NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

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2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Liver Trust
   b. British Association for the Study of the Liver
   c. British Society of Gastroenterology

The Royal College of Physicians endorses the statements produced by British Association for the Study of the Liver and the British Society of Gastroenterology

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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

ID1655: Atezolizumab with Bevacizumab for Untreated, Unresectable or Advanced Hepatocellular Carcinoma

Document B

Company evidence submission

April 2020

File name	Version	Contains confidential information	Date
ID1655_Atezo+Bev HCC_ACIC_Document B_REDACTED	1	Yes	14 April 2020

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Abbreviations

AASLD	The American Association of the Study of Liver Diseases
ADA	anti-drug antibodies
ADCC	antibody dependent cell-mediated cytotoxicity
AESI	Adverse events of special interest
AFP	Alpha-fetoprotein
AFT	Accelerated failure time
AIC	Akaike Information Criterion
AJCC TNM	American Joint Committee on Cancer tumour size, lymph nodes affected, metastases
APAC	Asia Pacific
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BCLC	Barcelona Clinic Liver Cancer
BIC	Bayesian Information Criterion
BID	Twice-daily
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CCOD	Clinical cut-off date
CEA	Cost-effectiveness analysis
CMA	Cost-minimisation analysis
CUA	Cost-utility analysis
DEB	Drug-eluting bead
DIC	Deviance information criterion
DOR	Duration of response
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG PS	Eastern Cooperative Oncology Group performance status
EGD	Esophagogastroduodenoscopy
EGFR	Endothelial growth factor receptor
EHS	Extrahepatic spread
EMA	European Medicines Agency

EORTC-QLQ	European Organisation for Research and Treatment of Cancer quality of life questionnaire
ESMO	European Society of Medical Oncology
FDA	US Food and Drug Administration
FPI	First patient in
GCP	Good clinical practice
GHS	Global health status
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
ICER	Incremental cost-effectiveness ratio
INR	International normalised ratio
INV	Investigator
ITC	Indirect treatment comparison
ITT	Intent-to-treat
LPLV	Last patient last visit
LYG	Life years gained
LYs	Life years
MDD	Minimum detectable difference
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MVI	Macrovascular invasion
NAFLD	Non-alcoholic fatty liver disease
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NHB	Net-health benefit
NPT	Non-protocol anti-cancer therapy
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PCR	Polymerase chain reaction

PFS	Progression-free survival
PIM	Promising innovative medicine
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal social services research unit
QALD	Quality-adjusted life day
QALY	Quality-adjusted life year
QOL	Quality of life
RECIST	Response evaluation criteria in solid tumours
RFA	Radiofrequency ablation
RWD	Real world data
SAE	Serious adverse event
SIRT	Selective intern
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	Standard of care
TACE	Transarterial chemoembolisation
TARE	Transarterial radioembolisation
TKI	Tyrosine kinase inhibitor
TTD	Time to deterioration
TTO	Time trade off
TTOT	Time to off treatment
TTP	Time to progression
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor
WTP	Willingness to pay

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication, i.e. [redacted].

The evidence provided in this submission is based on the population of the IMbrave150 phase III randomised clinical trial, which enrolled patients with locally advanced or metastatic and/or unresectable HCC (82% Barcelona Clinic Liver Cancer [BCLC] stage C [advanced] and 16% BCLC stage B [intermediate]). However, it is important to acknowledge [redacted].

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	The population covered within the submission will align with the currently anticipated European Marketing Authorisation (EMA): [redacted]	As per NICE final scope and in line with NICE reference case	N/A
Intervention	Atezolizumab (Tecentriq®) with bevacizumab (Avastin®)	As per NICE final scope and in line with NICE reference case	N/A
Comparator(s)	• Sorafenib • Lenvatinib • BSC	• Sorafenib • Lenvatinib	Consultant oncologists practising in NHS England have confirmed that treatments used to treat patients with unresectable HCC who are no longer candidates for locoregional treatments, would be sorafenib or lenvatinib in the first-line setting. Best supportive care is not a relevant comparator as patients considered eligible for Atezo+Bev would be eligible for alternative active treatment.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.	As per NICE final scope and in line with NICE reference case	N/A
Economic analysis	The cost-effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life year.	As per NICE final scope and in line with NICE reference case	N/A

	The lifetime time horizon will be used for estimating clinical and cost effectiveness 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 commercial arrangements for the intervention, and estimates for comparator and subsequent treatment technologies will be taken into account.		

B.1.2 Description of the technology being appraised

The technology being appraised is described in Table 2. See Appendix C for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Description of the technology

UK approved name and brand name	UK approved name (brand name): • Atezolizumab (Tecentriq®) • Bevacizumab (Avastin®)
Mechanism of action	**Atezolizumab** is a humanised IgG monoclonal antibody which directly and selectively binds to an immune checkpoint protein called programmed death-ligand 1 (PD-L1) on the surface of both tumour cells (TC) and tumour infiltrating immune cells (IC) (1, 2). PD-L1 binds to PD-1 and B7.1 on activated T cells to inhibit T cell proliferation, cytokine production and cytolytic activity, thereby inhibiting the anti-tumour immune response (3-5). This means that binding of PD-L1 by atezolizumab may therefore enhance an anti-tumour immune response. Overexpression of PD-L1 in tumour cells has been associated with a poor prognosis in patients with several cancers (6-9). Interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway with atezolizumab prevents down regulation of T-cell activity while allowing for the priming of new T cells (3, 10). Furthermore, atezolizumab is FcγR-binding deficient, therefore it cannot bind to Fc receptors on phagocytes and cause antibody dependent cell-mediated cytotoxicity (ADCC). This is important since ADCC-mediated depletion of tumour specific T cells could worsen autoimmunity rather than improve it (4, 11). Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth (12).
Marketing authorisation/CE mark status	An application for a license extension of atezolizumab for the following indication was submitted to the EMA on [redacted]. [redacted] Marketing authorisation for this indication is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Atezolizumab is currently approved by the EMA for the following indications (1): • As monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior

	platinum-containing chemotherapy or who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥5%. • In combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies. • As monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should have received targeted therapy if clinically indicated prior to receiving atezolizumab. • In combination with nab-paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC. • In combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). • In combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.
Method of administration and dosage	**Atezolizumab:** Intravenous (IV) infusion, 1,200 mg every 3 weeks until loss of clinical benefit or unmanageable toxicity **Bevacizumab:** IV infusion, 15 mg/kg q3w until disease progression or unacceptable toxicity
Additional tests or investigations	N/A
List price and average cost of a course of treatment	Atezolizumab: £3807.69 per 20ml vial (1,200mg) Bevacizumab: £242.66 per 4ml vial (100mg); £924.40 per 16ml vial (400mg) Average price per treatment cycle (3 weeks): £6423.00
Patient access scheme (if applicable)	Atezolizumab: [redacted](existing PAS) Bevacizumab: [redacted] (existing PAS)

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

B.1.3.1 Disease overview

Liver cancer comprises a number of diverse and histologically distinct primary hepatic neoplasms, of which hepatocellular carcinoma (HCC) is the most common form, representing 83% of all cases (13).

HCC is the sixth most common cancer in the world, and the fourth most deadly with approximately 782,000 deaths in 2018 (14).There are approximately 5,900 new cases of

liver cancer diagnosed in the UK every year, with more males affected than females. This incidence rate is projected to rise by 38% in the UK between 2014 and 2035, to 15 cases per 100,000 people by 2035. The incidence of liver cancer is strongly related to age; between 2014 and 2016, on average each year more than 4 in 10 (43%) new cases in the UK were in people aged 75 and over (15).

Liver cancer is the eighth most common cause of cancer death in the UK with approximately 5,400 deaths each year. Over the last decade, liver cancer mortality rates have increased by around half (51%) in the UK, with mortality rates projected to rise by 58% in the UK between 2014 and 2035, to 16 deaths per 100,000 people by 2035 (16).

Infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV), as well as heavy alcohol consumption are major drivers of cirrhosis and the downstream development of HCC. These aetiologies are differentially distributed worldwide, with HBV-associated HCC common in Asia (with the exception of Japan) and Africa, and HCV-associated HCC common in Europe, North America, and Japan (17). The incidence of HCC associated with alcohol consumption and non-alcoholic fatty liver disease (NAFLD), together with metabolic syndrome and obesity is increasing, especially in the Western world (18).

HCC is a debilitating condition but one that can progress silently in patients with sufficient liver function and escape early diagnosis. The most common presenting clinical features in patients with symptomatic HCC are right upper quadrant pain, weight loss and paraneoplastic syndrome, hypercholesterolemia, hypercalcemia, hypoglycaemia and anaemia or erythrocytosis (19). These are often superimposed on signs of cirrhosis (e.g. jaundice) and portal hypertension (e.g. ascites, varices) and may also be associated with increases in liver transaminases (20). Serious and often life threatening complications include hepatic vein occlusion and portal vein invasion and thrombosis, encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis (21).

Patients with HCC represent a heterogeneous and challenging-to-treat group given the majority (70–90%) of HCC patients have liver cirrhosis, therefore requiring management of both the malignancy and underlying liver disease (20). Staging of HCC is based on the Barcelona Clinic Liver Cancer Staging Classification (BCLC) system which links disease stage with treatment modalities (Table 3). The system assesses prognostic variables based on the number and size of tumours, performance status and liver function as measured by the Child-Pugh score. The BCLC system divides HCC into five stages: patients with early HCC who may benefit from curative therapies (stage 0 - A), those at intermediate stage who may benefit from interventional, local therapies (stage B), patients at an advanced stage

(stage C) who may benefit from systemic treatments and those with a very poor life expectancy (stage D) who are treated with best supportive care (22, 23).

Table 3: Barcelona Clinic Liver Cancer (BCLC) staging system for HCC

BCLC stage	Tumour stage	Child-Pugh class	ECOG PS	Recommended therapy
Stage 0 – Very early	Single nodule <2cm	A	0	Resection
Stage A – Early	Single or 3 nodules <3cm	A or B	0	Transplantation RFA
Stage B – Intermediate	Multinodular	A or B	0	TACE
Stage C – Advanced	Portal invasion, N1, M1	A or B	1–2	Systemic treatment (sorafenib)
Stage D – End stage	Any	C	>2	Best supportive care

Source: (22, 23)
ECOG PS, Eastern Cooperative Oncology Group performance status; M1, metastasis; N1, nodes; RFA, radiofrequency ablation; TACE, transarterial chemoembolisation

The BCLC B (intermediate) and BCLC C (advanced) stages of HCC include heterogeneous populations, with variations in tumour burden, liver function and clinical features such as performance status, macrovascular invasion and extra-hepatic spread. The American Association of the Study of Liver Diseases (AASLD) guidelines on the diagnosis, staging and management of HCC acknowledges this heterogeneity by stating that patients in both BCLC B and BCLC C groups include those with locally advanced or metastatic disease that is not amenable to curative surgical treatment, i.e. unresectable HCC (24). Clinically, the prognosis for these patients is typically very poor given that the tumour has grown or metastasised to the extent that surgical resection is not feasible. Up to 80% of patients first presenting with HCC have advanced, unresectable or metastatic disease because of the late appearance of symptoms (20, 25). In addition, up to 70% of patients who initially undergo potentially curative procedures (surgical resection, transplantation or ablation) will have recurrent disease within 5 years (25). HCC patients with unresectable disease have few approved systemic treatments and most have significant liver damage which can further limit therapy options. Their prognosis is dismal, with rapid progression and short overall survival (OS). Median survival is still less than one year: 4–8 months if untreated and 6–15 months with sorafenib treatment (26-29).

Several factors predicting outcome of HCC have been identified including tumour pathological factors, hepatitis status, alpha-fetoprotein levels and the patient's functional liver reserve (even for patients without HCC, the one- and two-year survival rates decline significantly with an increase in Child-Pugh score (30)). The presence or absence of vascular invasion is strongly correlated with disease progression and prognosis (31, 32); the risk of recurrence following orthotopic liver transplantation in patients with micro- or

macrovascular invasion increases 4.4 fold and 15-fold respectively compared with patients with no vascular invasion (33).

As many patients with HCC present late with multiple symptoms, advanced disease and limited survival, health-related quality of life (HRQoL) is a very important aspect in their general wellbeing. The complications and extra-hepatic manifestations of advanced disease in particular, have been shown to significantly affect HRQoL, including physical, emotional, and functional well-being (34). There is a paucity of published evidence reporting HRQoL data in HCC patients however, findings from a recent large-scale, global survey demonstrated the high burden that HCC has on patients' daily lives, including their mood, energy levels, ability to exercise and work and relationships with family and friends (35). The impact of the side effects related to late-stage treatment on QoL, specifically sorafenib, indicates the need for additional treatment options that focus on the maintenance of, if not improvement of HRQoL.

