follow-up Page 54, Table 11 18, 24, 36, 48, <u>60</u> months	The EAG has incorrectly referred to follow-up of 72 months in several places of the EAG report, instead of 60 months. As clarified in CQ A23, the latest presented OS data is from the updated analysis II (DCO: 1st March 2024), which was an exploratory analysis of OS at 60 months of median follow-up (5 years). The median follow-up for the STRIDE arm is 62.49, and 59.86 for sorafenib arm. A 6-year OS exploratory analysis has not been conducted, as the 5-year analysis is the most mature data available at the time of submission. The EAG report requires amendment throughout to refer to a 60-months/5 year OS analysis rather than 72 months/6 years.	In the text quoted the EAG has called "approximately 72 months" the maximum follow-up. EAG has not called 72 months the median follow-up. In CS Figure 4 (DCO: 1st March 2024) in STRIDE the last patient censored was at just over 72 months and in Sorafenib arm just less than 72 months. The last event inferred from the KM graph was at approximately 69 months for STRIDE and 60 months for Sorafenib.
Page 57 CS Document B, Figure 4 provided the OS Kaplan-Meier results to the maximum follow-up of 72 months; median survival was 16.3 months and 13.77 months respectively for STRIDE and sorafenib.	Page 57 CS Document B, Figure 4 provided the OS Kaplan-Meier results to the maximum follow-up of <u>60</u> months; median survival was 16.<u>43</u> months and 13.77 months respectively for STRIDE and sorafenib.	There is a typo in the EAG report relating to the median survival with STRIDE.	The EAG has amended as suggested by the company.

Page 58 The EAG requested the company to provide 6-year survival values visible in Figure 4 but not reported in Table 35 (EAG clarification document A23). The company confirmed the existence of 6-year data but declined to provide a 6-year OS exploratory analysis as it was not conducted. The EAG notes that, despite this response, the OS data at six years has been incorporated into the economic model.	Page 58 ~~The EAG requested the company to provide 6-year survival values visible in Figure 4 but not reported in Table 35 (EAG clarification document A23). The company confirmed the existence of 6-year data but declined to provide a 6-year OS exploratory analysis as it was not conducted. The EAG notes that, despite this response, the OS data at six years has been incorporated into the economic model.~~	As stated in CQ A21, the Company confirms the latest presented overall survival data are from the updated analysis II (DCO: 1st March 2024), which was an exploratory analysis of OS at 60 months of median follow-up (5 years). A 6-year median OS follow-up exploratory analysis has not yet been conducted. The median follow-up for the STRIDE arm is 62.49, and 59.86 for sorafenib arm in the latest analysis.	The EAG has deleted as suggested by the company.

Issue 7 Data cut-off confusion

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65 The reference provided for HIMALAYA was Abou-Alfa GK, Lau G, Kudo M, et al. NEJM Evid 2022;1(8) DOI: 10.1056/EVIDoa2100070 (this is reference number 4 in both Doc B and Appendix bibliographies); this provides a HR of 0.78, 95%CI: 0.78 (0.65, 0.93).	Page 65 ~~The reference provided for HIMALAYA was Abou-Alfa GK, Lau G, Kudo M, et al. NEJM Evid 2022;1(8) DOI: 10.1056/EVIDoa2100070 (this is reference number 4 in both Doc B and Appendix bibliographies); this provides a HR of 0.78, 95%CI: 0.78 (0.65, 0.93).~~	The company would like to clarify, to avoid the possibility of inaccurate interpretation, that while the reference listed in Table 20 of the CS links to the Abou-Alfa study¹⁰, it is merely a reference to the HIMALAYA trial characteristics, rather than a specific data cut-off. The HR of 0.78 (0.65, 0.93) does indeed refer to the Abou-Alfa study (primary analysis, DCO: 27th August 2021), however the write-up does not suggest this is the cut-off used in the NMA. Table 22 of the CS appendices clarifies the HR used in the NMA [REDACTED]	The EAG Table 16 lists data in the CS and in other publications about STRIDE. These were listed to try to identify what input data was used for the company NMA, since this important information was not found clearly presented in the CS document B. As far as the EAG can

		which based on the follow-up time outlined is sourced from the updated analysis II (DCO 1st March 2024).	ascertain no factual errors have been identified. The EAG acknowledges that the company's NMA inputs are presented in CS Appendix Table 22. The EAG text pg 65 has been changed accordingly.
Page 65 From information provided in the submission the EAG is unclear which HR and associated 95%CIs were used for the company's NMA and what justified this choice.	Page 65 ~~From information provided in the submission the EAG is unclear which HR and associated 95%CIs were used for the company's NMA and what justified this choice.~~	As evidenced in Table 22 of the CS appendices and the text below from page 63 of the CS, the company used [REDACTED] for the NMA, sourced from the updated analysis II (DCO 1st March 2024) – the longest OS follow-up available from HIMALAYA <i>For OS, using the 5-year OS data-cut from HIMALAYA, the NMA results found that STRIDE and atezolizumab + bevacizumab improved OS compared with sorafenib, with consistent point estimates to those seen in trial results</i>	No factual error. The NMA input was unclear for the EAG.
Page 65 The publication of Sangro et al., 2024 ¹⁵ appears to have the same cutoff date and number of events as provided in Appendix M Table 56, 23 January 2023 entry but they have differing point estimates of HR, although the 95%CIs (to 2 decimals) are identical. Appendix M Table 56 for the 23 January 2023 states 'Hazard ratio stratified by factors	Page 65 The publication of Sangro et al., 2024 ¹⁵ appears to have the same cutoff date and number of events as provided in Appendix M Table 56, 23 January 2023 entry but they have differing point estimates of HR, although the 95%CIs (to 2 decimals) are identical. The company clarifies the HR in Table 56 of the CS appendices should read "0.78 (0.67-0.92)", the same HR as the Sangro	The company have addressed a factual inaccuracy. The HR from the Sangro publication ¹⁵ relates to the exploratory updated analysis I (DCO2 23 Jan 2023), and has not been utilised in the model.	We are unable to identify where the factual error has been made by the EAG.

based upon the categories used in the randomisation system.’ The Sangro paper states ‘OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology of liver disease (hepatitis B or C virus or other/nonviral), ECOG performance status (0 or 1), and macrovascular invasion (yes or no).’ This may explain the different HR estimates.	publication.¹⁵ Appendix M Table 56 for the 23 January 2023 states ‘Hazard ratio stratified by factors based upon the categories used in the randomisation system.’ The Sangro paper states ‘OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology of liver disease (hepatitis B or C virus or other/nonviral), ECOG performance status (0 or 1), and macrovascular invasion (yes or no).’ This may explain the different HR estimates.		
Page 66 27 August 2021**** STRIDE events/ Patients: 280 / 393	Page 66 Delete table row, as it relates to durvalumab monotherapy (280 events), not STRIDE (262 events): ~~27 August 2021****~~ ~~STRIDE events/ Patients: 280 / 393~~ Delete reference ****, as it is the same publications as reference *	The EAG has incorrectly extracted the number of STRIDE events/patients from the primary analysis (DCO 27 Aug 2021) as published in the Abou Alfa pivotal paper.¹⁰ Following this correction, only the top row in Table 16 of the EAG report is required.	The EAG has corrected this row in Table 16 as suggested by the company.
Page 90 Survival is superior for STRIDE versus sorafenib and an adjusted HR of [REDACTED] versus sorafenib is reported. This HR is	Page 90 Survival is superior for STRIDE versus sorafenib and an adjusted HR of [REDACTED] versus sorafenib is reported. ~~This HR is less than the HR of 0.78 reported at a~~	As outlined in the title and reference of Figure 8, the HR refers to the HR obtained from the 5- year OS exploratory analysis - updated analysis II (DCO 1st March 2024), as presented by Rimassa at ESMO GI 2024.¹⁶ In contrast, Sangro et al 2024 refers to the 4-year OS exploratory analysis -	We have not identified any factual error.

less than the HR of 0.78 reported at a maximum follow-up of five years by Sangro et al., 2024. ¹⁵	~~maximum follow-up of five years by Sangro et al., 2024.~~ ¹⁵	updated analysis I (DCO: 23rd January 2023) ¹⁵	
Pg 99 “In CS Document B, the EAG could not find PFS results for a later DCO.” Pg 100 “It was unclear to the EAG whether data from the DCO in Figure 6 or from a later DCO was used.” Pg 106 “The DCO used appears to be later than that shown in CS Document B Figure 6 since the KM plot shows almost complete progression.” Pg 107 “(DCO used unclear but probably not Aug 27, 2021). “	“The DCO used for PFS was 27 August 2021”	The Company details all data cuts used for the survival analysis in Company Submission Document B Section B.3.3.2. For clarity, the text contained at the beginning of this section has been copied here: <i>As discussed in Section B.2.3.3, there are three key DCOs from the HIMALAYA trial:</i> <i>Primary analysis: The primary analysis was performed once 555 OS events had occurred in the STRIDE and sorafenib arms combined (representing 71% maturity), 46 months after the first patient was randomised (DCO: 27th August 2021)</i> <i>Updated analysis I: The updated analysis evaluated the OS and safety of STRIDE vs. sorafenib with 4 years of follow-up (DCO: 23rd January 2023)</i> <i>Updated analysis II: An additional five-year OS analysis has been conducted for STRIDE vs. sorafenib, representing the longest follow up period to date in Phase III studies in advanced or unresectable HCC (DCO: 1st March 2024).</i> <i>Within the model, efficacy data for STRIDE and sorafenib were informed by the most</i>	Pg 99 EAG refers to Document B (i.e., not to information in the Appendix). Text pgs 100 and 106 refer to difficulty encountered by the EAG and therefore do not constitute factual errors.