B.1.3.2 Current treatment practice

According to expert clinical advice obtained by Roche at a clinical advisory board meeting in February 2020, the main goals of treatment are to prolong survival and slow the deterioration in quality of life. Initial treatment choices are made on an individual patient basis, with patients preferring treatments that cause greater shrinkage of tumours, with fewer side effects and preserve/improve HRQoL (36).

First-line unresectable HCC treatment

Clinical experts confirmed to Roche that in UK clinical practice, 15–20% of unresectable, BCLC B (intermediate) patients receive an average of two rounds of transarterial chemoembolisation (TACE), and only upon progression would patients be referred for systemic treatments, although they acknowledged that by the time the patient had been referred, 40–50% would no longer be well enough to receive systemic therapy (36). It should be noted that Bruix et al. state that TACE is not suitable for all patients with intermediate-stage HCC and that its use should be restricted to patients with solitary or limited multinodular HCC with preserved liver function (37). UK clinical experts also advised that there is considerable disparity around the country in terms of TACE practice and the timing of referral for systemic treatment, with treatment decisions made on an individual basis at multidisciplinary team meetings (36).

Systemic treatment options for patients with unresectable disease remain very limited. Prior to the approval of sorafenib, there was no globally approved systemic treatment for these patients. Sorafenib, an oral multikinase inhibitor, was approved in 2007 by the US FDA and

EMA and is currently considered the global standard of care (SoC) for the first-line treatment of patients with advanced HCC. NICE recommends sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment (38).

Sorafenib has demonstrated a survival benefit of sorafenib vs. placebo of 2–3 months in two large, randomised Phase III trials (26, 27). However, sorafenib can be very difficult to tolerate as dose reductions and drug discontinuations due to adverse events (AEs) (e.g. diarrhoea, fatigue, infection, hand foot skin reaction) are common (39, 40).

Since the approval of sorafenib, there have been a number of Phase III trial failures in first-line HCC in head-to-head comparisons with sorafenib. Recently, lenvatinib was shown to be non-inferior to sorafenib in terms of OS in a Phase III study (REFLECT) (41) and thus does not offer any further survival benefit over sorafenib. Lenvatinib was approved in 2018 by the FDA and EMA for use in the same population as sorafenib and is now available in the UK for patients who cannot tolerate sorafenib (NICE TA551 (42)).

With the addition of just one new treatment option for unresectable or advanced HCC which did not improve OS, the treatment standard has remained largely unchanged for over a decade, highlighting the ongoing high unmet medical need for more efficacious, better tolerated treatments for patients with unresectable HCC.

Second-line unresectable HCC treatment

Only one systemic therapy has been approved by NICE for previously treated advanced HCC - regorafenib is recommended as an option for treating advanced unresectable HCC in adults who have had sorafenib (NICE TA555) (43). Advice obtained from UK clinical experts confirmed that only 20–25% of unresectable HCC patients might receive second-line therapy, with treatment decisions based on numerous factors including prior systemic therapy, performance status and liver function. All patients would receive best supportive care, with an estimated 10–15% of patients enrolling into clinical trials. Of the patients eligible for second-line therapy, 15–25% would receive regorafenib providing they had previously received and tolerated sorafenib; there are no second-line systemic therapy options for patients who had previously received lenvatinib. UK clinical experts confirmed that chemotherapy is seldom used as a second-line treatment option for patients with unresectable HCC due to limited survival benefit (36, 44).

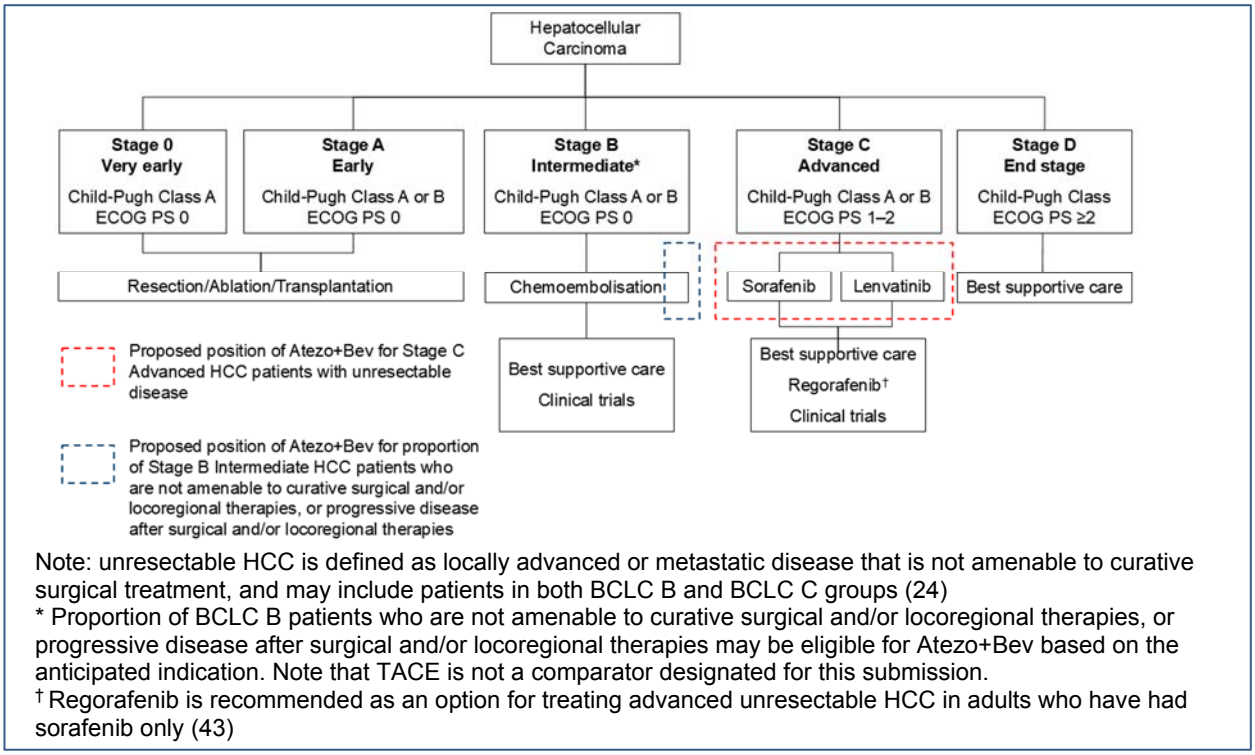
B.1.3.3 Proposed position of atezolizumab+bevacizumab in the treatment pathway

The combination of anti-PD-L1 and anti-vascular endothelial growth factor (VEGF) therapies has shown synergy and positive outcomes in Phase I to III studies (45), therefore the

combination of atezolizumab and bevacizumab provides an innovative treatment option to target the highly vascularised HCC tumour. This is based on the rationale that bevacizumab may enable efficient priming and activation of T-cell responses against tumour antigens, and normalise the tumour vasculature, thereby increasing infiltration of T-cells into the tumour. Bevacizumab may also reprogramme the tumour microenvironment from immune suppressive to immune permissive (46-48) and therefore may enhance the effect of a checkpoint inhibitor. See section B.2.12 for further details.

The proposed treatment pathway and position of atezolizumab in combination with bevacizumab (referred to hereafter as Atezo+Bev) for the treatment of adult patients with unresectable HCC who have not received prior systemic therapy is summarised below. Note that in addition to Stage C advanced patients, the eligible population may also include unresectable Stage B intermediate patients who are not amenable to locoregional therapy and/or those with progressive disease, providing they are deemed fit enough for systemic therapy. Based on the anticipated marketing authorisation, Atezo+Bev combination will provide an innovative treatment option for adult patients with unresectable HCC who have not received prior systemic therapy.

Figure 1: Proposed positioning of Atezo+Bev in treatment pathway for adult patients with unresectable HCC



Note: unresectable HCC is defined as locally advanced or metastatic disease that is not amenable to curative surgical treatment, and may include patients in both BCLC B and BCLC C groups (24)
* Proportion of BCLC B patients who are not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies may be eligible for Atezo+Bev based on the anticipated indication. Note that TACE is not a comparator designated for this submission.
† Regorafenib is recommended as an option for treating advanced unresectable HCC in adults who have had sorafenib only (43)

B.1.4 Equality considerations

No equality issues related to the use of Atezo+Bev have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Table 4: Clinical effectiveness evidence

Study	YO40245, IMbrave150 (NCT03434379) (49) **Study publications:** • Primary analysis results (ESMO ASIA) (50) • Patient-reported outcomes (ASCO GI) (51) • Clinical study report (52)				
Study design	Phase III, open-label, multicentre, global, randomised study				
Population	• Patients with untreated locally advanced or metastatic and/or unresectable HCC • Child-Pugh class A • At least one measurable (per RECIST v1.1) untreated lesion • ECOG PS 0–1				
Intervention(s)	Atezolizumab in combination with bevacizumab (Atezo+Bev)				
Comparator(s)	Sorafenib				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	IMbrave150 is a Phase III trial providing efficacy and safety evidence for the combination of Atezo+Bev in patients with untreated, unresectable or advanced HCC. Data from IMbrave150 (clinical cut-off date 29 Aug 2019) were used to inform the efficacy and safety of Atezo+Bev in the economic model.				
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.				
All other reported outcomes	• Time to progression • Patient-reported outcomes				

ASCO GI, American Society of Clinical Oncology; Atezo+Bev, atezolizumab in combination with bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

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

Unless otherwise stated, information on the IMbrave150 study was sourced from the clinical study report and protocol (52, 53).

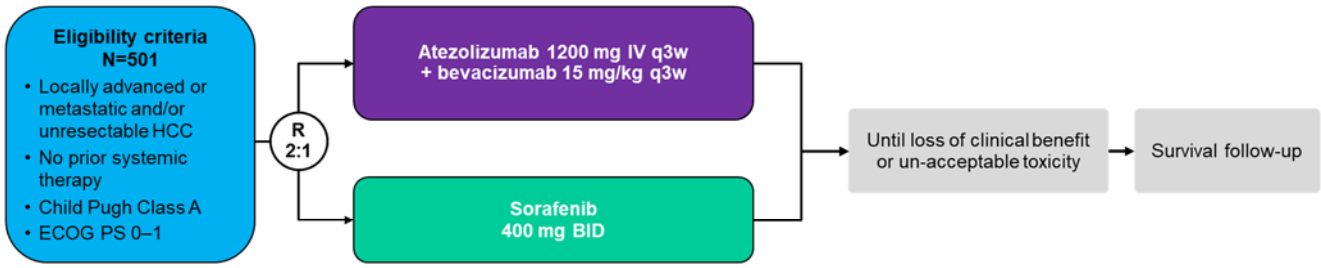
B.2.3.1 Study design

IMbrave150 is an ongoing Phase III, randomised, multicentre, open-label study designed to evaluate the efficacy and safety of Atezo+Bev versus sorafenib in patients with locally advanced or metastatic and/or unresectable HCC who had not received prior systemic treatment. The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the following sections of the protocol.

This study aimed to enrol approximately 480 patients across all sites in the global enrolment phase, randomised in a 2:1 ratio to one of two treatment arms:

- Atezo+Bev: (atezolizumab 1200 mg IV infusions, three weekly dosing [Q3W] + bevacizumab 15 mg/kg Q3W)
- Sorafenib (400 mg oral, twice per day [BID], continuously)

Figure 2: IMbrave150 study design schema



[a]Japan is included in rest of world. [b]Time from randomisation to first decrease from baseline of ≥10 points maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks. [c]Time from randomization to the first increase from baseline of ≥ 10 points in the symptom scales maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.

Patients were to receive atezolizumab and/or bevacizumab or sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the Investigator after an integrated assessment of radiographic and biochemical data, and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). In the absence of unacceptable toxicity, patients who met criteria for disease progression per RECIST v1.1 while receiving atezolizumab and/or bevacizumab or sorafenib were permitted to continue the study treatment if they met all of the following criteria:

- Evidence of clinical benefit, as determined by the Investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease

- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients randomised to the Atezo+Bev arm who transiently withheld or permanently discontinued either atezolizumab or bevacizumab were to continue on single-agent therapy as long as they were experiencing clinical benefit in the opinion of the Investigator and after discussion with the Medical Monitor (i.e., patients who transiently withheld or permanently discontinued bevacizumab for adverse effects could continue atezolizumab monotherapy and vice versa).

An independent Data Monitoring Committee (iDMC) was established to evaluate safety data during the study on a periodic basis (approximately every 6 months) until the time of the primary PFS and first OS interim analysis. No efficacy interim analyses were conducted by the iDMC.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date when safety follow-up is received from the last patient, whichever occurs later. The study is therefore still ongoing.

B.2.3.2 Summary of study methodology

	IMbrave150 (NCT03434379)
Settings and locations of data collection	501 patients were enrolled at 111 study sites in 17 countries/regions: **Countries, number of patients (centres)** • China, mainland 78 (15) • United States 74 (19) • Japan 61 (13) • Republic of Korea 47 (6) • France 42 (10) • Taiwan 41 (5) • Hong Kong 18 (2) • Russian Federation 24 (2) • Poland 23 (5) • Italy 17 (6) • Singapore 17 (2) • Germany 16 (7) • United Kingdom 13 (4) • Spain 11 (5) • Australia 9 (4) • Canada 5 (4) • Czech Republic 5 (2)

Trial design	Phase III, multicentre, open-label randomized study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic and/or unresectable HCC.
Eligibility criteria	**Inclusion criteria** • Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/cytology or clinically by American Association for the Study of Liver Diseases criteria in cirrhotic patients • Disease that was not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies • No prior systemic therapy (including systemic investigational agents) for HCC • Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolisation, transarterial embolisation, etc.) were eligible provided the target lesion(s) had not been previously treated with local therapy or the target lesion(s) within the field of local therapy had subsequently progressed in accordance with RECIST v1.1. • Child-Pugh class A within 7 days prior to randomisation • Adequate haematologic and end organ function within 7 days prior to randomisation o Serum bilirubin ≤3x ULN o Serum albumin ≥28 g/L (2.8 g/dL) without transfusion o For patients not receiving therapeutic anticoagulation: INR or aPTT ≤2x ULN • Documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test • At least one measurable (per RECIST v1.1) untreated lesion • ECOG PS of 0 or 1 within 7 days prior to randomisation • For patients with active HBV: o HBV DNA <500 IU/mL obtained within 28 days prior to initiation of study treatment, and o Anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study **Exclusion criteria** • History of malignancy other than HCC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer • Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC • Moderate or severe ascites • History of hepatic encephalopathy • Co-infection of HBV and HCV Patients with a history of HCV infection who were negative for HCV RNA by PCR were considered non-infected with HCV.

	• Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrolment. Patients who have undergone an EGD within 6 months of prior to initiation of study treatment do not need to repeat the procedure • A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment **Exclusion criteria related to medications** Patients who met any of the following criteria were excluded from study entry: • Prior allogeneic stem cell or solid organ transplantation • History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins • Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulation • Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogues) or St. John's wort • Treatment with any agent that may interfere with the immunostimulatory nature of atezolizumab • All patients had to meet several bevacizumab-specific criteria based on the known safety profile of this drug. These criteria excluded patients with evidence of or a possibility for bleeding issues, uncontrolled hypertension, and/or gastrointestinal perforations
Trial drugs and concomitant medications	**Trial drugs** • **Atezolizumab:** Intravenous (IV), 1200 mg on Day 1 of each 21-day cycle (every three weeks) until investigator-assessed unacceptable toxicity or loss of clinical benefit • **Bevacizumab:** Intravenous (IV), 15 mg/kg on Day 1 of each 21-day cycle • **Sorafenib:** 400 mg (2–200mg tablets), PO, BID, starting on Day1 of Cycle1 **Dose modifications** • No dose modification for **atezolizumab** or **bevacizumab** was allowed • Temporary interruption or dose modification of **sorafenib** was allowed for the management of toxicities. When dose reduction was necessary, the sorafenib dose was reduced to 400 mg once daily. If additional dose reduction was required, sorafenib was reduced to a single 400 mg dose every other day. Once a dose reduction was made, the sorafenib dose could be re-escalated at the discretion of the investigator if the patient had been on a stable dose for 3 weeks or more without further toxicities requiring dose modification. **Concomitant medications** **Permitted concomitant medications:** • Oral contraceptives • Hormone-replacement therapy • Inactivated influenza vaccines

	• Megestrol acetate administered as an appetite stimulant • Mineralocorticoids • Corticosteroids • Low-dose aspirin • Prophylactic use of low-dose anticoagulation, unfractionated heparin or low molecular weight heparin • Palliative radiotherapy • Radiotherapy to the brain • Other local therapy (surgery, stereotactic radiosurgery, radiofrequency ablation) **Prohibited concomitant medications:** • Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), was prohibited for various time periods prior to starting study treatment, depending on the agent and during study treatment, until disease progression was documented and the patient had discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances • Investigational therapy was prohibited within 28 days prior to initiation of study treatment and during study treatment • Live, attenuated vaccines were prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the last dose of atezolizumab • Systemic immunostimulatory agents were prohibited within 4 weeks or 5 half-lives of the drug (whichever was longer) prior to initiation of study treatment and during study treatment • Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) • Full dose anticoagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy • Warfarin or Coumadin-like products • Concomitant chronic use of NSAIDs
Primary outcome	**Co-primary endpoints:** • OS (time from randomisation to death due to any cause • PFS (time from randomisation to the first documented disease progression as determined by an IRF according to RECIST Version 1.1 or death from any cause [whichever occurred first]).
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** • PFS, ORR, DOR, and TTP determined by the investigator according to RECIST v1.1 • ORR, DOR and TTP determined by an IRF according to RECIST v1.1 • PFS, ORR, DOR and TTP determined by an IRF according to HCC mRECIST **Exploratory objectives:** • To evaluate the PROs of Atezo+Bev versus sorafenib by the following endpoint: • TTD of selected symptoms per EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires

	• To evaluate potential effects of ADAs to atezolizumab on the efficacy, safety, and pharmacokinetics of atezolizumab **Safety endpoints:** • Safety and tolerability of atezolizumab administered in combination with bevacizumab compared with sorafenib monotherapy **Patient-reported outcomes:** • TTD of physical functioning, role functioning and global health status/quality of life per EORTC QLQ-C30 questionnaire
Pre-planned subgroups	**Pre-planned subgroup analyses** • Predefined subgroups based on key baseline demographics and HCC disease characteristics, including stratification factors

ADA, anti-drug antibodies; BID, twice daily; DNA, deoxyribonucleic acid; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGD, esophagogastroduodenoscopy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalised ratio; IRF, Independent Review Facility; IV, intravenous; NSAID, non-steroidal anti-inflammatory; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PCR, polymerase chain reaction; PO, oral; PRO, patient-reported outcomes; (m)RECIST, (modified) response evaluation criteria in solid tumours; RNA, ribonucleic acid; TTD, time to deterioration; TTP, time to progression; ULN, upper limit of normal

B.2.3.3 Patient demographics and baseline characteristics

Patient demographics were generally well balanced between the two treatment arms in the ITT population. The patient population was predominantly Asian (56.7%) or White (34.9%), male (82.6%), and had a median age of 65.0 years. At baseline, an ECOG PS of 0 and 1 was reported for 62.3% and 37.7% of patients, respectively.

The primary HCC aetiology was HBV (47.9%) followed by non-viral and HCV (30.5% and 21.6%, respectively). At baseline, the majority of patients presented with advanced stage disease (50.3%, American Joint Committee on Cancer tumour size, lymph nodes affected, metastases [AJCC TNM] Stage IVB; 81.6% BCLC Stage C) and all but one patient (99.8%) were scored as Child-Pugh class A. The single Child-Pugh Class B7 patient was incorrectly scored as Child-Pugh Class A at the time of randomisation into the Atezo+Bev arm and was reported as a protocol deviation.

At screening, alpha-fetoprotein (AFP) levels of ≥400 ng/mL were observed in 37.3% of patients in the ITT population. Other negative prognostic factors for HCC common in these patients included the presence of macrovascular invasion (MVI; 39.9%) and extrahepatic spread (EHS; 60.9%). In total, 75.4% of patients presented with MVI and/or EHS at baseline. The median baseline sum of target lesion diameter for the ITT population as assessed by the Investigator was 74.0 mm (range: 10.0–321.0 mm). Overall, these characteristics are reflective of an advanced HCC population.

Table 5: IMbrave150 - key demographic and baseline disease characteristics

	Atezo+Bev n=336	Sorafenib n=165	All patients N=501
Key baseline demographics			
Median age, years	64.0	66.0	65.0
Male, n (%)	227 (82.4)	137 (83.0)	414 (82.6)
Race, n (%)			
Asian	188 (56.0)	96 (58.2)	284 (56.7)
White	123 (36.6)	52 (31.5)	175 (34.9)
Geographic region			
Asia (exc Japan)	133 (39.6)	68 (41.2)	201 (40.1)
Rest of World	203 (60.4)	97 (58.8)	300 (59.9)
ECOG PS, n (%)			
0	209 (62.2)	103 (62.4)	312 (62.3)
1	127 (37.8)	62 (37.6)	189 (37.7)
PD-L1 category 1, n (%)	n=124	n=58	n=182
TC and IC <1%	45 (36.6)	25 (43.1)	70 (38.5)
TC or IC ≥1%	79 (63.7)	33 (56.9)	112 (61.5)
PD-L1 category 2, n (%)	n=124	n=58	n=182
TC and IC <5%	78 (62.9)	41 (70.7)	119 (65.4)
TC or IC ≥5%	46 (37.1)	17 (29.3)	63 (34.6)
PD-L1 category 3, n (%)	n=124	n=58	n=182
TC and IC <10%	112 (90.3)	53 (91.4)	165 (90.7)
TC or IC ≥10%	12 (9.7)	5 (8.6)	17 (9.3)
HCC history and disease characteristics			
BCLC stage at study entry, n (%)			
A1	5 (1.5)	3 (1.8)	8 (1.6)
A4	3 (0.9)	3 (1.8)	6 (1.2)
B	52 (15.5)	26 (15.8)	78 (15.6)
C	276 (82.1)	133 (80.6)	409 (81.6)
Aetiology of HCC			
HBV	164 (48.8)	76 (46.1)	240 (47.9)
HCV	72 (21.4)	36 (21.8)	108 (21.6)
Non-viral	100 (29.8)	53 (32.1)	153 (30.5)
Extrahepatic spread (EHS) present at study entry, n (%)			
Yes	212 (63.1)	93 (56.4)	305 (60.9)
Macrovascular invasion (MVI) present at study entry, n (%)			
Yes	129 (38.4)	71 (43.0)	200 (30.9)
EHS and/or MVI present at study entry			
Yes	258 (76.8)	120 (72.7)	378 (75.4)
Child Pugh category	n=334	n=165	n=499
A5	239 (71.6)	121 (73.3)	360 (72.1)
A6	94 (28.1)	44 (26.7)	138 (27.7)
A7	1 (0.3)	0	1 (0.2)
Median baseline sum of target lesion diameter, mm (range)	71.8 (10.0–321.0)	83.2 (10.0–312.0)	74.0 (10.0–321.0)
AFP category at screening			
<400 ng/mL	210 (62.5)	104 (63.0)	314 (62.7)
≥400 ng/mL	126 (37.5)	61 (37.0)	187 (37.3)
Varices at time of enrolment, n (%)			
Yes	88 (26.2)	43 (26.1)	131 (26.1)

Type of prior local therapy, n (%)	n=161	n=85	n=246
Radiofrequency ablation	47 (14.0)	24 (14.5)	71 (14.2)
Transarterial chemoembolisation	130 (38.7)	70 (42.4)	200 (39.9)
Prior cancer radiotherapy, n (%)			
Yes	34 (10.1)	17 (10.3)	51 (10.2)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MVI, macrovascular invasion; PD-L1, programmed death-ligand 1

The participant flow and details on patient study and treatment withdrawal for IMbrave150 is presented in Appendix D.

More patients in the sorafenib arm compared with patients in the Atezo+Bev arm received follow-up HCC systemic therapy (44.2% vs. 20.5%, respectively), which is consistent with the higher frequency of patients from the sorafenib arm having discontinued study treatment at the time of the clinical cutoff date.

The most common follow-up systemic therapy for patients was tyrosine kinase inhibitors (26.1% and 18.8% for the sorafenib and Atezo+Bev arms, respectively). The second most common follow-up systemic therapy for patients receiving treatment with sorafenib was immunotherapy (18.8%) and for patients receiving treatment with Atezo+Bev was immunotherapy and chemotherapy (1.2% each) (see Appendix D).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Unless otherwise stated, information on the IMbrave150 study was sourced from the clinical study report and protocol.

Determination of sample size

Approximately 480 patients were planned for enrolment during the global enrolment phase of the IMbrave150 study. The sample size of the study was determined based on the number of deaths required from the patients randomized in the global enrolment phase to demonstrate efficacy in terms of OS.