		<i>mature DCO available for the outcome in question: OS was informed by the updated analysis II DCO, while PFS and TTD were informed by the primary analysis.</i>	

Issue 8 Inaccurate conclusions about the Company's NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Summary comment related to the EAGs conclusions on the Company's NMA: We have identified a significant number of factual inaccuracies regarding the EAG's interpretation of the Company's NMA, including: - Comparing the results of the Company NMA to other NMAs using different trial data cuts, study populations and endpoints, and concluding, incorrectly, that discrepancies in data exist in the NMA caused by the size of the network - Concluding the Company used less relevant evidence than other NMAs including the EAG's preferred NMA. The Company NMA included the same studies as the EAG's preferred NMA, and with more mature data from the HIMALAYA study - Determining the inclusion of other comparators would change the results of the existing NMA. This is inaccurate and additional comparators would not inform the indirect evidence results for the current comparators. This conclusion is misaligned with NMA methodology The Company NMA is aligned with previous NMAs.^{6, 17} The justification behind performing an NMA rather than using an existing study was two-fold: 1) to ensure that the updated 5-year HIMALAYA OS data was included in the network; 2) to ensure that the appropriate endpoints for the economic model were included (e.g., PFS per INV not per BICR).			There is considerable disagreement about the company's NMA; which does not necessarily imply factual error.
Pg 67 "The eligibility criteria for the NMA lacks detail. There appear to be no exclusion criteria other than that implied by: "Not including any combinations with other therapies". Little justification for this restriction is offered. There is also no clear guidance on whether abstracts or conference proceedings of Phase III RCTs were or were not included."	~~"The eligibility criteria for the NMA lacks detail. There appear to be no exclusion criteria other than that implied by: "Not including any combinations with other therapies". Little justification for this restriction is offered. There is also no clear guidance on whether abstracts or conference proceedings of Phase III RCTs were or were not included."~~ We recommend that the EAG removes this sentence or clarifies the exact issues with restricting the network to the treatments of interest to the decision problem, consistent with the final scope of the appraisal.	The eligibility criteria were detailed in Company Submission Document B Section B.2.9.2. The NMA was based on the systematic review of clinical studies, which included a search of abstracts and conference proceedings. If these were relevant to the network and the decision problem, these were used. It is common for NMAs to be restricted to treatments of interest to the decision problem to align with	This text refers to the opinion of the EAG, as such does not constitute a factual error but a divergence of opinion.

		the NICE final scope. For example, TA666 restricted the final evidence network to three trials (see TA666 Company Submission Figure 7). ⁶	
Pg 68 "The company did not perform a literature search specifically designed to identify published studies to be assessed for inclusion in their NMA"	~~"The company did not perform a literature search specifically designed to identify published studies to be assessed for inclusion in their NMA"~~	The Company conducted a systematic literature review in August 2020 (original SLR), then first updated in October 2021 (first SLR update) and once again in April 2024 (second SLR update), to identify and synthesise relevant clinical evidence on the efficacy and safety of STRIDE and other first-line treatments in patients with unresectable, advanced HCC, as outlined in CS Appendix D Identification, selection, and synthesis of clinical evidence. These SLRs informed the NMA analysis outlined later in the same appendix. The references considered for inclusion within the NMA, grouped by study, are summarised in Table 15 of the CQ document, alongside reasons for exclusion from the NMA if relevant. Studies were assessed for eligibility for the NMA as per Table 17, Section B.2.9.9 of the CS. It is factually incorrect to state a literature search to inform the NMA has not been conducted.	EAG have re-worded this sentence for clarity to: "The literature searches for the company's original SLR, which (along with the SLR updates) informed the NMA, were not specifically designed to identify studies for the NMA (they are missing terms for the intervention and important synonyms for hepatocellular carcinoma."

Pg 68 “The company noted that there were no statistical differences in pairwise results between comparators. This may be attributable to the limited data feeding into the NMA. The STA examining atezolizumab + bevacizumab versus sorafenib reported a statistically significant HR of 0.58 (95%CI: 0.42, 0.79) which seems considerably different to the inference of insignificance and HR of ■ from the company NMA. The wide CrIs highlight the considerable imprecision associated with the NMA results.”	“The company noted that there were no statistical differences in pairwise results between comparators. ~~This may be attributable to the limited data feeding into the NMA. The STA examining atezolizumab + bevacizumab versus sorafenib reported a statistically significant HR of 0.58 (95%CI: 0.42, 0.79) which seems considerably different to the inference of insignificance and HR of 0.66 from the company NMA. The wide CrIs highlight the considerable imprecision associated with the NMA results.~~” To compare the Company NMA to published evidence, specifically the comparison of atezolizumab plus bevacizumab to sorafenib, the following was conducted: • Compared to the updated efficacy results from IMbrave150 (Cheng 2022: 0.66, [0.52, 0.85])¹⁸ • Compared the width of the credible interval from the TA666 NMA, which also reported a wider and non-statistically significant CrI (0.58 [0.35, 0.99]). However, it should be noted in this comparison that this NMA was based on the first interim analysis for IMbrave150 (Cheng 2019: 0.58 [0.42, 0.79])¹⁹ • Compared to Vogel 2023 (0.66 [0.41, 1.04])¹⁷ From this, the Company NMA is consistent with expectation of treatment effect for	Factually incorrect conclusions are drawn from an assessment of the Company NMA credible intervals (CrI) which the EAG further justified, incorrectly, with a comparison to the HR and confidence interval from the IMBrave150 trial, which also used completely different data cuts. The EAG is quoting the Company NMA random effects model, which accounts for additional uncertainty due to between-study heterogeneity in the network. This is what leads the NMA estimates to have broader CrI than the confidence intervals reported in head-to-head studies. As expected, in the fixed effects models presented in the CS Appendix, the CrI are much narrower (see Company Submission Appendix Table 26). A comparison of the NMA conducted for TA666 with the NMA conducted in this submission shows that CrIs from the TA666 NMA are much wider than the confidence interval from IMBrave150 (Table 18 in TA666 submission - atezolizumab + bevacizumab vs. sorafenib: 0.58 [0.35, 0.99]).⁶ It is factually inaccurate to say that there were no statistical differences	The context of this text includes CS Doc B Tables 15 and 16 that summarise the results from the company's NMA that were employed in the company's cost effectiveness model. EAG cannot identify a factual error. There is clearly a divergence of opinion about whether the comparison is relevant.

	atezolizumab plus bevacizumab for OS in HCC. The reported 0.58 (95%CI: 0.42, 0.79) result is not the most mature HR from the IMBrave150 trial for this endpoint (i.e., the data were reported from the first interim cut from the trial).	in pairwise results between comparators because of “the limited data feeding into the NMA”. Please see response to Issue 9 for more detail.	
Pg 68 - 69 “Table 18 implies that the published data in Abou-Alfa et al., 2022 was used for HIMALAYA. This paper, however, reports an adjusted HR of 0.78 (95%CI: 0.65, 0.93) for overall survival of STRIDE versus sorafenib, whereas the HR estimate used in the NMA appears to be [REDACTED], derived from the latest cut-off analysis presented in CS Document B.” And “The company submission did not tabulate the HR inputs it used in its NMA; the EAG is unclear about what data (HRs) were used. though the HIMALAYA study Abou-Alfa 2022 (maximum follow-up 40 months) was specified as the relevant study (CS Appendix D Table 2), the HR input for OS appears to have come from a later cutoff analysis of HIMALAYA. Because the company’s NMA diagram specifies selected interventions (i.e. only sorafenib and STRIDE) from HIMALAYA (CS Document B Figure 4) the date of cut-off used for data extraction remains unclear.”	~~“Details of the company’s NMA methodology were presented in Appendix D Tables 20, and 24 through to 27. Table 18 implies that the published data in Abou-Alfa et al., 2022 was used for HIMALAYA. This paper, however, reports an adjusted HR of 0.78 (95%CI: 0.65, 0.93) for overall survival of STRIDE versus sorafenib, whereas the HR estimate used in the NMA appears to be [REDACTED], derived from the latest cut-off analysis presented in CS Document B.”~~ ~~“The company submission did not tabulate the HR inputs it used in its NMA; the EAG is unclear about what data (HRs) were used. though the HIMALAYA study Abou-Alfa 2022 (maximum follow-up 40 months) was specified as the relevant study (CS Appendix D Table 2), the HR input for OS appears to have come from a later cutoff analysis of HIMALAYA. Because the company’s NMA diagram specifies selected interventions (i.e. only sorafenib and STRIDE) from HIMALAYA (CS Document B Figure 4) the date of cut-off used for data extraction remains unclear.”~~	EAG’s Table 18 is based on Table 20 in the Company Appendix, which details the study characteristics of each study included in the NMA. As Abou-Alfa et al., 2022¹⁰ is the primary publication for HIMALAYA, it contains the most detail on the study characteristics and was hence referenced here. Table 22 in the Company Submission Appendix states which data informed the Company NMA. The Company used the 5-year OS data in the NMA ([REDACTED]).¹⁶ A reference to Table 22 from the Company Submission Appendix has been omitted from the EAG report.	The EAG cannot identify a factual error. The dispersion of information about the NMA across CS Document B and different sections of the Appendix led to difficulties in identifying the input for the company’s NMA. A simple tabulation of inputs was looked for but could not be found. The EAG acknowledges that the company did in fact tabulate NMA inputs in CS Appendix Table 22 and have modified text accordingly.