Co-primary endpoint: overall survival

To detect an improvement in OS using a log-rank test at a two-sided significance level of 0.048, approximately 312 deaths were required at the final OS analysis to achieve an overall 80% power assuming a target hazard ratio (HR) of 0.71 (median OS improvement vs. control of 4.9 months). The minimum detectable difference (MDD) of OS is an HR of 0.783 (median OS improvement vs. control of 3.3 months). This analysis is expected to occur approximately 33 months after first patient in (FPI).

The estimates of the number of events required to demonstrate efficacy in the ITT population with regard to OS were based on the following assumptions:

- Patients were to be randomised to the Atezo+Bev and Sorafenib arms in a 2:1 ratio
- OS followed a one-piece exponential distribution
- The median OS in the control arm was to be 12 months
- The stopping boundaries of two interim analyses and the final analysis of OS were to use the O'Brien-Fleming boundaries approximated using the Lan-DeMets method
- The dropout rate was to be 5% for the Atezo+Bev arm and 10% for the Sorafenib arm over 12 months for OS
- The recruitment of approximately 480 patients was to take place over approximately 10 months

Co-primary endpoint: progression-free survival by IRF-assessment per RECIST v1.1

To detect an improvement in IRF-PFS using a log-rank test at a two-sided significance level of 0.002, approximately 308 events were required for the primary PFS analysis to achieve approximately 97% power with a target HR of 0.55 (median PFS improvement vs. control of 3.3 months). The MDD was a PFS HR of 0.688 (median PFS improvement vs. control of 1.8 months). The clinical cutoff date for this primary PFS analysis was expected to occur approximately 16 months after the first patient was enrolled in the study.

The estimates of the number of events required to demonstrate efficacy in the ITT population with regard to PFS were based on the following assumptions:

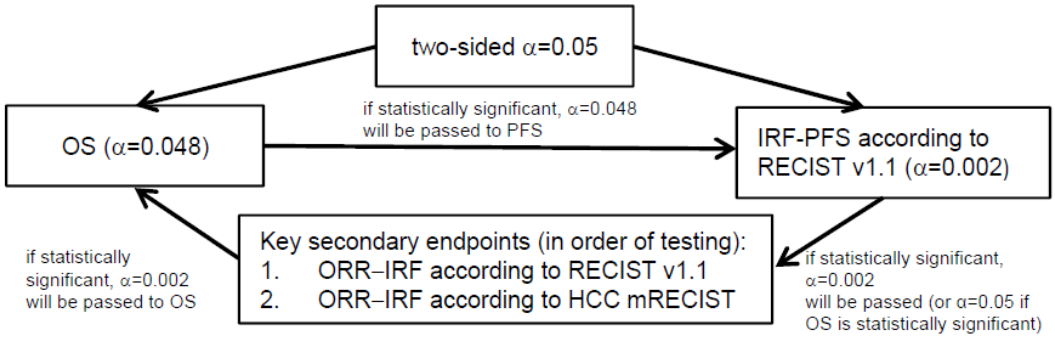
- Patients were to be randomised to the Atezo+Bev and Sorafenib arms in a 2:1 ratio
- OS followed a one-piece exponential distribution
- The median PFS in the control arm was to be 4 months
- The dropout rate was to be 5% for the Atezo+Bev arm and 10% for the Sorafenib arm over 12 months for PFS
- The recruitment of approximately 480 patients was to take place over approximately 10 months

Overall Type I error control

The overall type I error rate for this study was strongly controlled at a two-sided significance level of 0.05, which was split into a two-sided significance level of 0.048 for the testing of OS and a two-sided significance level of 0.002 for the testing of PFS initially. If OS was statistically significant, the allocated two-sided significance level of 0.048 could be recycled to PFS such that PFS could be tested at a two-sided significance level of 0.05 instead of 0.002. If the analysis of PFS was statistically significant, then the two-sided significance level of 0.002 (or 0.05 if OS was statistically significant) was recycled to key secondary endpoints

(IRF-assessed ORR according to RECIST v1.1 and HCC mRECIST) for hierarchical testing. If PFS and both key secondary endpoints were statistically significant at a two-sided significance level of 0.002, then OS could be tested at a two-sided significance level of 0.05 instead of 0.048.

Figure 3: Overview of the Type I error control for co-primary and key secondary endpoints



HCC mRECIST, hepatocellular carcinoma-specific modified Response Evaluation Criteria in Solid Tumours; IRF, independent review facility; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; IRF-PFS, progression-free survival as assessed by Independent Review Facility

If the co-primary endpoint of IRF-PFS according to RECIST v1.1 was statistically significant, then ORR-IRF according to RECIST v1.1 and ORR-IRF according to HCC mRECIST were to be hierarchically tested.

These key secondary endpoints were to be tested at a two-sided alpha of 0.002 if the co-primary endpoint PFS-IRF per RECIST v1.1 had reached statistical significance at a two-sided alpha of 0.002, but OS had not reached statistical significance at the first interim analysis that was to be conducted at the time of the primary PFS analysis. On the other hand, if both co-primary endpoints of PFS and OS have reached statistical significance at the specified two-sided alpha level at the time of the primary PFS analysis, key secondary endpoints were to be tested at a two-sided alpha of 0.05.

Analysis timing

There were no interim analyses planned for the co-primary endpoint of IRF-PFS in this study.

The primary analysis of IRF-PFS per RECIST v1.1 was to be conducted when approximately 308 PFS events had occurred in the ITT population. The clinical cutoff date for this primary PFS analysis was expected to occur approximately 16 months after the first patient was enrolled in the study.

Two interim analyses were planned for OS. The first interim analysis was to be performed at the time of the primary PFS analysis. It was anticipated that at that time, approximately 172 deaths would have been observed. The respective MDD OS hazard ratio was 0.633 (median

OS improvement vs. control of 6.9 months). The second OS interim analysis is planned to be conducted when approximately 243 deaths have been accumulated, estimated to occur approximately 24 months after the first patient was enrolled in the study. The respective MDD OS hazard ratio is 0.728 (median OS improvement vs. control of 4.6 months).

The final OS analysis is planned after approximately 312 deaths in the ITT population, which is expected to occur approximately 33 months after the enrolment of the first patient. The respective MDD OS hazard ratio is 0.783 (median OS improvement vs. control of 3.3 months).

Statistical hypothesis

Overall survival

Overall survival was defined as the time from the date of randomisation to the date of death from any cause.

The null and alternative hypotheses regarding OS can be phrased in terms of the survival functions SA(t) and SB(t) for Arm A (Atezo+Bev) and Arm B (sorafenib), respectively:

H0: $S_{OS\_A}(t) = S_{OS\_B}(t)$ versus H1: $S_{OS\_A}(t) \neq S_{OS\_B}(t)$

Progression-free survival

IRF-PFS was defined as the time from randomisation to the occurrence of disease progression as determined by IRF according to RECIST v1.1, or death from any cause, whichever occurred first.

The null and alternative hypotheses regarding IRF-PFS can be phrased in terms of the PFS functions SA(t) and SB(t) for Arm A (Atezo+Bev) and Arm B (sorafenib), respectively:

H0: $S_{PFS\_A}(t) = S_{PFS\_B}(t)$ versus H1: $S_{PFS\_A}(t) \neq S_{PFS\_B}(t)$

Efficacy analyses

Unless otherwise specified, efficacy analyses were conducted based on the ITT population, with geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and baseline AFP (<400 vs. ≥400 ng/mL) per IxRS at randomisation used in all stratified analyses.

Table 6: Efficacy outcome measures and analysis methodology

Outcome measure	Analysis methodology	Censoring/sensitivity analyses/subgroup analyses
Primary efficacy endpoints		
OS	Kaplan-Meier methodology, stratified log-rank test, and stratified Cox proportional hazards model. Stratification factors for OS were the same as for PFS. Treatment comparisons were to be conducted at the two-sided significance level of 0.048. If the null hypotheses of the PFS and key secondary endpoints testing were all rejected at a two-sided significance level of 0.002, OS was to be tested at a two-sided significance level of 0.05.	<u>Censoring</u> Data for patients who were alive at the time of the clinical cutoff date were censored at the last date they were known to be alive. Data for patients with no post-baseline information were censored at the date of randomisation. <u>Subgroup Analyses</u> Examination of consistency of OS including, but not necessarily limited to, demographic and baseline disease characteristics. OS data including the unstratified HR estimated from a Cox proportional hazards model and Kaplan-Meier estimates of median OS are displayed for each subgroup in a Forest plot.
PFS-IRF (per RECIST v1.1)	Kaplan-Meier methodology, stratified two-sided log-rank test, and stratified Cox proportional hazards model. Stratification factors (as per IxRS): • Geographic region (Asian exc. Japan vs. rest of world) • MVI and/or EHS (presence vs. absence) • Baseline AFP (<400 vs. ≥400 ng/mL). Treatment comparisons were to be conducted at the two-sided significance level of 0.002. If the null hypothesis of the OS testing was rejected at a two-sided significance level of 0.048, PFS was to be tested at the two-sided significance level of 0.05.	<u>Censoring</u> Data for patients who were alive and had not experienced PD at the time of the clinical cutoff date were to be censored at the date of the last tumour assessment on or prior to the clinical cutoff date. Data for patients with no post-baseline tumour assessment were to be censored at the date of randomisation. <u>Sensitivity analysis</u> If >5% of patients missed two or more consecutive tumour assessments scheduled immediately prior to the date of PD or death in any treatment arm, patients were censored at the last tumour assessment prior to the missed visits. <u>Subgroup analyses</u> Examination of consistency of PFS by IRF per RECIST v1.1 including, but not necessarily limited to, demographic and baseline disease characteristics. PFS data including the unstratified HR estimated from a Cox proportional hazards model and Kaplan-Meier estimates of median PFS are displayed for each subgroup in a Forest plot

Secondary efficacy endpoints		
ORR-IRF (per RECIST v 1.1. and HCC mRECIST)	Two-sided Cochran Mantel Haenszel test was used for formal testing of confirmed ORR between the two treatment arms ORR-IRF was calculated for each treatment arm and the difference in ORR-IRF between treatment arms was computed. The 95% CI for ORR-IRF for each arm was derived using the Clopper Pearson method. The 95% CI for difference in ORR was computed by normal approximation. Objective responses, confirmation not required and confirmation required (CR or PR at two consecutive tumour assessments at least 28 days apart), were separately considered for the ORR analysis. Patients with no post-baseline tumour assessments were considered non-responders.	n/a
ORR-INV (per RECIST v 1.1)	Similar to the analysis methods described for ORR-IRF.	n/a
DOR-IRF (per RECIST v1.1 and HCC mRECIST) **DOR-INV** (per RECIST v1.1)	Similar to the analysis methods described for PFS-IRF. The analysis of DOR was based on a non-randomised subset of patients (patients who achieved an objective response); therefore, comparisons between treatment arms were to be made for descriptive purposes only.	<u>Censoring</u> Data for patients who were alive and who have not experienced PD at the clinical cutoff date were censored at the date of the last tumour assessment. If no tumour assessments were performed after the date of the first occurrence of a documented CR or PR, DOR was censored at the date of the first occurrence of a documented CR or PR.
PFS-IRF (per HCC mRECIST) **PFS-INV** (per RECIST v1.1)	Similar to the analysis methods described for PFS-IRF.	<u>Censoring</u> Data for patients who were alive and had not experienced PD at the time of the clinical cutoff date were censored at the date of the last tumour assessment on or prior to the clinical cutoff date. Data for patients with no post-baseline tumour assessment were censored at the date of randomisation.

TTP-IRF (per RECIST v1.1 and HCC mRECIST)] **TTP-INV** (per RECIST v1.1)	Similar to the analysis methods described for PFS-IRF.	Censoring Patients without tumour progression at clinical cutoff date were censored at the last tumour assessment date. Patients who had no post-baseline tumour assessment were censored at the date of randomisation.
PFS-IRF by baseline AFP (per RECIST v 1.1) **OS by baseline AFP**	Similar to the analysis methods described for PFS-IRF and OS Stratification factors used: • Geographic region (Asian exc. Japan vs rest of world) • MVI and/or EHS (presence vs absence)	Censoring Same as described for PFS-IRF and OS.
TTD in GHS/QoL, physical function or role function (per EORTC QLQ-C30)	The Kaplan-Meier methods used for the analysis of TTD are similar to those described for PFS-IRF.	Censoring Patients who did not have an observed deterioration prior to the clinical cutoff date or at discontinuation from study treatment or initiation of non-protocol anti-cancer therapy (NPT), were censored at the last available assessment date prior to or at the time of discontinuation from study treatment or initiation of NPT or the clinical cutoff date, whatever was earlier. Patients without a post-baseline assessment were censored at randomisation date.

AFP, alpha-fetoprotein; atezo, atezolizumab; BCLC, Barcelona Clinic Liver Cancer; bev, bevacizumab; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire for cancer; GHS/QoL, global health status/quality of life; HCC, hepatocellular carcinoma; HR, hazard ratio; INV, Investigator; IRF, independent review facility; ITT, intention to treat; MVI, macrovascular invasion; NPT, non-protocol anti-cancer therapy, ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; (m)RECIST, (modified) Response Evaluation Criteria in Solid Tumours; TTD, time to deterioration; TTP, time to progression.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trial was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D. A summary is presented below.

Table 7: Clinical effectiveness evidence quality assessment

Study question	IMbrave150 (NCT03434379)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A (open label study)
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Clinical effectiveness results of the relevant trials

The primary analysis presented in this submission is based on the final PFS and first interim analysis of OS, including the results for secondary and exploratory efficacy endpoints. At the time of the clinical cutoff date of 29 August 2019, 306 PFS events and 161 death events had occurred (median duration of survival follow up 8.6 moths) (50, 52).

B.2.6.1 Primary efficacy endpoints

Overall survival

The IMbrave150 study met its co-primary efficacy endpoint of OS at the time of the first interim analysis. There was a statistically significant and clinically meaningful improvement in OS (stratified HR: 0.58 [95% CI: 0.42, 0.79], log-rank p-value= 0.0006) with Atezo+Bev over sorafenib in the ITT population. The observed OS HR translated into a 42% reduction in the risk of death in the Atezo+Bev arm compared with sorafenib (50).

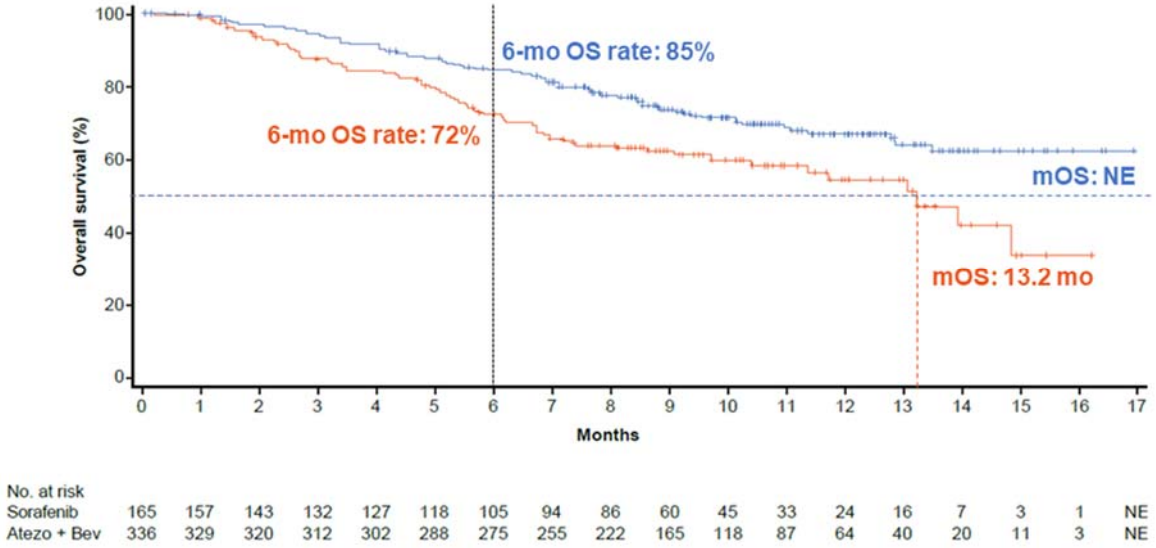
The Kaplan-Meier (KM) estimated median OS was 13.2 (95% CI: 10.4, NE) months in the sorafenib arm and was not reached in the Atezo+Bev arm. Of note, the KM curves demonstrated early separation in favour of the Atezo+Bev arm at only one month after randomisation. The 6-month OS event-free rate was higher in the Atezo+Bev arm (84.8% [95% CI: 80.9, 88.7]) compared with the sorafenib arm (72.2% [95% CI: 65.1, 79.4]).

Table 8: IMbrave150 – overall survival (ITT)

	Atezo+Bev n=336	Sorafenib n=165
Patients with event, n (%)	96 (28.6)	65 (39.4)
Median time to event, months (95% CI)	NE NE	13.2 (10.4, NE)
Stratified HR (95% CI) log-rank p value	0.58 (0.42, 0.79) p=0.0006	
Patients remaining event free at 6 months, % (95% CI)	84.8 (80.9, 88.7)	72.0 (65.1, 79.4)
Patients remaining event free at 12 months, % (95% CI)	67.2 (61.3, 73.1)	54.6 (45.2, 64.0)

NE, not estimable
CCOD: 29 August 2019

Figure 4: IMbrave150 – overall survival Kaplan-Meier curve



Progression-free survival (IRF-assessment per RECIST v1.1)

The IMbrave150 study also met its co-primary endpoint of PFS based on IRF-assessment per RECIST v1.1. A statistically significant and clinically meaningful improvement in PFS based on IRF-assessment per RECIST v1.1 was observed (stratified HR: 0.59; 95% CI: 0.47, 0.76; log-rank p-value <0.0001) with Atezo+Bev over sorafenib in the ITT population. The observed PFS HR translated into a 41% reduction in the risk of disease progression or death in the Atezo+Bev arm compared with the sorafenib arm (50).

The median PFS was longer in the Atezo+Bev arm (6.8 months, 95% CI: 5.7, 8.3) compared with the sorafenib arm (4.3 months, 95% CI: 4.0, 5.6), translating into an increase of 2.5 months in the Atezo+Bev arm.

The 6-month PFS event-free rate was higher in the Atezo+Bev arm (54.5% [95% CI: 49.1, 60.0]) compared with the sorafenib arm (37.2% [95% CI: 29.0, 45.3]).

The KM curves showed early separation at the time of the first tumour assessment in favour of the Atezo+Bev arm compared with the sorafenib arm.

Table 9: IMbrave150 – PFS (IRF-assessment per RECIST v1.1) (ITT)

	Atezo+Bev n=336	Sorafenib n=165
Patients with event, n (%)	197 (58.6)	109 (66.1)
Earliest contributing event, (%) Death Disease progression	 34 163	 29 80
Median time to event, months (95% CI)	6.8 (5.6, 8.3)	4.3 (4.0, 5.6)
Stratified HR (95% CI) log-rank p value	0.59 (0.47, 0.76) p<.0001	
Patients remaining event free at 6 months, % (95% CI)	54.5 (49.1, 60.0)	37.2 (29.0, 45.3)
Patients remaining event free at 12 months, % (95% CI)	34.0 (27.9, 40.1)	9.2 (0.0, 18.5)

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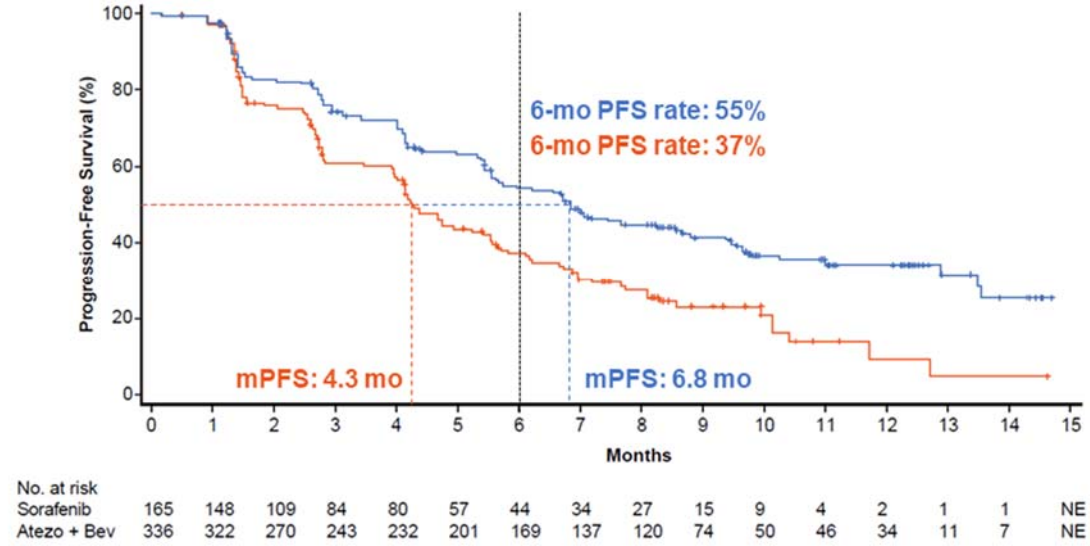
Figure 5: IMbrave150 – PFS (IRF-assessment per RECIST v1.1) Kaplan-Meier curve



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B.2.6.2 Secondary efficacy endpoints

Objective response rate based on IRF-assessment per RECIST v1.1

The secondary efficacy endpoint of confirmed ORR based on IRF-assessment per RECIST v1.1 showed a statistically significant and clinically meaningful improvement in the Atezo+Bev arm over the sorafenib arm (27.3% and 11.9%, respectively), with a 15.4% (95% CI; 7.9, 22.8; p-value <0.0001) difference in confirmed ORR in favour of Atezo+Bev (50, 52).

Notably, there were 18 patients (5.5%) with a confirmed complete response in the Atezo+Bev arm and no complete responders in the sorafenib arm.

Table 10: Confirmed ORR based on IRF-assessment per RECIST v1.1 (ITT Population with measurable disease at baseline)

	Atezo+Bev n=326	Sorafenib n=159
Responders, n (%) 95% CI	89 (27.3) (22.5, 32.5)	19 (11.9) (7.4, 18.0)
Stratified analysis Difference in ORR, % (95% CI) Odds ratio (95% CI) Cochran-Mantel-Haenszel p value	15.4 (7.9, 22.8) 2.90 (1.68, 5.01) p<0.0001	
Complete response, n (%) 95% CI	18 (5.5) (3.3, 8.6)	0 (0.0, 2.3)
Partial response, n (%) 95% CI	71 (21.8) (17.4, 26.7)	19 (11.9) (7.4, 18.0)
Stable disease, n (%) 95% CI	151 (46.3) (40.8, 51.9)	69 (43.4) (35.6, 51.5)
Progressive disease, n (%) 95% CI	64 (19.6) (15.5, 24.4)	39 (24.5) (18.1, 32.0)
Not evaluable, n (%) Missing, n (%)	8 (2.5) 14 (4.3)	14 (8.8) 18 (11.3)

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Objective response rate based on IRF-assessment per HCC mRECIST

The secondary efficacy endpoint of confirmed ORR based on IRF-assessment per HCC mRECIST also showed a statistically significant and clinically meaningful improvement in the Atezo+Bev arm over the Sorafenib arm (33.2% and 13.3%, respectively), with a 19.9% (95% CI; 12.1, 27.8; p-value <0.0001) difference in confirmed ORR in favour of Atezo+Bev (52).

Notably, there were 33 patients (10.2%) with a confirmed complete response in the Atezo+Bev arm vs. 3 patients (1.9%) with a confirmed complete response in the sorafenib arm.

Table 11: Confirmed ORR based on IRF-assessment per RECIST v1.1 (ITT Population with measurable disease at baseline)

	Atezo+Bev n=325	Sorafenib n=158
Responders, n (%) 95% CI	108 (33.2) (28.1, 38.7)	21 (13.3) (8.4, 19.6)
Stratified analysis Difference in ORR, % (95% CI) Odds ratio (95% CI) Cochran-Mantel-Haenszel p value	19.9 (12.1, 27.8) 3.39 (2.02, 5.71) p<0.0001	
Complete response, n (%) 95% CI	33 (10.2) (7.1, 14.0)	3 (1.9) (0.4, 5.5)
Partial response, n (%) 95% CI	75 (23.1) (18.6, 28.1)	18 (11.4) (6.9, 17.4)
Stable disease, n (%) 95% CI	127 (39.1) (33.7, 44.6)	66 (41.8) (34.0, 49.9)
Progressive disease, n (%)	66 (20.3)	40 (25.3)

95% CI	(16.1, 25.1)	(18.7, 32.8)
Not evaluable, n (%) Missing, n (%)	10 (3.1) 14 (4.3)	14 (8.9) 17 (10.8)

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Objective response rate based on Investigator-assessment per RECIST v1.1

The results of the confirmed ORR based on investigator-assessment per RECIST v1.1 were consistent with the confirmed ORR based on IRF-assessment per RECIST v1.1. The confirmed ORR was higher in the Atezo+Bev arm (86 patients: 25.6%) compared with the sorafenib arm (9 patients: 5.5%), with a 20.1% (95% CI; 13.8, 26.4) difference in confirmed ORR in favour of the Atezo+Bev arm (52).