(CS Appendix D Table 2), the HR input for OS appears to have come from a later cutoff analysis of HIMALAYA. Because the company's NMA diagram specifies selected interventions (i.e. only sorafenib and STRIDE) from HIMALAYA (CS Document B Figure 4) the date of cut-off used for data extraction remains unclear." And (pg 63) "CS Appendix D Table 20 provides references to studies included in the company's NMA."	"Details of the company's NMA methodology were presented in the Appendix D. Appendix D Table 22 provides the details of the data used to inform the NMA". "CS Appendix D Table 20 provides references to studies included in the company's NMA, and Table 22 provides the details of the data used to inform the NMA."		
Pg 69 "For example, for the HIMALAYA trial, data from the durvalumab arm were excluded from the NMA. The company's exclusion of durvalumab appears to be based on the opinion that it is not used in UK clinical practice."	"For example, for the HIMALAYA trial, data from the durvalumab arm were excluded from the NMA. The company's exclusion of durvalumab is ~~appears to be~~ as it is not licenced by the MHRA for the treatment of patients in this setting and therefore is not used in UK clinical practice."	The Company's exclusion of durvalumab is not solely based on clinical opinion that is not used in UK clinical practice, but also that it is not licenced by the MHRA. The NICE final scope for the appraisal does not include durvalumab monotherapy as a result. It is therefore not required to include in the NMA.	The EAG has modified the text, taking account of the suggestion from the company, to: For example, for the HIMALAYA trial, data from the durvalumab arm were excluded from the NMA. The company's exclusion of durvalumab was based on the fact that it is unlicensed in UK and on clinical advice that because of lack of license it

			was unused in UK clinical practice.
Pg 69 “While inclusion of the third arm of HIMALAYA (durvalumab) would undoubtedly complicate the NMA analyses, its inclusion would have likely influenced both the NMA HR estimates and their associated 95% credible intervals.”	~~“While inclusion of the third arm of HIMALAYA (durvalumab) would undoubtedly complicate the NMA analyses, its inclusion would have likely influenced both the NMA HR estimates and their associated 95% credible intervals.”~~	This statement is factually incorrect and inconsistent with NMA methodology. The durvalumab connection can only be made through the HIMALAYA trial (i.e., a connection through tremelimumab plus durvalumab and sorafenib). Its inclusion would not influence the results in a fixed effects network, since the information is coming from one trial that is already included in the network. There cannot be inconsistency between results in a 3-arm trial.²⁰ It would also not influence the HR in the random effects network, although there may be a minor impact on the credible interval. The results for relevant comparators included in the final scope would not change with the inclusion of the durvalumab arm from HIMALAYA into the network.	As suggested, the EAG has deleted.
Pg 79 “Since the PH assumption was violated in some cases, the approach taken to fit curves to patient-level data is a good one. However, the choice to avoid more complex models (such as	~~“Since the PH assumption was violated for in REFLECT and HIMLAYA in some cases. For REFLECT, the exploration of time-varying hazards showed that the application of a constant HR for lenvatinib in the economic model may overestimate the long-term effect of~~	The EAG omitted consideration of the proportional hazards assumption assessment and time-varying analysis performed by the Company, which showed that the application of a constant HR for	We have amended the text in our report to ‘The proportional hazard assumption was violated for REFLECT and HIMALAYA.

fractional polynomial or piecewise models) may oversimplify the time-dependent nature of survival benefits, especially considering the shorter follow-up period in IMBrave150” And Pg 95 “The company’s NMA uses HR inputs from four included studies, irrespective of the proportional hazards violation .”	treatment, and therefore yields conservative cost-effectiveness estimates when compared with STRIDE. For HIMALAYA, the approach taken to fit curves to patient-level data is a good one. There is no suggestion from the published IMBrave150 data that the proportional hazards assumption is violated, but this may be hard to assess accurately given the shorter follow-up period of this trial. However, the choice to avoid more complex models (such as fractional polynomial or piecewise models) may oversimplify the time-dependent nature of survival benefits, especially considering the shorter follow-up period in IMBrave150” And Pg 95 “The company’s NMA uses HR inputs from four included studies, irrespective of the proportional hazards violation .”	lenvatinib in the economic model is conservative. The Company found the PH violation for STRIDE vs. sorafenib (from HIMALAYA) for PFS and OS, and for lenvatinib vs sorafenib (from REFLECT) for PFS and OS. There was no evidence of a PH violation for atezolizumab plus bevacizumab vs. sorafenib (from IMBrave150). As there was evidence of non-proportional hazards for REFLECT, the Company presented an analysis in which a time-varying treatment effect for the efficacy of lenvatinib versus sorafenib was explored (Appendix N). This showed that the application of a constant HR for lenvatinib in the economic model may overestimate the long-term effect of treatment, and therefore yields conservative cost-effectiveness estimates when compared with STRIDE. As PH violation was not found for atezolizumab plus bevacizumab given the published trial evidence, and more complex models were not warranted.	For REFLECT, the exploration of time-varying hazards as undertaken by the company showed that the application of a constant HR for lenvatinib in the economic model may overestimate the long-term effect of treatment, and therefore yields conservative cost-effectiveness estimates when compared to STRIDE. The company found the proportional hazard violation for STRIDE versus sorafenib (from HIMALAYA) for PFS and OS, and for lenvatinib vs sorafenib (from REFLECT) for PFS and OS. There was no evidence of a proportional hazard violation for atezolizumab plus bevacizumab versus sorafenib (from IMBrave150). As there was evidence of non-proportional hazards for REFLECT, the company presented an analysis in which a time-varying treatment effect for the efficacy of lenvatinib versus sorafenib was explored (Appendix N). This showed that the application of a constant HR for lenvatinib in the economic model may

			overestimate the long-term effect of treatment, and therefore yields conservative cost-effectiveness estimates when compared with STRIDE.' Also, we made changes to, 'The company's NMA uses HR inputs from three included studies (four interventions), irrespective of the proportional hazards violation.'

Issue 9 Inappropriate comparison to other NMAs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 70 "Several recently published NMAs include much more data than the company's NMA. Consequently, most of these HR estimates have a narrower 95%CrI estimate. All except Celsa et al. and Leigh et al. reported HRs with CrIs. The EAG suggests that the NMA should include all the available data from the included studies	~~"Several recently published NMAs include much more data than the company's NMA. Consequently, most of these HR estimates have a narrower 95%CrI estimate. 64-75 All except Celsa et al. and Leigh et al. reported HRs with CrIs.~~ The EAG suggests that the NMA should include all the available data from the included studies and that the results relevant to the economic model and decision problem should then be selected for input to the economic model. The NMA appears to ignore potentially relevant evidence and may have missed the	It is factually inaccurate to state recently published NMAs include more relevant data than the Company's NMA, as the comparators that additional data are available for are outside the scope of this appraisal and not included in the final scope. None of the additional studies included in the published NMAs contained any additional data compared to the Company's NMA for the treatments relevant to the decision problem. The Company identified all	EAG reiterate why they considered alternative NMAs to that conducted by the company: A] Because the company ignored the existence of published NMAs; thereby neglecting to place their NMA in the context of the current literature. B] Because the company NMA HR for the PFS

and that the results relevant to the economic model and decision problem should then be selected for input to the economic model. The NMA appears to ignore potentially relevant evidence and may have missed the purpose of the NMA, namely, to synthesise all evidence bearing on the performance of first-line interventions in studies for the defined population.”	~~purpose of the NMA, namely, to synthesise all evidence bearing on the performance of first-line interventions in studies for the defined population.”~~	relevant evidence for the treatments contained in the decision problem through a systematic literature review. This is a common approach for ITCs used to inform technology appraisals. For example, TA666 restricted their network to three studies (see TA666 Company Submission, Figure 7).⁶ The assertion that the Company has ‘ignored potentially relevant evidence’ is factually inaccurate, and the Company’s NMA contains the equivalent studies as the three NMAs the EAG has focused on. There are some key differences for IMBrave150 with respect to data cuts and subgroups across these published NMAs; the Company NMA has utilised the most mature available evidence across trials relevant to the decision problem. Expanding the network to include the studies which Vogel 2023 included would not change the point estimates because none of the additional evidence contained in the Vogel NMA informs the primary comparisons of interest for the decision problem either directly or indirectly, e.g., via a new loop or by improving connectivity between the relevant nodes in the network. Additionally, the extended network does not contain any links with two or more studies, and	comparison of atezolizumab + bevacizumab versus sorafenib of [REDACTED] was an outlier relative to all other NMAs in the public domain that also employed similar inputs to those used by the company. The company NMA used investigator assessed PFS from IMbrave150, while other NMAs used blinded independent assessment of PFS from IM brave. C] Because the [REDACTED] HR value mentioned above will have an appreciable influence on the costs incurred by atezolizumab + bevacizumab treatment since in the company’s economic model PFS is used as a proxy for TTD. D] Because the [REDACTED] HR value from the company NMA mentioned above leads to a HR of 0.5 for PFS of atezolizumab + bevacizumab versus STRIDE, that suggests that under the assumption of proportional hazards PFS is prolonged two-fold for atezolizumab +

		therefore does not provide any additional evidence to inform the between-study heterogeneity parameter in the random effects NMA.	bevacizumab relative to STRIDE which seems clinically implausible. EAG note that most published NMAs, like that developed by the company, do not adjust for violations of the proportional hazard assumption. The EAG have not claimed that published NMAs are “more relevant”. The stated EAG opinion regarding published NMAs is that the results are relevant to the development of an economic model. The EAG have added the following text to acknowledge that TA666 NMA submitted by Roche had similar properties to that submitted by the company. The EAG notes that the EAG for TA666 remarked “<i>It is not unreasonable to conduct an NMA of HRs for the purpose of answering the question whether there is evidence of an average treatment effect ignoring any treatment-by-time interaction over the duration of the observed studies. However,</i>

			<i>using HRs from NMAs in the context of an economic evaluation is inappropriate in order to estimate population mean benefit.”</i> During the lifetime horizon of the company’s economic model for varying periods many patients are receiving a variety of further treatments including some of those considered in published NMAs as first-line treatment.
Pg 70/71 Assessment of previously conducted NMAs provided in Table 20 And All text on pg 76-77 in the comparison of the Company NMA to the Wang 2024 NMA	EAG to update the assessment and commentary around Wang (2024)²¹ in light of a missing study (REFLECT). EAG to also reconsider the appropriateness of the comparison on pg 76-77.	The Company recommend the EAG reconsider some of their commentary around Wang 2024,²¹ particularly given their criticisms of the Company’s NMA: Wang 2024²¹ reports an OS HR for ‘immunotherapy + tyrosine kinase inhibitors’, including LEAP-002. LEAP-002 compares pembrolizumab plus lenvatinib to lenvatinib plus placebo. Wang 2024 excludes the REFLECT trial, which could be used to connect pembrolizumab plus lenvatinib to the network (through lenvatinib vs. sorafenib). Instead, the authors assume equivalent	The EAG have modified text referring to the Wang et al. NMA, which now reads: ‘It should be noted that Wang et al., performed an NMA comparing classes of first line treatments for HCC and that (a) the REFLECT study was not included; (b) data from HIMALAYA arm with durvalumab alone was not included.’