Duration of response based on IRF-assessment per RECIST v1.1

Treatment with Atezo+Bev resulted in a prolonged DOR compared with sorafenib based on IRF-assessment per RECIST v1.1 (stratified HR: 0.23; 95% CI; 0.08, 0.70). Among the confirmed responders, more patients in the Atezo+Bev arm (86.5%) had ongoing responses by the cutoff date compared with the sorafenib arm (68.4%). The median DOR in confirmed responders was 6.3 months (95% CI; 4.7, NE) in the sorafenib arm and was not reached in the Atezo+Bev arm (52).

The 6-month event-free rate was higher in the Atezo+Bev arm (87.6%) compared with the sorafenib arm (59.1%).

Table 12: IMbrave150 – duration of confirmed response (IRF-assessment per RECIST v1.1) (confirmed responders)

	Atezo+Bev n=326	**Sorafenib n=159**
Patients included in analysis, n	89	19
Patients with event, n (%)	12 (13.5)	6 (31.6)
Earliest contributing event, (%) Death Disease progression	 5 7	 1 5
Median time to event, months (95% CI)	NE (NE)	6.3 (4.7, NE)
Stratified HR (95% CI) log-rank p value	0.23 (0.08, 0.70) p=0.0051	
Event free rate at 6 months, % (95% CI)	87.6 (79.9, 95.3)	59.1 (31.3, 86.6)
Event free rate at 12 months, % (95% CI)	79.2 (67.7, 90.8)	NE NE

NE, not estimable
CCOD: 29 August 2019

Duration of response based on IRF-assessment per HCC mRECIST

Treatment with Atezo+Bev resulted in a prolonged DOR compared with sorafenib based on IRF-assessment per HCC mRECIST (HR: 0.30; 95% CI; 0.12, 0.73). Among the confirmed responders, more patients in the Atezo+Bev arm (77.8%) had ongoing responses by the cutoff date compared with the sorafenib arm (61.9%). The median DOR in confirmed responders was 6.3 (95% CI; 4.86, NE) months in the sorafenib arm and was not reached in the Atezo+Bev arm (52).

The 6-month event-free rate was higher in the Atezo+Bev arm (82.3%) compared with the sorafenib arm (62.5%).

Table 13: IMbrave150 – duration of confirmed response (IRF-assessment per HCC mRECIST v1.1) (confirmed responders)

	Atezo+Bev n=325	**Sorafenib n=158**
Patients included in analysis, n	108	21
Patients with event, n (%)	24 (22.2)	8 (38.1)
Earliest contributing event, (%) Death Disease progression	 8 16	 1 7
Median time to event, months (95% CI)	NE (NE)	6.3 (4.9, NE)
Stratified HR (95% CI) log-rank p value	0.30 (0.12, 0.73) p=0.0048	
Event free rate at 6 months, % (95% CI)	82.3 (74.3, 90.2)	62.5 (38.3, 86.7)
Event free rate at 12 months, % (95% CI)	65.3 (52.8, 77.6)	NE NE

NE, not estimable
CCOD: 29 August 2019

Duration of response based on investigator-assessment per RECIST v1.1

Among the confirmed responders (Atezo+Bev: 86 patients [25.6%]), sorafenib: 9 patients [5.5%]), more patients in the Atezo+Bev arm (69 patients: 80.2%) had ongoing responses by the cutoff date compared with the sorafenib arm (6 patients: 66.7%) (HR: 0.59; 95% CI; 0.16, 2.15). The median DOR was 13.1 (95% CI; 13.1, NE) months in the Atezo+Bev arm and not reached in the sorafenib arm (52).

The 6-month event-free rate was higher in Atezo+Bev arm (83.5%) compared with the Sorafenib arm (63.5%).

Progression-free survival (IRF-assessment per HCC mRECIST)

In the analysis of PFS based on the IRF-assessment per HCC mRECIST, Atezo+Bev numerically prolonged PFS with a 41% reduction in the risk of disease progression or death compared to sorafenib (stratified HR: 0.59; 95% CI: 0.46, 0.74).

A clinically meaningful longer median PFS was observed in the Atezo+Bev arm (6.8 months; 95% CI: 5.7, 7.7) compared with the sorafenib arm (4.2 months; 95% CI: 4.0, 5.5) (52).

Table 14: IMbrave150 – PFS (IRF-assessment per HCC mRECIST) (ITT)

	Atezo+Bev n=336	**Sorafenib n=165**
Patients with event, n (%)	199 (59.2)	111 (67.3)
Earliest contributing event, (%) Death Disease progression	 35 164	 29 82
Median time to event, months (95% CI)	6.8 (5.7, 7.7)	4.2 (4.0, 5.5)
Stratified HR (95% CI) log-rank p value	0.59 (0.46, 0.74) p<0.0001	
Patients remaining event free at 6 months, % (95% CI)	54.3 (48.9, 59.8)	36.4 (28.3 44.6)
Patients remaining event free at 12 months, % (95% CI)	33.4 (27.4, 39.5)	8.5 (0.0, 17.1)

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Progression-free survival (Investigator-assessment per RECIST v1.1)

The PFS results by investigator-assessment per RECIST v1.1 were consistent with those seen for the IRF-assessment per RECIST v1.1, supporting the observed PFS benefit with Atezo+Bev compared with sorafenib.

A lower proportion of patients experienced PFS events in Atezo+Bev arm (58.9%) compared with the sorafenib arm (79.4%). Atezo+Bev numerically prolonged PFS with a 55% relative risk reduction compared to sorafenib (HR: 0.45; 95% CI: 0.36, 0.57).

A clinically meaningful longer median PFS was observed in the Atezo+Bev arm (7.1 months; 95% CI: 5.7, 8.4) compared with the sorafenib arm (2.9 months; 95% CI: 2.8, 4.2) (52).

Time to progression (IRF-assessment per RECIST v1.1)

At the time of the clinical data cutoff date, 163 patients (48.5%) in the Atezo+Bev arm and 80 patients (48.5%) in the sorafenib arm had progressed based on IRF-assessment per RECIST v1.1.

The estimated median time to progression was longer in the Atezo+Bev arm at 8.6 months (95% CI: 6.8, 9.9) compared to 5.6 months (95% CI: 4.2, 7.7) in the sorafenib arm (stratified HR: 0.70 [95% CI: 0.53, 0.92]).

The 6-month event-free rate was higher in the Atezo+Bev arm (58.8%) compared with the sorafenib arm (47.6%) (52).

Time to progression (IRF-assessment per HCC mRECIST)

At the time of the clinical data cutoff date, 164 patients (48.8%) in the Atezo+Bev arm and 82 patients (49.7%) in the sorafenib arm had progressed based on IRF-assessment per HCC mRECIST.

The estimated median time to progression was longer in the Atezo+Bev arm at 8.3 months (95% CI: 6.8, 9.9) compared to 5.6 months (95% CI: 4.2, 7.7) in the sorafenib arm (stratified HR: 0.69 [95% CI: 0.52, 0.90]).

The 6-month event-free rate was higher in the Atezo+Bev arm (58.6%) compared with the sorafenib arm (32.5%) (52).

Time to progression (Investigator-assessment per RECIST v1.1)

At the time of the clinical data cutoff date, 167 patients (49.7%) in the Atezo+Bev arm and 114 patients (69.1%) in the sorafenib arm had progressed based on Investigator-assessment RECIST v1.1.

The estimated median time to progression was longer in the Atezo+Bev arm at 8.5 months (95% CI: 6.9, 9.9) compared to 4.0 months (95% CI: 2.8, 4.3) in the sorafenib arm (stratified HR: 0.44 [95% CI: 0.35, 0.57]).

The 6-month event-free rate was higher in the Atezo+Bev arm (58.9%) compared with the sorafenib arm (32.5%) (52).

B.2.6.3 Patient-reported outcomes

Compliance rates

In the ITT population, rates of compliance (defined by the number of patients who completed at least one question) for the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires in both treatment arms were ≥92% from baseline until Cycle 17. Compliance rates were ≥80% from Cycle 18 until Cycle 24, which was the last timepoint at which at least one patient remained in the ITT population in either arm. Of note, fewer than 50% of patients in the sorafenib arm remained in the ITT population by Cycle 5, and in the Atezo+Bev arm by Cycle 12 (36, 51).

PRO: secondary efficacy endpoints

Compared with sorafenib, Atezo+Bev resulted in a clinically meaningful delay in deterioration of patient-reported physical functioning (median TTD: 13.1 versus 4.9 months; stratified HR 0.53; 95% CI: 0.39, 0.73), role functioning (median TTD: 9.1 versus 3.6 months; stratified HR 0.62; 95% CI: 0.46, 0.84) and GHS/QoL (median TTD: 11.2 versus 3.6 months; stratified HR 0.63; 95% CI: 0.46, 0.85) (36, 51).

Table 15: IMbrave150 – summary of PRO secondary efficacy endpoints (ITT)

Endpoint/scale	Atezo+Bev n=336	Sorafenib n=165
Physical functioning per EORTC-QLQ-C30		
Patients with event, n (%)	114 (33.9)	64 (38.8)
Median TTD, months (95% CI)	13.1 (3.9, 6.8)	4.9 (3.5, 6.2)
Stratified HR (95% CI)	0.53 (0.39, 0.73)	
Role functioning per EORTC-QLQ-C30		
Patients with event, n (%)	136 (40.5)	69 (41.8)
Median TTD, months (95% CI)	9.1 (6.5, NE)	3.6 (2.2, 6.0)
Stratified HR (95% CI)	0.62 (0.46, 0.84)	
GHS/QoL per EORTC-QLQ-C30		
Patients with event, n (%)	132 (39.3)	66 (40.0)
Median TTD, months (95% CI)	11.2 (6.0, NE)	3.6 (3.0, 7.0)
Stratified HR (95% CI)	0.63 (0.46, 0.85)	

GHS/QoL, Global Health Status/quality of life; NE, not estimable; TTD, time to deterioration
CCOD: 29 August 2019

PRO: exploratory efficacy endpoints

Treatment with Atezo+Bev resulted in a clinically meaningful delay in deterioration of patient-reported appetite loss, diarrhoea, fatigue, pain, and jaundice compared with sorafenib (36, 51).

Table 16: IMbrave150 – summary of time to deterioration of patient-reported symptoms – EORTC QLQ-C30 and EORTC QLQ-HCC18 (ITT)

Scale (Questionnaire)	Median TTD, months (95% CI)		Stratified HR (95% CI)
	Atezo+Bev n=336	Sorafenib n=165	
Appetite Loss (EORTC QLQ-C30)	NE (4.14, NE)	7.62 (3.48, NE)	0.57 (0.40, 0.80)
Diarrhoea (EORTC QLQ-C30)	NE (9.69, NE)	4.44 (3.48, 5.59)	0.23 (0.16, 0.34)
Fatigue (EORTC QLQ-C30)	5.68 (4.30, 7.10)	2.10 (1.45, 4.83)	0.61 (0.46, 0.81)
Fatigue (EORTC QLQ-HCC18)	5.65 (4.30, 9.03)	2.14 (1.64, 2.83)	0.60 (0.45, 0.80)
Pain	9.72	2.79	0.46

(EORTC QLQ-C30)	(7.16, NE)	(2.14, 4.30)	(0.34, 0.62)
Pain (EORTC QLQ-HCC18)	NE (2.83, NE)	9.82 (4.27, NE)	0.65 (0.46, 0.92)
Pain (EORTC QLQ-HCC18)	10.55 (6.93, NE)	6.47 (5.55, NE)	0.76 (0.55, 1.07)

NE, not estimable; TTD, time to deterioration
CCOD: 29 August 2019

Proportion of patients with clinically meaningful deterioration – EORTC QLQ-C30 and EORTC QLQ-HCC18

At visits through Cycle 5, when fewer than 50% of sorafenib patients remained in the PRO-evaluable population, mean scores and mean score changes from baseline on patient-reported physical functioning, role functioning, GHS/QoL, appetite loss, diarrhoea, fatigue, pain, and jaundice favoured the Atezo+Bev arm over the sorafenib arm. Furthermore, a greater proportion of patients in the sorafenib arm experienced a clinically meaningful deterioration of patient-reported physical functioning, role functioning, GHS/QoL, appetite loss, diarrhoea, fatigue, pain, and jaundice compared with the patients in Atezo+Bev arm (36, 51).

B.2.7 Subgroup analysis

The generalisability of the observed treatment effect with Atezo+Bev relative to sorafenib on OS and IRF-assessment of PFS and ORR per RECIST v1.1 was investigated in predefined subgroups based on key baseline demographics and HCC disease characteristics, including stratification factors. It is important to note that the study was not powered to detect differences in the individual subgroups and that in some subgroups, the small sample size and the wide 95% CIs preclude the ability to draw definitive conclusions about the consistency of the treatment effect, therefore the results of these subgroups (see Appendix E) should be interpreted with caution (36, 50).

B.2.8 Meta-analysis

A meta-analysis was not feasible as only one study was identified.

B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to head trial evidence of Atezo+Bev vs. lenvatinib, an indirect treatment comparison (ITC) was necessary to enable a comparison for the purposes of this submission.

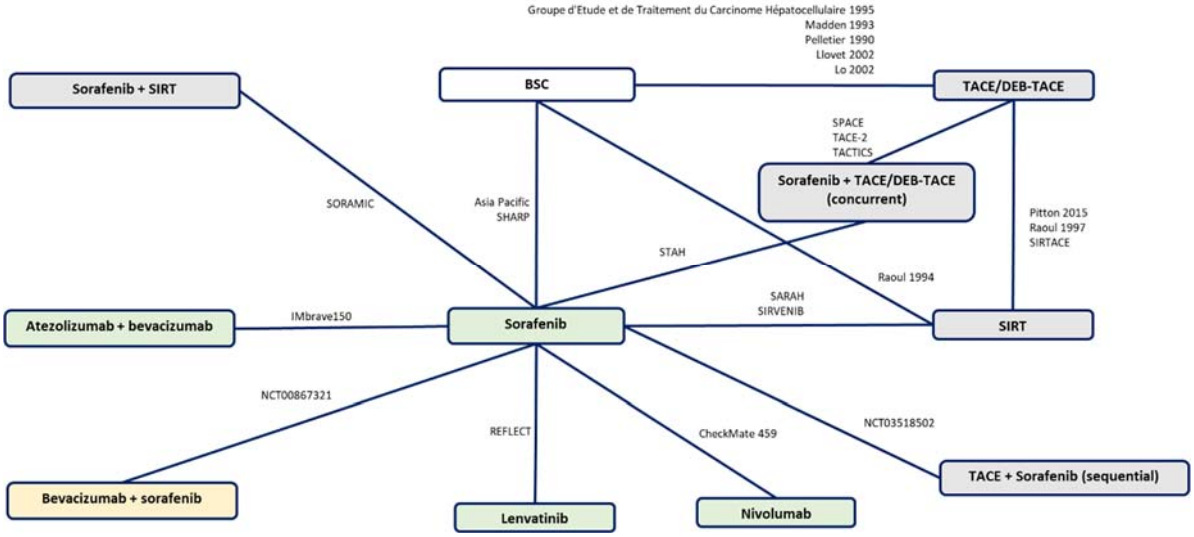
Systematic literature review (SLR)

A SLR was conducted to identify relevant studies to inform indirect comparisons between the interventions of interest. The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design, and is outlined in Appendix D. The SLR and feasibility was restricted to RCTs conducted in adult patients with locally advanced or metastatic and/or unresectable HCC and with no prior systemic therapy for HCC.

The comparators of interest included in the SLR reflect the comparators considered in the decision problem addressed in this submission (Section B.1.1). Please note that additional interventions were included in the eligibility criteria for the SLR, to account for comparator interventions in first-line HCC. However, these interventions are not included in the scope of this appraisal; the relevant studies were taken into account in the SLR for the purpose of informing future updates of the ITC network of evidence.

Twenty-three trials were identified (including IMbrave150 (54)), which formed a connected network for inclusion into the SLR. (Figure 6) (55-76).

Figure 6: Total connected evidence network



Note: Green node denotes level 1 intervention/comparator of interest; orange node denotes level 2 comparator of interest; grey node denotes level 3 comparator of interest; Abbreviations: BSC, best supportive care; DEB, drug-eluting bead; SIRT, selective Intern

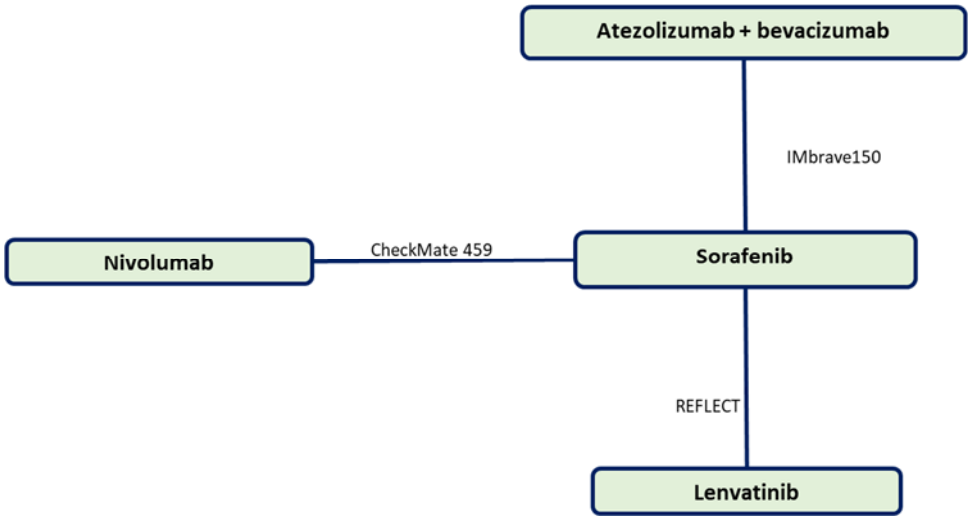
Following clinical input, it was determined at feasibility stage to categorise the comparators of interest for the analysis into three levels to allow for a step-wise assessment of the evidence:

- **Level 1**: current systemic therapies which are considered standard of care or alternative first-line options in HCC (indicated by green nodes: sorafenib, nivolumab and lenvatinib)

- **Level 2**: Any systemic therapies: All therapies listed in bullet 1 (indicated by green nodes) [Level 1], bevacizumab plus sorafenib (indicated by orange node) [Level 2]
- **Level 3**: studies that investigate any systemic or local therapies: All therapies listed in bullets 1 and 2 (indicated by green [Level 1] and orange nodes [Level 2], respectively), TACE/DEB-TACE (indicated by grey nodes) [Level 3], SIRT (indicated by grey nodes) [Level 3]

The final evidence networks for the ITC were restricted to RCTs conducted after the 2007 approval of sorafenib in the US that reported outcome data for OS and/or PFS; evidence networks including IMbrave150 were feasible for level 1 (54, 55, 61) (Figure 7). This included the comparators in the decision problem and was used for the base case analysis. Further details on the level 3 network is provided in appendix N.

Figure 7: Evidence network for level 1 comparators reporting OS and PFS



Base case ITC

The level 3 network includes five trials (54, 55, 57, 61, 76) (Appendix N) and represents the most comprehensive network considered in the ITC. The level 1 network (Figure 7) is restricted to three of these five trials (54, 55, 61). The level 1 network covers all systemic therapies, while level 3 includes also local therapies. As local therapies are different from systemic therapies and target a different type of patient, the level 1 network is used as the base case ITC.

Comparison of patient characteristics

An assessment of trial populations has been conducted on all trials included in the level 3 network. Details of patient characteristics reported across the trials of the network are provided in Appendix N.

Level 1 network

The patient populations are broadly comparable across most of the demographic and disease status factors across the three trials of the network (54, 55, 61), including age, gender, ECOG PS, Child-Pugh status, BCLC stage, AFP status and prior therapy. However, instances of variability include:

- **Asia-Pacific regions:** All three trials were conducted in mixed populations, with REFLECT enrolling a larger proportion of patients from the Asia-Pacific region (67%) compared with IMbrave150 and REFLECT (40% across both trials) (61).
- **Viral aetiology:** CheckMate 459 (55) includes a larger proportion of patients with non-viral aetiology (45%) compared with IMbrave150 (30-32%) (54) and REFLECT (26-28%) (61).
- **PD-L1 status:** CheckMate 459 (55) reports a substantially lower proportion of patients with PD-L1 positive disease (19% and 18% in each arm) compared with IMbrave150 (64% and 57% in each arm) (54). The PD-L1 status is not reported in REFLECT, but PD-L1 is not reported to be a prognostic factor in HCC (77).
- **Macroscopic vascular invasion (MVI):** The proportion of patients with MVI was higher in IMbrave150 (38% and 43% in each arm) (54) compared with REFLECT (23% and 19%) (61) [not reported in CheckMate459].

Methods of analysis

Modelling approach

Bayesian ITC analyses for OS and PFS were conducted using the log-HRs from each study using a normal likelihood with an identity link (78). The goodness of fit of model specifications were assessed in a Bayesian framework using the deviance information criterion (DIC).

ITC analyses were also conducted in a frequentist framework (fixed effect [FE] only) and the results of the analyses were consistent with Bayesian approach[1].

Bayesian analysis

The Bayesian models were all run using the gemtc-package, an R package for conducting Bayesian ITC (79). Information relating to model convergence are available on request.

[1] Results from the frequentist FE are available on request

Priors for basic parameters

In all Bayesian analyses, the priors for the basic parameters were set using the om.scale parameter equal to 5 in the gemtc package (79).

Priors for between-study heterogeneity in random effects models

An estimation of the between-trial standard deviation τ (i.e. the standard deviation of the random effects [RE]) requires a sufficiently large number of degrees of freedom. The degrees of freedom available for the estimation of τ depend on the number of trials per contrast and on the network geometry. It is generally accepted that the estimation of τ is not feasible with 5 or less degrees of freedom and only becomes so with 10 or more degrees of freedom. The estimation of τ with between 5 and 10 degrees of freedom is not definitively accepted.

As illustrated in Figure 7 (level 1 comparators) and Appendix N (level 3 comparators), the current evidence networks contain too few studies to allow for a robust estimation of the RE variance. Therefore, informative priors for the RE variance (τ^2) which are based on empirical evidence, were used (Table 17) (80, 81).

Table 17: Prior distributions for between study heterogeneity (RE variance)

Endpoint	Prior distributions
PFS	τ^2 ~ Log-normal (-2.94, 1.79^2) *Source in Turner (2015) Table IV: Internal/external structure related outcomes, pharmacological vs pharmacological (81)*
OS	Log-normal (-4.18, 1.41^2) *Source in Turner (2015) Table IV: All-cause mortality, pharmacological vs pharmacological (81)*

Abbreviations: OS, overall survival; PFS, progression-free survival; RE, random effect; vs, versus.

Fixed effect and random effect models

The RE models were deemed more appropriate than the FE models as they acknowledge the presence of heterogeneity. Therefore, the RE models with the Turner prior for between study standard deviation were considered for the primary model (81). This rule was only deviated from if the DIC favoured the FE model. Differences in DIC of less than 5 points were not considered meaningful.

Consistency assessment

The SLR did not identify any closed loops from different trials in any of the evidence networks suitable for analysis. Statistical consistency analysis was therefore not possible.

ITC results

Results of the level 3 network are provided in Appendix N.

OS: Level 1 network

The results of the primary ITC model for OS are presented in Table 18. All HRs suggest that Atezo+Bev is associated with a lower hazard of death compared with all comparators. However, the 95% credible intervals (CrIs) for HRs include the null value of 1 for the comparisons with lenvatinib. Based on this model, Atezo+Bev performs better than all comparators with >90% probability.

Table 18: OS ITC results from the RE model (base-case). Matrix of HRs (95% CrI) and probability of AB being better.

Treatment B	Treatment A			P (Atezo+Bev better than comparator), %*
	Atezo+Bev	Lenvatinib	Sorafenib	
Atezo+Bev		1.59 (0.80, 3.12)	1.73 (1.01, 2.86)	
Lenvatinib	0.63 (0.32, 1.25)		1.09 (0.69, 1.68)	94
Sorafenib	0.58 (0.35, 0.99)	0.92 (0.60, 1.44)		98

N.B HR (95% CrIs) are presented for treatment A (column) versus treatment B (row).
Atezo+Bev, atezolizumab plus bevacizumab; CrI, credible interval; HR, hazard ratio; OS, overall survival; RE, random effect. * HR<1 for the comparison of AB versus comparators.

Sensitivity analyses

The results of the FE ITC model are presented in Appendix N. It should be noted that for the FE ITC, the CrI for the HRs comparing Atezo+Bev with lenvatinib did not include the null value (HR=1).

A series of sensitivity analyses using subpopulations from each of the trials were conducted to investigate the impact of geographical region (Asia-Pacific vs non-Asia-Pacific regions), virology aetiology (HBV vs HCV vs non-viral) and MVI and extrahepatic spread (EHS) [MVI negative and EHS negative vs MVI positive and/or EHS positive, vs EHS negative]. The model fit statistics for the ITCs exploring subpopulation data sets were consistent with those when using the ITT datasets[2].