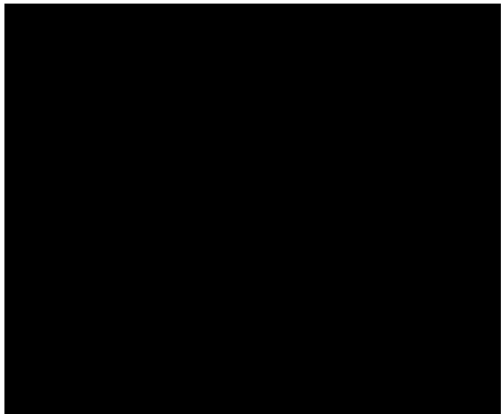
		between sorafenib and lenvatinib. The Company's NMA does not make this assumption, and when this was assumed in the CEM, the EAG favour an NMA that includes RELFECT The Company notes that there is an inconsistency between the critique of the Company for excluding the durvalumab monotherapy arm from HIMALAYA in the Company NMA, to remain consistent with the final scope, whilst not reporting that Wang 2024 also excludes durvalumab monotherapy from their analyses.	
All text on pg 74 – 76 in the comparison of the Company NMA to the Vogel 2023 NMA	The EAG omit clarification of the differences between the different endpoint definitions, subgroups and data-cuts used in Vogel 2023 vs. the Company NMA, which explain the differences in the results between the studies, particularly as the EAG inaccurately conclude that: “company HR (■■■) clearly appears to be an outlier, the EAG believe that this introduces a bias that may have impacted the economic model.” The current conclusions in this section inaccurately concludes there are bias in the Company NMA results, when the results are	There are three key factual accuracies omitted when comparing the Company NMA results to the Vogel NMA¹⁷ results: Endpoint definitions: Vogel 2023 uses PFS per BICR (reported to be 0.59 [0.47, 0.76] from Finn⁸ for the ITT population and 0.62 [0.35, 1.09] from Breder²² for the VP4 population). The Company NMA uses PFS per investigator, reported to be ■■■ (0.36-0.57) in Finn 2020	The EAG have modified the EAG report text to acknowledge the company's tabulation of NMA inputs (CS Appendix Table 22). The NMA PFS input ■■■ for IMbrave was taken from the supplementary appendix of Finn et al., An updated analysis of PFS by Cheng et al., with longer follow-up than Finn and more mature

	not expected to align between these sources given the differences mentioned. The Company request the report is updated to include the differences between the Company NMA and the Vogel NMA, including clarity regarding the drivers of these differences (due to differences in subgroups, data-cuts and endpoint definitions)	supplementary appendix.⁸ This is clearly outlined in the Company submission appendix Table 22. PFS per BICR could not be used in the Company NMA as this was not measured in the HIMALAYA trial. Please note that the Company NMA PFS result for atezolizumab plus bevacizumab is much more aligned to the Finn 2020 PFS per investigator result compared to the 0.66 from Vogel. 2. Subgroups: Vogel uses a subgroup from IMbrave150 where VP4 patients are excluded. Vogel reports the ITT results in the Supplementary material, but the EAG appear to quote the subgroup base case results in Table 21 in the EAG report. The Company NMA uses the ITT IMBrave150 data. 3. Data cuts: The atezolizumab plus bevacizumab results are based on the interim data from IMBrave50 trial, rather than the updated efficacy results in Cheng 2022. The Company NMA uses the most up-to-date results for OS	data reported a Stratified HR 0.65 (95%CI: 0.53, 0.81). In the opinion of the EAG this 0.65 value from mature data is more appropriate than the investigator assessed [REDACTED] input. It also aligns with the Vogel NMA output of 0.66 (95%CrI: 0.27, 1.59).

		(Cheng 2022) but uses the Finn 2020 results for PFS as Cheng 2022 does not provide updated results of PFS per investigator.	

Issue 10 Misunderstanding of CEM structure and TTD assumptions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 84-85 "...the model structure does not account for important subgroups within the "progression-free" and "progressed disease" health states. Specifically, there are two sub-states for each of these: "on treatment" and "off treatment." "On treatment" refers to patients who are still receiving the primary treatment (e.g., STRIDE), while "off treatment" refers to those who have discontinued primary treatment and are undergoing subsequent treatments. The costs associated with patients on primary treatment and those on subsequent treatments differ substantially. The EAG argues that collapsing these subgroups into single health states oversimplifies the illustrative model	"...the model structure does not account for important subgroups within the "progression-free" and "progressed disease" health states. Specifically, there are two sub-states for each of these: "on treatment" and "off treatment." "On treatment" refers to patients who are still receiving the primary treatment (e.g., STRIDE), while "off treatment" refers to those who have discontinued primary treatment <u>and are undergoing subsequent treatments</u>. The costs associated with patients on primary treatment and those on subsequent treatments differ substantially. The EAG argues that collapsing these subgroups into single health states oversimplifies the illustrative	The EAG seems to have misunderstood the model structure. Patients in progression-free but who have discontinued first-line treatment do not receive subsequent treatments. Subsequent treatments are only received once a patient moves into the progressed disease state. This is consistent across treatment arms in the model. We are unsure what model structure the EAG is proposing specifically but subsequent treatments are not received in the progression-free health state in the current structure used by the Company. The model	The company's justification for the proposed amendment does not align with the evidence derived from its submitted model. The EAG maintains that the critiques outlined in the original report (referenced on pages 84-85, 115, and 124) are valid, as follows: 1. PFS and TTD in STRIDE treatment are not equivalent: In the company's model for the STRIDE arm, PFS is not equivalent to TTD (see figure 1). A considerable proportion of patients receiving STRIDE discontinue the primary treatment while still classified within the progression-free health state.

structure, especially when a considerable proportion of patients in the progression-free state transition to subsequent treatments.” And “... the company assumed that progression-free survival (PFS) serves as a proxy for time-to-treatment discontinuation (TTD) in treatments of atezolizumab + bevacizumab and lenvatinib. This implies that all patients in the progression-free state remain on primary treatment, while all patients in the progressed disease state receive subsequent therapies. The EAG contends that this approach introduces inconsistencies across treatments, which could lead to bias and ultimately weaken the robustness of the model.”	model structure, ~~especially when a considerable proportion of patients in the progression-free state transition to subsequent treatments.~~” “... the company assumed that progression-free survival (PFS) serves as a proxy for time-to-treatment discontinuation (TTD) in treatments of atezolizumab + bevacizumab and lenvatinib. This implies that all patients in the progression-free state remain on primary treatment, while all patients in the progressed disease state receive subsequent therapies, ~~which is consistent with the approach used in the STRIDE and sorafenib arm. The EAG contends that this approach introduces inconsistencies across treatments, which could lead to bias and ultimately weaken the robustness of the model.~~”	structure used by the Company is aligned with all other key technology appraisals in this indication.^{6, 23}	 Figure 1: PFS and TTD in STRIDE treatment 2. Drug costs for STRIDE treatment are based on TTD: The company calculated STRIDE treatment costs using TTD. In the model, the drug costs for durvalumab are assigned not only to the progression-free (PF) health state but also to the progressed disease (PD) state. Specifically, there are costs related to durvalumab in the "Progressed (on treatment)" health state, as shown in worksheet 'Engine (1)' (cells BY41:BY2128). This contradicts the company's justification that mentioned to the treat-to-progression protocol for these regimens. 3. Subsequent treatment costs for STRIDE are also based on TTD: The company claims that subsequent treatments are initiated only in
Pg 115 A. “lack of evidence does not seem a sound justification for the assumption made” And pg 124 “The assumption of equivalence for PFS and TTD is difficult to justify	Pg 115 ~~“lack of evidence does not seem a sound justification for the assumption made”~~ And pg 124	Given the treat-to-progression protocol of these regimens, and the lack of data, this is a reasonable assumption which is consistent with other NICE technology appraisals in this indication (e.g., TA666).⁶	

and limited available evidence suggests the assumption is ill-founded.”	~~“The assumption of equivalence for PFS and TTD is difficult to justify and limited available evidence suggests the assumption is ill-founded.”~~		the progressed disease state. However, in the model, the subsequent treatment costs for STRIDE are calculated using TTD values and incorporated into the progressed disease health state. This approach inherently allocates a portion of these costs to the progression-free health state. Specifically, in the post-clarification model (worksheet 'Engine (1)'), cells DX41:DX2128 for STRIDE subsequent treatment costs link back to TTD calculations (via cells AA41:AA2128). If the company had based the calculation of subsequent treatment costs on PFS, its amendments and justification would have been valid. 4. Different assumptions for TTD and PFS across treatments: For atezolizumab + bevacizumab and lenvatinib, the company assumes that PFS and TTD are equivalent, consistent with their justification that subsequent treatments are initiated only in the progressed disease state. However, for STRIDE and sorafenib, the company uses separate curves for PFS and TTD, introducing inconsistencies across treatments. EAG’s position: The EAG finds the company’s assumptions problematic and insufficiently supported by

			evidence. The inconsistency in applying PFS and TTD equivalence affects cost estimations, particularly for atezolizumab + bevacizumab, which shows increased costs due to extended use of primary treatment (a more expensive option compared to subsequent treatments). In contrast, for STRIDE, the evidence indicates that PFS and TTD are not interchangeable, as a notable proportion of patients discontinue treatment while still progression-free. This discrepancy highlights the need for consistency and robust justification in the model. The EAG believes that using PFS uniformly as a proxy for TTD across all treatments would provide a more appropriate and transparent approach, given the cost implications and the lack of compelling evidence supporting the company's differential assumptions. Consequently, the company's justification for the amendment appears to reinforce the EAG's concerns regarding the model's assumptions.
Pg 115 B. "the assertion that there is a lack of evidence is incorrect" And pg 124	Pg 115 "the assertion that there is a lack of evidence for lenvatinib is incorrect" And pg 124	There is a TTD curve available for lenvatinib from TA551 which the Company had not identified. However, there is a lack of published evidence for atezolizumab plus bevacizumab.	We do not consider that this is a factual accuracy, but for clarity we have amended the statement to, "the assertion that there is a lack of evidence for lenvatinib is incorrect" (Pg 115) And "There is evidence about TTD for lenvatinib in the public domain but this was not recognised by the company." (pg 124)

“There is evidence about TTD in the public domain but this was not recognised by the company.”	“There is evidence about TTD for lenvatinib in the public domain but this was not recognised by the company.”		
Pg 115. “ C. Previous TAs (TA551 lenvatinib vs sorafenib, and ID1655) have modelled TTD using IPD from the relevant trials and have modelled observed TTD; committee papers indicate that their approach was acceptable to committee (i.e., PFS as proxy for TTD was not used).” And Pg 124 “Previous STA analyses of first line HCC therapy (atezolizumab + bevacizumab versus sorafenib and lenvatinib versus sorafenib) both rejected using PFS as proxy for TTD and this decision was not contradicted by the relevant NICE committees.”	“ C. Previous TAs (TA551 lenvatinib vs sorafenib, and ID1655) have modelled TTD using IPD from the relevant trials and have modelled observed TTD where possible; committee papers indicate that their approach was acceptable to committee. TA666 used PFS as proxy for TTD where data was not available, i.e., for lenvatinib. Committee papers indicate that their approach was acceptable to committee. (i.e., PFS as proxy for TTD was not used).” And pg 124 “Previous STA analyses of first line HCC therapy (atezolizumab + bevacizumab versus sorafenib and lenvatinib versus sorafenib) both rejected using PFS as proxy for TTD and this decision was not contradicted by the relevant NICE committees.” “Similar to the Company, TA666 also employed the assumption of TTD equivalence to PFS and this	TA666 used observed TTD data for atezolizumab plus bevacizumab and sorafenib, as they had TTD data collected in the Company trial (IMBrave150) for this.⁶ They used PFS as a proxy for TTD for lenvatinib, “TTD data for lenvatinib was not available” (Company Submission pg 108).	We have amended the text as suggested, which now reads, ‘C. Previous TAs (TA551 lenvatinib vs sorafenib, and ID1655) have modelled TTD using IPD from the relevant trials and have modelled observed TTD where possible; committee papers ~~indicate~~ suggest that their approach was acceptable to committee. TA666 used PFS as proxy for TTD where data was not available, i.e., for lenvatinib. Committee papers ~~indicate~~ suggest that their approach was acceptable to committee. We have deleted but replaced with, ‘The assumption of equivalence for PFS and TTD is difficult to justify, and limited available evidence suggests the assumptions although potentially ill-founded may be necessary from lack of alternative evidence. For example, although there is TTD data from TA666 this is redacted and unusable by the EAG. It is disappointing that lack of evidence resulted in the use of PFS as a proxy for TTD. This adds an extra-layer of uncertainty in the company’s cost-effectiveness analysis. For most of the observed period to 3.5 years PFS and TTD for STRIDE do not align with each other (Figure 42). This will likely result in different treatment cost estimations of STRIDE

	was accepted by the NICE committee.”		over 3.5 years from the two models. Modelling extrapolation beyond the observed time again adds uncertainty. Based on information provided in committee papers it appears that time to discontinuation of treatment data exists for the trials of interest (HIMALAYA, REFLECT, and IMbrave 150). Because of CIC redactions this data seems unavailable to both EAGs and to commercial companies making submissions to NICE. As a result, PFS has been used as a proxy out of necessity rather than choice.’
Pg 125 “The EAG’s economic analysis uses PFS as proxy for TTD. An advantage of this is that it allows use of network meta-analysis information and avoids naïve comparisons. A disadvantage is that it introduces inconsistency with previous STAs of atezolizumab + bevacizumab and of lenvatinib as first line treatments for HCC since both these rejected the use of proxy PFS.”	“The EAG’s economic analysis uses PFS as proxy for TTD. An advantage of this is that it ~~allows use of network meta-analysis information and~~ avoids naïve comparisons. ~~A disadvantage is that it introduces inconsistency with previous STAs of atezolizumab + bevacizumab and of lenvatinib as first line treatments for HCC since both these rejected the use of proxy PFS.~~”	Using PFS as a proxy for TTD does not use NMA information. As explained above, TA666 uses TTD as a proxy for PFS for lenvatinib and uses the observed TTD data for atezolizumab plus bevacizumab and sorafenib. Whilst there are some inconsistencies in how different treatments are costed differently with this approach, it is assumed a justified assumption particularly for treat-to-progression regimens.	We have amended to, ‘A disadvantage is that it follows previous STAs (atezolizumab + bevacizumab and of lenvatinib) since both of these appear to adopt proxy PFS out of necessity from lack of evidence’
Pg 116.	“The EAG notes that TTD plots from REFLECT lack the bends in	Lenvatinib is administered daily, and so the TTD may be	We have amended to, ‘The EAG notes that TTD plots from REFLECT lack the bends in

"The EAG notes that TTD plots from REFLECT lack the bends in trajectory seen for early times in TTD plots from HIMALAYA."	trajectory seen for early times in TTD plots from HIMALAYA, <i>which may be driven by the daily oral administration of lenvatinib.</i>"	expected to be a more continuous function. Please see Company response to Issue 13 regarding the steps observed in the KM plots for STRIDE.	trajectory seen for early times in TTD plots from HIMALAYA, likely reflecting more frequent assessment times than in HIMALYA.
Pg 118 "The company models based on PFS TTD equivalence are not endorsed by committee papers from previous STAs of first line treatment for unresectable hepatocellular carcinoma"	<i>"The company models based on PFS TTD equivalence are not endorsed by committee papers from previous STAs of first line treatment for unresectable hepatocellular carcinoma"</i>	PFS and TTD equivalence was used and accepted in TA666 where there was a lack of published evidence available to inform the lenvatinib TTD.	We have amended the text to 'PFS and TTD equivalence was used and accepted in TA666 where there was a lack of published evidence available to inform the lenvatinib TTD; thus, proxy PFS became a necessity.'
Pg 155 Table 48 "Equivalent to EAG model of atezolizumab + bevacizumab's PFS"	Please could the EAG clarify their approach	The EAG claims to use PFS to TTD equivalence for all comparators but deviates here. Please could the EAG clarify their approach.	The EAG has not identified any inaccuracy here. However, we have provided a response for the company to clarify our approach. The reference to "Equivalent to EAG model of atezolizumab + bevacizumab's PFS" in Table 48 reflects the EAG's preference for using PFS as a proxy for TTD. Specifically, the EAG prefers using the "Constant HR: HR vs sorafenib = 0.66 (CrI: 0.27, 1.59)" to represent TTD for atezolizumab + bevacizumab. In contrast, the company's approach has used an HR of ■ as a proxy for TTD for atezolizumab + bevacizumab.

Issue 11 Time Horizon

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 89 “As described subsequently in this report, our analyses demonstrate that around 1% of people are projected to survive beyond 20 years.”	“As described subsequently in this report, the EAG’s amendment to the modelling assumptions lead to our analyses demonstrate that around 1% of people are projected to survive beyond 20 years.”	The EAG should clarify it is after the amendments they have made to the modelling assumptions that this proportion changes. The Company model calculates that 4% of patients in the intervention arm are projected to survive beyond 20 years, hence the extension of the time horizon beyond 20 years, which is aligned with the NICE reference case.²⁴	We do not consider that this is a factual accuracy, but for clarity we have amended the statement to, ‘As described subsequently in this report, the EAG’s amendment to the modelling assumptions lead to around 1% of people are projected to survive beyond 20 years.’
Pg 137 Table 42 “With only 1.1% of patients projected to survive beyond 20 years, a 20-year horizon is more appropriate for capturing costs and benefits, aligning with NICE guidelines and previous STAs.”	“With only 1.1% of patients projected to survive beyond 20 years when the EAG amends the model based on their assumptions, a 20-year horizon is more appropriate for capturing costs and benefits, aligning with NICE guidelines and previous STAs.”	The EAG should be clear that this is after they have amended the model assumptions.	We do not consider that this is a factual accuracy.

Issue 12 Misunderstanding consistency issues and the inappropriate use of Vogel 2023 in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 95-96 “In the opinion of the EAG there appears to be possible inconsistency in the company’s methodology:	<i>The amendment to this factual inaccuracy applies to the entire report and beyond the text detailed on pages 95-96. The clarification of this factual inaccuracy extends to any place where claims that the use of clinical trial data for all relevant comparators in the HIMALAYA</i>	The Company’s approach is consistent with NICE guidance with respect to modelling of comparators. Consistent with NICE guidance, the PH assumption was assessed and	We have deleted the text but replaced it with: The company use IPD for each arm of HIMALAYA to

A. Between use of HRs from the anchored NMA (Lenvatinib and atezolizumab + bevacizumab) and use of IPD data (STRIDE and sorafenib). B. Between the modelling of STRIDE overall survival and progression-free survival (using IPD from HIMALAYA) and the modelling of these outcomes for the comparators Lenvatinib and atezolizumab + bevacizumab (using hazard ratios from the NMA) It seems the inconsistency could be eliminated in either of two ways: 1. By using NMA-delivered HRs for all compared treatments (i.e., including STRIDE) 2. By using trial-based IPD of overall survival and progression-free survival for all compared treatments (i.e. STRIDE, lenvatinib, and atezolizumab + bevacizumab) representing a naïve comparison. The company analysed reconstructed IPD for REFLECT (Submission Appendix N). IPD analysis from IMbrave150 was not reported."	<i>trial combined with using a HR for all other comparators is inappropriate. This is a very common methodology employed in NICE appraisals and the methodology used in Company Submission is consistent with NICE guidelines.</i>^{6, 25} <i>"In the opinion of the EAG there appears to be possible inconsistency in the company's methodology:</i> <i>A. ——— Between use of HRs from the anchored NMA (Lenvatinib and atezolizumab + bevacizumab) and use of IPD data (STRIDE and sorafenib).</i> <i>B. ——— Between the modelling of STRIDE overall survival and progression-free survival (using IPD from HIMALAYA) and the modelling of these outcomes for the comparators Lenvatinib and atezolizumab + bevacizumab (using hazard ratios from the NMA)</i> <i>It seems the inconsistency could be eliminated in either of two ways:</i> <i>1. ——— By using NMA-delivered HRs for all compared treatments (i.e., including STRIDE)</i> <i>2. ——— By using trial-based IPD of overall survival and progression-free survival for all compared treatments (i.e. STRIDE, lenvatinib, and atezolizumab + bevacizumab) representing a naïve comparison. The company analysed reconstructed IPD for</i>	concluded as holding for atezolizumab plus bevacizumab vs sorafenib. Whilst it didn't hold for lenvatinib, a time-varying analyses showed the assumption of a constant HR may be bias in favour of lenvatinib. It concluded that it did not hold for STRIDE vs sorafenib. NICE guidance specifies that independent models should be explored when the PH assumption is violated. This is detailed in the response to Issue 8 above. Given this conclusion, the approach used in the model was not considered inconsistent, but to be the preferred option with the evidence available for all comparators. Given that the STRIDE and sorafenib data used in the model come from the same trial, and given that the relative effects generated from the NMA are assumed to hold across the populations as no differences in treatment effect modifiers across studies were identified (see Company Submission Appendix D.1.6), the methods employed by the company are not inconsistent. The suggestion of the EAG to use trial-based IPD of overall survival and progression-free survival for all compared treatments (i.e. STRIDE, lenvatinib, and atezolizumab +	model OS for STRIDE and OS for sorafenib. The approach used to model OS for the comparators atezolizumab + bevacizumab and Lenvatinib is to apply NMA HRs to the sorafenib IPD. Two different approaches may lead to inconsistency. Similarly, the EAG for the atezolizumab + bevacizumab STA remarked that it is inappropriate to estimate the relative treatment effects of lenvatinib versus atezolizumab + bevacizumab using an HR from a random effects NMA, whilst estimating the effect of sorafenib versus atezolizumab + bevacizumab using arm-based parametric survival model. The EAG for the atezolizumab + bevacizumab STA additionally considered that using HRs from NMAs in the context of an economic evaluation is inappropriate in

And pg 108 - 110 “The EAG considers the difference in methods may lead to inequitable comparison between STRIDE vs atezolizumab + bevacizumab and between STRIDE versus lenvatinib. The EAG therefore investigated using the same method for atezolizumab + bevacizumab and lenvatinib PFS as that used by the company for STRIDE.”	~~REFLECT (Submission Appendix N). IPD analysis from IMbrave150 was not reported.”~~ ~~“The EAG considers the difference in methods may lead to inequitable comparison between STRIDE vs atezolizumab + bevacizumab and between STRIDE versus lenvatinib. The EAG therefore investigated using the same method for atezolizumab + bevacizumab and lenvatinib PFS as that used by the company for STRIDE.”~~	bevacizumab) representing a naïve comparison” and effectively assumes that absolute outcomes can be predicted from the covariates. This assumption is very strong, and largely considered impossible to meet.²⁶	order to estimate population mean benefit.
Pg 96 “the EAG derived a STRIDE model by applying the NMA HR (■) to the sorafenib model and compared this with the IPD-derived model proposed by the company (Figure 14). The comparison shows that if the model for STRIDE is derived consistently with those for comparators, the overall survival is noticeably poorer than the company’s spline model used in the economic model and suggests a potential impact on the economic model results.”	<i>Similar to the above, the proposed amendment extends to all comparator plots on pages 96-97</i> “the EAG derived a STRIDE model by applying the NMA HR (■) to the sorafenib model and compared this with the IPD-derived model proposed by the company (Figure 14), <i>although this extrapolation should be considered in the context of the proportional hazards assumption not holding. Furthermore, a comparison of the KM curve for STRIDE from HIMALAYA to this extrapolation shows a poor fit to the data and that this approach underestimates survival. Therefore this approach should not be used</i>”. ~~“The comparison shows that if the model for STRIDE is derived consistently with those for comparators, the overall survival is noticeably poorer than the company’s spline model used in the economic model and suggests a~~	Considering the evidence that the PH assumption is violated for STRIDE vs sorafenib for OS, the text explaining this plot should include this statement. The omission of a description of the PH violation is misleading, and it is inaccurate to apply a constant HR when the PH assumption doesn’t hold. This is consistent with NICE TSD DSU guidelines.²⁵ Validation of the extrapolation with the KM curve for STRIDE from HIMALAYA has been omitted from the report. If this was included, the very poor fit to the data would be apparent, which is expected given that the PH assumption was violated.	The EAG has deleted this text and replaced it with: If the NMA point estimate ■ HR for STRIDE versus sorafenib is applied the resulting spline model aligns well with the IPD model over the bulk of the observed data but differs during the 6.4-fold extrapolation to a 40-year time horizon (Figure 14). Note that the 95%CrIs for the ■ HR were wide: ■.

	potential impact on the economic model results.”		
Pg 122 Figure 40 and “NMA HR-adjusted models of OS and PFS for all three treatments (STRIDE, atezolizumab + bevacizumab, and lenvatinib) have negligible survivors by 24 years. In contrast STRIDE models based on IPD generate superior OS and PFS compared to NMA_HR-adjusted STRIDE models and exhibit survivors beyond 24 years. The methodology used of generating models appears to bias in favour of STRIDE relative to lenvatinib and atezolizumab + bevacizumab.” And pg 124 “The method for modelling OS and PFS of STRIDE (using IPD from HIMALAYA) differed from that for atezolizumab + bevacizumab and for lenvatinib (using NMA HR output applied to the spline model for sorafenib). The difference may introduce bias	Pg 122 ~~“NMA HR-adjusted models of OS and PFS for all three treatments (STRIDE, atezolizumab + bevacizumab, and lenvatinib) have negligible survivors by 24 years. In contrast STRIDE models based on IPD generate superior OS and PFS compared to NMA_HR-adjusted STRIDE models and exhibit survivors beyond 24 years. The methodology used of generating models appears to bias in favour of STRIDE relative to lenvatinib and atezolizumab + bevacizumab.”~~ Removal of Figure 40 And pg 124 “The method for modelling OS and PFS of STRIDE (using IPD from HIMALAYA) differed from that for atezolizumab + bevacizumab and for lenvatinib (using NMA HR output applied to the spline model for sorafenib). ~~The difference may introduce bias into the comparison of STRIDE versus each of atezolizumab + bevacizumab and lenvatinib.~~”	The EAG omitted consideration of the proportional hazards assumption assessment with the conclusions provided here. As explained above, the Company found the PH violation for STRIDE vs. sorafenib (from HIMALAYA) for PFS and OS and therefore fitting independent models to the data was the best approach and follows NICE DSU guidelines.²⁵ The Company also found the PH violation for lenvatinib vs sorafenib (from REFLECT) for PFS and OS. Time-varying analysis for REFLECT showed that the application of a constant HR for lenvatinib in the economic model may overestimate the long-term effect of treatment, and therefore yields conservative cost-effectiveness estimates when compared with STRIDE. As PH violation was not found for atezolizumab plus bevacizumab given the published trial evidence, more complex models were not warranted, and the application of a constant HR to sorafenib was considered reasonable.	Please refer to our response earlier.

into the comparison of STRIDE versus each of atezolizumab + bevacizumab and lenvatinib.”		Based on this evidence, the approach taken by the Company and the resulting extrapolations are not considered bias.	

Issue 13 Commentary around the survival analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 95 “In practice the company spline model(s) and generalised gamma models predict very similar lifetime survival that in the case of STRIDE suggests apparently “cured” patients (see Figure 13).”	EAG to add full justification for selection of generalised gamma for the sorafenib OS extrapolation beyond selecting the model with the lowest AIC/BIC, particularly as it has a very similar fit to the Company base case.	EAG should justify switching away from the Company base case which has been clinically validated. The EAG have omitted detail on whether they considered anything beyond AIC/BIC statistics to inform their selection, which is not consistent with NICE DSU TSD 14 guidelines.^{25, 27}	We have considered clinical plausibility for UK population and consulted with our clinical advisors.
Pg 99 - 100 “As is characteristic of many PFS KM plots the company’s PFS plot has notable “bends” in trajectory reflecting the timing of visits to assess whether progression has occurred. Such plots obviously cannot accurately reflect “true” progression times (irrespective of how judged) which will be far more randomly distributed than implied by the “bends” due to imposed assessment times...	“As is characteristic of many PFS KM plots the company’s PFS plot has notable “bends” in trajectory reflecting the timing of visits to assess whether progression has occurred. Such plots obviously cannot accurately reflect “true” progression times (irrespective of how judged) which will be far more randomly distributed than implied by the “bends” due to imposed assessment times. However, given that progression in clinical practice will often be assessed and observed at scheduled follow-up	In clinical practice, progression will likely be assessed and observed at scheduled follow-up visits rather than when “true progression” occurs. Even though there are notable steps (or ‘bends’) in the PFS curve, it is considered to reflect clinical reality. Given this, and the fact that these steps are commonly observed in PFS curves, the EAG should reassess the use of goodness-of-fit statistics to assess model fit, in line	The EAG do not consider this there to be a factual error made.

close fitting to a bendy trajectory clearly will not reflect the reality of actual progression times because the event times of patients will be more randomly distributed than implied by the “observed” bendy plot which is compounded by assessment times and actual progression. In general, the closer the spline model is to the bendy PFS plot, the less likely it will reflect actual progression times and in extrapolation beyond 41.8 months of observation the more likely it will be influenced by the last bend(s) captured by the spline model’s knots or by the long flat tail of the KM from approximately 18 months. In brief, because of the uneven (bendy) trajectory of the observed data, it is unlikely that AIC BIC values will necessarily be meaningful in determining “a good” model of actual progression times (i.e. reflective of event times).” Ang Pg 124 “The spline model for PFS may reflect visit times more strongly than it does progression times.”	visits, the identification of ‘true progression’ is not necessary for the economic model.” ~~...close fitting to a bendy trajectory clearly will not reflect the reality of actual progression times because the event times of patients will be more randomly distributed than implied by the “observed” bendy plot which is compounded by assessment times and actual progression. In general, the closer the spline model is to the bendy PFS plot, the less likely it will reflect actual progression times and in extrapolation beyond 41.8 months of observation the more likely it will be influenced by the last bend(s) captured by the spline model’s knots or by the long flat tail of the KM from approximately 18 months. In brief, because of the uneven (bendy) trajectory of the observed data, it is unlikely that AIC BIC values will necessarily be meaningful in determining “a good” model of actual progression times (i.e. reflective of event times).”~~ And on Pg 111: “The spline model for PFS may reflect visit times more strongly than it does progression times, ~~although this likely reflects clinical reality.”~~ And on Pg 111: “To the EAG, the company’s TTD KM plot seemed ~~unexpectedly~~ “bendy” over the first six months, as ~~though it might be~~ influenced in	with NICE DSU TSD 14 guidelines.^{25, 27} Similarly, decisions to discontinue treatment will be made by the clinician, and it is expected for these to happen at follow-up visits with the clinician. Furthermore, as durvalumab is administered every 4 weeks, steps in the TTD curve are expected. As with PFS, even though there are notable steps (or ‘bends’) in the TTD curve, it is considered to reflect clinical reality.	

Similarly on Pg 111 “To the EAG, the company’s TTD KM plot seemed unexpectedly “bendy” over the first six months, as though it might be influenced in some way by visit times making it rather like PFS KM plots, and it lacked 95% CIs.”	~~some way~~ by visit times making it rather like PFS KM plots, and it lacked 95% CIs.”		
Pg 105 “In the opinion of the EAG, the company model with three knots may “overfit” the observed data and may not reflect the progression of an average 64-year-old patient since the model is influenced strongly by imposed visit times and by the post 17-month PFS data that relies on only 14% of the population.”	“In the opinion of the EAG, the company model with three knots may “overfit” the observed data and may not reflect the progression of an average 64-year-old patient since the model ~~is~~ may be influenced strongly by imposed visit times and by the post 17-month PFS data that relies on only 14% of the population. However, clinical advisors interviewed by the Company did confirm that the Hazard 3 knot model was clinically plausible for the STRIDE extrapolation.”	Given that the data is relatively complete, many models provide a similarly good fit to the data, and as such, clinical validation of the expectations of the long-term PFS was considered important in selecting the most appropriate model. The EAG omitted this commentary from their write-up. The Company interviewed clinical advisors who agreed that for STRIDE, the hazard 3 knot model was most clinically plausible. This is detailed in the Company submission.	The EAG does not consider there to be a factual inaccuracy; hence, no amendment was made to the text.
Pg 119 “Shaded areas representing credible 95% CIs are wide (because of the imprecision associated with credible 95% CIs in the NMA HRs) with an overlapping area where it is	Pg 119 “Shaded areas representing credible 95% CIs are wide (because of the imprecision associated with credible 95% CIs in the NMA HRs) with an overlapping area where it is possible for more patients to be in unprogressed state than there are live	The Company model appropriate captures the uncertainty associated with the efficacy estimates from the NMA using probabilistic sensitivity analysis. In cases during the sampling where OS < PF or PD, a structural	We have amended the text to include that the model structure does not allow for more people to be in an unprogressed state than there are live patients in the model.

possible for more patients to be in unprogressed state than there are live patients.” And Pg 120 “Figure 38 shows the same analysis for lenvatinib. The credible interval associated with PFS almost completely envelop that for OS, indicating that at most time points it is possible that the proportion of unprogressed individuals may be greater than the proportion alive.”	patients. However, the model structure does not allow this to occur” Pg 120 “Figure 38 shows the same analysis for lenvatinib. The credible interval associated with PFS almost completely envelop that for OS, indicating that at most time points it is possible that the proportion of unprogressed individuals may be greater than the proportion alive. However, the model structure does not allow this to occur”	assumption is in place in the model which prevents more patients being in the progression-free state that than there are dead.	
Pg 123 “The NMA output for these comparisons delivered wide 95% credible intervals that indicate considerable imprecision in estimates that threaten the integrity of modelled extrapolations beyond observed data to the lifetime horizon of 40 years.”	“The NMA output for these comparisons delivered wide 95% credible intervals that indicate considerable imprecision in point estimates, however this is appropriately explored in the probabilistic sensitivity analysis that threaten the integrity of modelled extrapolations beyond observed data to the lifetime horizon of 40 years.”	The impact of the wide confidence intervals is appropriately captured in the modelling and does not threaten the integrity of the modelled extrapolations.	The EAG do not consider there to be a factual inaccuracy.
Page 151 “The inconsistent application of individual patient data and hazard ratios across treatments has resulted in unrealistic overall	~~“The inconsistent application of individual patient data and hazard ratios across treatments has resulted in unrealistic overall survival projections, particularly for STRIDE (see Section 4.2.6).”~~	The EAG has not presented any analysis or evidence which supports this statement, nor reported any clinical opinion which says that the extrapolations in the Company base case are unrealistic.	The EAG consulted with their clinical advisors about the company’s overall survival extrapolations. It was suggested that given the population in the HIMALAYA trial, then a few young patients might be cured or

survival projections, particularly for STRIDE (see Section 4.2.6)."			survive that long, but 40 years seemed excessive/optimistic.

Issue 14 Inappropriate comparison to absolute values from REFLECT and IMBRAVE150

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 108 Table 30 and: "As can be seen there are differences between RCT and company model medians that are particularly large for atezolizumab + bevacizumab. The differences exist even though HRs from IMbrave150 and REFLECT were input to the NMA and it might be expected that the relationship of medians would be more consistent."	"The differences exist even though HRs from IMbrave150 and REFLECT were input to the NMA ~~and it might be expected that the relationship of medians would be more consistent.~~ however, given differences in potentially prognostic characteristics between studies, some differences in a naïve comparison may be expected."	The comparison performed by the EAG represents a naïve comparison and should be reported as such. Naïve comparisons assume that all effect modifiers and prognostic factors are accounted for, which is a very strong assumption, and considered largely impossible to meet.²⁶ Whilst an assessment of between-trial heterogeneity identified no concerning imbalances in treatment effect modifiers between studies, there may be prognostic differences between trials that would lead to bias in a naïve comparison such as this.	We have amended the title of Table 30 to 'NMA HR modelled median PFS and naïve comparison with RCT reported median PFS.'
Pg 109 Figure 24 reflects a naïve comparison to PFS per BICR.	Remove the Figure 24 and text comparing it to the Company survival analysis.	Figure 24 is misleading as not only is it a naïve comparison, but it is also comparing across different definitions of PFS. The Company used PFS per investigator as explained in response to Issue 9. It is not clear where the EAG reconstructed the	We do not consider this a factual inaccuracy; however, for clarity we have changed the caption to 'Figure 24: Reconstructed KM PFS IMbrave150 based on Finn et al. Naïve comparison with

		KM from for IMbrave150 as no reference was provided, but the Company can only locate a published PFS per BICR from the IMBrave150 trial. Given this, this figure and comparison should be removed.	company model of atezolizumab + bevacizumab.'
Pg 109 – 110 "Because the REFLECT trial of lenvatinib was a non-inferiority trial and since the proportional hazards assumption (Sorafenib versus lenvatinib) did not hold the company model for lenvatinib was made equivalent to that for sorafenib." And "Figure 26 KM plots of PFS for sorafenib and lenvatinib based on RCTs Note the company interprets their sorafenib model to be equal to their model for lenvatinib and this differs considerably from PFS seen in the RCT."	Removal of this comparison and Figure 26. ~~"Because the REFLECT trial of lenvatinib was a non-inferiority trial and since the proportional hazards assumption (Sorafenib versus lenvatinib) did not hold the company model for lenvatinib was made equivalent to that for sorafenib."~~ ~~And "Figure 26 KM plots of PFS for sorafenib and lenvatinib based on RCTs~~ ~~Note the company interprets their sorafenib model to be equal to their model for lenvatinib and this differs considerably from PFS seen in the RCT."~~	The Company used this approach for OS, but not PFS. As explained in Company Submission B Section B.3.3.2. The REFLECT study was a non-inferiority study, which concluded that lenvatinib was statistically non-inferior compared with sorafenib in terms of OS. Accordingly, a HR for lenvatinib vs. sorafenib of 1 was used in the base case for OS. For PFS, statistical non-inferiority was not observed in REFLECT, and thus the HR from the NMA was used, which may be considered a conservative approach.	The EAG has deleted Figure 26 and modified the text to provide further clarity and correct the error. The associated text in the EAG report now becomes: The company model for lenvatinib PFS was derived by applying a HR of [REDACTED] to the HIMALAYA IPD-based spline model for sorafenib. The input to the NMA was [REDACTED] (CS Appendix Table 22). The company's NMA HRs and their use in PFS modelling are summarised in Table

Issue 15 Hernandez of utilities not following NICE reference case

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 129 "4. Age-adjustment for general population utilities: While the	~~While~~ The company has incorporated age-adjustment coefficients for utilities in the model, <u>using the NICE reference case (HSE</u>	The Company used HSE 2014 (Hernandez Alava 2022)²⁸ in the model, which is aligned with the	The company has confirmed that the source of age-adjustment coefficients for

company has incorporated age-adjustment coefficients for utilities in the model, the source of these coefficients is unclear. The EAG supports the inclusion of age-adjusted utilities but considers the company's chosen source, in comparison with TA666,14 to be more optimistic. The EAG prefers the use of the Ara & Brazier (2010)¹ coefficients, which were employed in a previous STA, as a more appropriate reference for this purpose."	~~2014, Hernandez Alava 2014) the source of these coefficients is unclear. The EAG supports the inclusion of age-adjusted utilities but considers the company's chosen source, in comparison with TA666,14 to be more optimistic. The EAG prefers the use of the Ara & Brazier (2010)¹ coefficients, which were employed in a previous STA, as a more appropriate reference for this purpose."~~ Please also update Table 42 on page 138	NICE reference case.²⁴ The Company mistakenly left out this reference in Document B, but it is included in the CEM excel file. Unless the EAG have a rationale to deviate from the NICE reference case in favour of Ara & Brazier, the Company request the EAG reconsider their conclusions.	utilities was initially unclear in the submission. NICE does not recommend a specific source for age-adjustment but refers to common sources such as the Health Survey for England (HSE), Ara & Brazier (2010), and Janssen & Szende (2014)²⁸. The use of Hernández Alava et al. (2017) is recommended in the most recent NICE reference case (2023) for the mapping function of utility²⁴. The EAG prefers the use of Ara & Brazier (2010) coefficients, as they provide a smoother trend in age-adjustment and are consistent with previous STAs. However, the EAG has also conducted scenario analyses using the company's approach for comparison.
Pg 151 "The unclear source of age-adjustment coefficients for utilities appears overly optimistic, which could skew the model results."	~~"The unclear source of age-adjustment coefficients for utilities appears overly optimistic, which could skew the model results."~~	As above, the source used is aligned with the NICE reference case.	See above EAG response

Issue 16 Misrepresenting Company approach to utility analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 128 “While acknowledging the company's approach, the EAG has several critiques: 1. Utility changes and treatment duration: Given that treatment duration for patients with untreated advanced or unresectable hepatocellular carcinoma is often short, the EAG questions whether observable changes in utility based on health states (PF, PD) are feasible or accurately estimable.”	~~“Utility changes and treatment duration: Given that treatment duration for patients with untreated advanced or unresectable hepatocellular carcinoma is often short, the EAG questions whether observable changes in utility based on health states (PF, PD) are feasible or accurately estimable.”~~	This bullet infers that the utilities are only measured for the time a patient is on randomised treatment, which is not the case. The utility values were derived across the trial time horizon (on and off treatment) and so capture the utility off-treatment too.	The EAG notes on page 128 of the report that it prefers an approach consistent with TA666 (atezolizumab with bevacizumab, NICE, 2020), where utilities are derived based on on/off-treatment time-to-death utility values. While the company asserts that utilities were measured across the trial horizon, the submitted data do not clarify if time-to-death utilities differ for patients transitioning directly from progression-free to death versus those from progressed disease. Evidence from TA666 demonstrates such differences exist, suggesting that accounting for these distinctions could improve model accuracy. Retaining this critique emphasizes the importance of precise utility estimates to better capture the benefits of treatments in the model. Thus, the EAG does not support deleting this point.

Pg 129 “3. Utility values for primary and subsequent treatments: If utility values reflect treatment-specific AEs, it is inappropriate to assign the same utility for patients on primary treatment (e.g., STRIDE) and those on subsequent treatments. For instance, patients who discontinue STRIDE and begin sorafenib (as subsequent treatment) should not be assumed to have the same utility as those still on STRIDE. Given that the company assigns a lower utility value for sorafenib, and that sorafenib is a common subsequent treatment, it is more reasonable to assume that the utility for patients on subsequent treatments would be at most equal to that of sorafenib. This adjustment would improve consistency and the face validity of the model.”	~~“3. Utility values for primary and subsequent treatments: If utility values reflect treatment-specific AEs, it is inappropriate to assign the same utility for patients on primary treatment (e.g., STRIDE) and those on subsequent treatments. For instance, patients who discontinue STRIDE and begin sorafenib (as subsequent treatment) should not be assumed to have the same utility as those still on STRIDE. Given that the company assigns a lower utility value for sorafenib, and that sorafenib is a common subsequent treatment, it is more reasonable to assume that the utility for patients on subsequent treatments would be at most equal to that of sorafenib. This adjustment would improve consistency and the face validity of the model.”~~	This bullet infers that the utilities are only measured for the time a patient is on randomised treatment, which is not the case. The utility values were derived across the trial time horizon (on and off treatment) and so capture the utility when patients receive subsequent treatment, e.g., sorafenib, too.	The company's approach to utilities incorporates treatment-related values, which vary by treatment and include adverse event impacts within the model. While it seems, the company tends to follow an aggregate approach in incorporating utility values, the EAG observes inconsistencies between this approach and the treatment-related utility framework the company claims to follow. Specifically, assigning the same utility to patients on primary treatment (e.g., STRIDE) and subsequent treatment (e.g., sorafenib) fails to reflect treatment-specific differences. Given that sorafenib is commonly used as a subsequent treatment and has a lower assigned utility, the EAG believes that differentiating utility values for subsequent treatments would better align with established methodologies from prior STAs and improve model validity. Therefore, the EAG does not agree with deleting this critique.

Pg 151 "Furthermore, the utility values derived from health states may not accurately reflect the short treatment durations typical for patients with advanced disease."	~~"Furthermore, the utility values derived from health states may not accurately reflect the short treatment durations typical for patients with advanced disease."~~	The EAG seems to have misunderstood how these utility values were derived. The utility values were derived across the trial time horizon (on and off treatment) and so capture the utility off-treatment and subsequent treatments too.	It appears that the company has misunderstood the intent of this critique. The comment addresses the nature of the disease and highlights that using mean utility values derived over a time horizon may not accurately capture the short treatment durations typical for patients with advanced disease. This approach could lead to applying the same utility value across different health states (as we can see here). EAG's clinical adviser has confirmed this concern.

Issue 17 Severity modifier

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 137 and Page 151 "The company applied a QALY weight of 1.2 in its model, which is based on sorafenib. However, to accurately calculate the severity modifier, it is essential to use the QALYs associated with the established treatments currently available within NHS practice in the UK. Presently, patients with untreated advanced or unresectable HCC have access to	~~"The company applied a QALY weight of 1.2 in its model, which is based on sorafenib. However, to accurately calculate the severity modifier, it is essential to use the QALYs associated with the established treatments currently available within NHS practice in the UK. Presently, patients with untreated advanced or unresectable HCC have access to atezolizumab + bevacizumab treatment through the NHS. As indicated in Table 41, if the total QALYs expected for patients receiving atezolizumab + bevacizumab~~	The Company applied the x1.2 weight to the sorafenib and lenvatinib comparisons only. This is not mentioned by the EAG. Sorafenib and lenvatinib can be considered standard of care within NHS practice in the UK for a substantial proportion of patients who would benefit from oral therapy or are contraindicated to atezolizumab-bevacizumab. They should therefore also be considered	The EAG explicitly addressed the use of a severity modifier of 1.2 for comparisons with lenvatinib and sorafenib, as detailed in section 4.2.10 (pages 136–137) and Table 41. Additionally, issue 11 on page 29 clarifies that the company applied a severity modifier of 1 for comparisons with atezolizumab + bevacizumab. This

atezolizumab + bevacizumab treatment through the NHS. As indicated in Table 41, if the total QALYs expected for patients receiving atezolizumab + bevacizumab treatment is considered, the QALY weight for this technology appraisal should be adjusted to 1, when comparing STRIDE against all comparators.”	~~treatment is considered, the QALY weight for this technology appraisal should be adjusted to 1, when comparing STRIDE against all comparators.~~ The Company applied a QALY weight of 1.2 for the comparisons of STRIDE vs. sorafenib and STRIDE vs. lenvatinib. The Company applied no QALY weight for the comparison of STRIDE versus atezolizumab plus bevacizumab”	in the severity modifier calculations. The same QALY weight need not apply to all comparisons in these cases.	demonstrates that the company's claim—"this is not mentioned by the EAG"—is inaccurate. To calculate the severity modifier, the highest baseline utility among established treatments (lenvatinib, sorafenib, or atezolizumab + bevacizumab) should be used. This reflects the best achievable health outcomes within current NHS practice, avoids overestimating severity, ensures fair comparisons, and aligns with efficient and equitable resource allocation principles in health technology assessments.
Pg 151 “Finally, regarding the severity modifier, the weight should reflect established treatments like atezolizumab + bevacizumab currently available within NHS practice.”	“The severity modifier is appropriately applied across treatments”. ~~“Finally, regarding the severity modifier, the weight should reflect established treatments like atezolizumab + bevacizumab currently available within NHS practice.”~~	As explained above, the 1.2 severity modifier is used for lenvatinib and sorafenib, and not for the comparison to atezolizumab plus bevacizumab.	See above EAG response

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