The relative treatment effect results and the posterior probability of Atezo+Bev being better than the comparators from the sensitivity analyses are presented in Table 19 and Table 20, respectively. The results of the sensitivity analyses exploring region and MVI/EHS subgroups are consistent with those of the base-case analysis.

[2] Model fit statistics from the ITC models exploring subpopulations available on request

Table 19: OS ITC relative results from the RE model using the trial subpopulations.

Subgroup	Treatment comparison, HR (95% CrI)	
	Atezo+Bev vs lenvatinib	Atezo+Bev vs sorafenib
All-comers	0.63 (0.32, 1.25)	0.58 (0.35, 0.99)
APAC	0.61 (0.28, 1.33)	0.53 (0.28, 1.02)
Ex-APAC	0.56 (0.27, 1.20)	0.61 (0.35, 1.10)
HBV	0.51 (0.24, 1.10)	0.43 (0.23, 0.81)
HCV	0.40 (0.16, 1.05)	0.37 (0.17, 0.83)
Non-Viral	0.91 (0.31, 2.88)	0.94 (0.48, 1.91)
MVI- and EHS-	0.65 (0.23, 1.91)	0.68 (0.27, 1.77)
EHS-	0.86 (0.37, 2.05)	0.90 (0.45, 1.86)
MVI+ and/or EHS+	0.63 (0.32, 1.27)	0.55 (0.33, 0.96)

Atezo+Bev, atezolizumab plus bevacizumab; APAC, Asia-Pacific; CrI, credible interval; EHS, extrahepatic spread; ex, excluding; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival; RE, random effect; vs, versus.

Table 20: OS ITC posterior probability results from the RE model using the trial subpopulations.

Subgroup	Treatment comparison, posterior probability that AB is superior to comparator (HR<1)	
	Atezo+Bev vs lenvatinib	Atezo+Bev vs sorafenib
All-comers	94%	98%
APAC	91%	97%
Ex-APAC	95%	96%
HBV	96%	99%
HCV	97%	99%
Non-Viral	56%	57%
MVI- and EHS-	79%	79%
EHS-	65%	62%
MVI+ and/or EHS+	93%	98%

Atezo+Bev, atezolizumab plus bevacizumab; APAC, Asia-Pacific; CrI, credible interval; EHS, extrahepatic spread; ex, excluding; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival; RE, random effect; vs, versus

PFS: Level 1 network

The results of the primary ITC model for PFS are presented in Table 21. Note, in the model all outcome data across the trials were obtained according to RECIST v1.1.

All HRs suggest that Atezo+Bev associated with a lower hazard of progression compared with all comparators. However, the 95% CrIs for HRs include the null value of 1 for the comparisons with lenvatinib and sorafenib.

Based on this model, the probability that Atezo+Bev performs better than lenvatinib and sorafenib is 62% and >92%, respectively (Table 21).

Table 21: PFS ITC results from the RE model (base-case). Matrix of HRs (95% CrI) and probability of AB being better

Treatment B	Treatment A			P (Atezo+Bev better than comparator), %*
	Atezo+Bev	Lenvatinib	Sorafenib	
Atezo+Bev		1.10 (0.27, 4.36)	1.69 (0.64, 4.43)	
Lenvatinib	0.91 (0.23, 3.65)		1.53 (0.59, 4.15)	62
Sorafenib	0.59 (0.23, 1.58)	0.65 (0.24, 1.71)		92

N.B HR (95% CrIs) are presented for treatment A (column) versus treatment B (row).
Atezo+Bev, atezolizumab plus bevacizumab; CrI, credible interval; HR, hazard ratio; PFS, progression free survival; RE, random effect. * HR<1 for the comparison of AB versus comparators.

Sensitivity analyses

Subgroup data were not available across the trials of the network for PFS based on the RECIST 1.1 criteria. Therefore, sensitivity analyses were not feasible.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

The section below outlines some uncertainties and limitation of the ITCs performed.

- There were different levels of detail available for the studies included. For all included studies except IMbrave150, only published aggregate data were available. Patient-level data would be preferred to aggregate data, as fewer assumptions regarding censoring would be required, and patient-level covariates could be included in meta-regression models to adjust for patient characteristics.
- There was high uncertainty in the ITC results as demonstrated by the width of the 95% CrIs. This is driven by the low number of events in some outcomes, most notably OS where censoring was required for a high proportion of patients in some trials, which further restricts the interpretation of results. However the results were robust base on confirmation from clinical experts.
- Statistically the ITC increases uncertainty due to how the variance of the indirect comparisons are computed, in both a frequentist and Bayesian approach.
- Some trial endpoints had to be discarded due to the use of different methodologies, e.g. RECIST v.1.1 vs mRECIST
- The small numbers of studies within the outcome-specific evidence networks limits the ability to explore potential sources of heterogeneity via meta-regression.

In summary, the approach taken recognises the uncertainties and limitations and attempts to provide the most robust analyses possible to aid decision making in their presence. Despite the limitations, consistent trends in favour of Atezo+Bev were observed for all outcomes across comparisons, thus suggestive of a clinical benefit to be achieved with Atezo+Bev.

B.2.10 Adverse reactions

The safety population consisted of all randomised patients who received at least one full or partial dose of any study treatment, with patients grouped according to the actual treatment received.

Patients who received any amount of atezolizumab and/or bevacizumab were assigned to the Atezo+Bev treatment arm for safety analyses even if atezolizumab/bevacizumab was given in error. An overview of safety in the safety-evaluable (SE) population is provided below (36).

Table 22: IMbrave150 – overview of adverse events (safety-evaluable population)

n, (%)	Atezo+Bev n=329	Sorafenib n=156
Total number of patients with at least one AE	323 (98.2)	154 (98.7)
Total number of AEs, n	3058	1299
Total number of patients with at least one		
AE related to any study treatment	276 (83.9)	147 (94.2)
AE related to atezolizumab	252 (76.6)	n/a
AE related to bevacizumab	241 (73.3)	n/a
Grade 3–4 AE	186 (56.5)	86 (55.1)
Treatment-related Grade 3–4 AE	117 (35.6)	71 (45.5)
Grade 5 AE	15 (4.6)	9 (5.8)
Treatment-related Grade 5 AE	6 (1.8)	1 (0.6)
Serious AE	125 (38.0)	48 (30.8)
Related serious AE	56 (17.0)	24 (15.4)
AE leading to withdrawal from any study treatment	51 (15.5)	16 (10.3)
AE leading to withdrawal from atezolizumab	28 (8.5)	0
AE leading to withdrawal from bevacizumab	48 (14.6)	0
AE leading to withdrawal from Atezo+Bev	23 (7.0)	0
AE leading to dose modification/interruption of any study treatment	163 (49.5)	95 (60.9)
AE leading to dose interruption of any study treatment	163 (49.5)	64 941.0)
AE leading to dose reduction of sorafenib	n/a	58 (37.2)

AE, adverse event
CCOD: 29 August 2019

Extent of exposure to study treatment

In both study arms, study drugs were administered in 3-week cycles.

In the SE population, patients in the sorafenib arm had a median treatment duration of 2.8 months (range: 0–16). Sorafenib was administered twice daily and each dose was counted

separately. The median number of doses was 149 (range: 6–908). The median dose intensity was 96% (range: 27–100%).

In the Atezo+Bev arm the duration of exposure to study treatment was longer compared to the sorafenib arm: the median treatment duration was 7.4 months (range: 0–16 months) for atezolizumab and 6.9 months (range 0–16 months) for bevacizumab. The median number of doses was 11 (range: 1–24) for atezolizumab and 10 (range: 1–23) for bevacizumab. The median dose intensity was 98% (range: 54–104%) for atezolizumab and 97% (range: 44–104%) for bevacizumab.

Table 23: IMbrave150 – extent of exposure to study treatment (safety-evaluable population)

	Atezo+Bev n=329		Sorafenib n=156
	Atezolizumab	Bevacizumab	
Treatment duration (months)			
n	329	329	156
Mean (SD)	6.8 (4.1)	6.5 (4.0)	4.1 (3.5)
Median	7.4	6.9	2.8
Min–Max	0–16	0–16	0–16
Treatment duration (months), n (%)			
n	329	329	156
<3	75 (22.8)	78 (23.7)	89 (57.1)
3 to <6	48 (14.6)	58 (17.6)	22 (14.1)
6 to <9	100 (30.4)	97 (29.5)	28 (17.9)
9 to < 12	76 (23.1)	69 (21.0)	12 (7.7)
≥12	39 (9.1)	27 (8.2)	5 (3.2)
Dose intensity (%)			
n	329	329	156
Mean (SD)	95.1 (6.9)	93.3 (9.6)	83.8 (20.1)
Median	98.0	97.0	96.0
Min–Max	54–104	44–404	27–100
No. of doses received			
n	329	329	156
Mean (SD)	10.4 (5.8)	9.8 (5.5)	215.1 (194.6)
Median	11.0	10.0	149.0
Min–Max	1–24	1–23	6–908
Total cumulative dose (mg)			
n	329	329	156
Mean (SD)	12440.3 (6917.4)	10485.1 (6467.4)	84784.6 (76639.8)
Median	13200.0	10543.5	64100.0
Min–Max	1200–28800	723–30510	2400–362800

SD, standard deviation
CCOD: 29 August 2019

Common adverse events

The majority of patients in each treatment arm experienced at least one AE of any grade (sorafenib: 98.7%; Atezo+Bev: 98.2%). The most common (≥10% of patients in any

treatment arm) system organ classes (SOCs) in which AEs were reported is summarised below.

Table 24: IMbrave150 – adverse events with an incidence rate of at least 10% in any treatment arm by SOC and preferred term (safety-evaluable population)

n, (%)	Atezo+Bev n=329	Sorafenib n=156
Gastrointestinal disorders		
Total no. of pts with at least one AE	193 (58.7)	118 (75.6)
Total no. of events	525	293
Diarrhoea	62 (18.8)	77 (49.4)
Abdominal pain	40 (12.2)	27 (17.3)
Constipation	44 (13.4)	22 (14.1)
Nausea	40 (12.2)	25 (16.0)
Vomiting	33 (10.0)	13 (8.3)
General disorder and administration site conditions		
Total no. of pts with at least one AE	166 (50.5)	77 (49.4)
Total no. of events	278	105
Fatigue	67 (20.4)	29 (18.6)
Pyrexia	59 (17.9)	15 (9.6)
Asthenia	22 (6.7)	21 (13.5)
Skin and subcutaneous disorder		
Total no. of pts with at least one AE	123 (37.4)	107 (68.6)
Total no. of events	197	187
Pruritus	64 (19.5)	15 (9.6)
Palmar-plantar erythrodysaesthesia syndrome	3 (0.9)	75 (48.1)
Rash	41 (12.5)	27 (17.3)
Alopecia	4 (1.2)	22 (14.1)
Investigations		
Total no. of pts with at least one AE	159 (48.3)	68 (43.6)
Total no. of events	518	223
Aspartate aminotransferase increased	64 (19.5)	26 (16.7)
Blood bilirubin increased	43 (13.1)	22 (14.1)
Alanine aminotransferase increased	46 (14.0)	14 (9.0)
Platelet count decreased	35 (10.6)	18 (11.5)
Weight decreased	37 (11.2)	15 (9.6)
Metabolism and nutrition disorders		
Total no. of pts with at least one AE	129 (39.2)	66 (42.3)
Total no. of events	214	118
Decreased appetite	58 (17.6)	38 (24.4)
Respiratory, thoracic and mediastinal disorders		
Total no. of pts with at least one AE	130 (39.5)	47 (30.1)
Total no. of events	219	71
Cough	39 (11.9)	15 (9.6)
Epistaxis	34 (10.3)	7 (4.5)
Vascular disorders		
Total no. of pts with at least one AE	108 (32.8)	42 (26.9)
Total no. of events	160	52
Hypertension	98 (29.8)	38 (24.4)
Renal and urinary disorders		
Total no. of pts with at least one AE	86 (26.1)	20 912.8)

Total no. of events	120	24
Proteinuria	66 (20.1)	11 (7.1)
Injury, poisoning and procedural complications		
Total no. of pts with at least one AE	46 (14.0)	6 (3.8)
Total no. of events	61	7
Infusion-related reaction	37 (11.2)	0

AE, adverse event
CCOD: 29 August 2019

Treatment-related adverse events

Overall, a higher proportion of patients in the sorafenib arm (94.2%) experienced at least one AE (any grade) that was assessed by the investigator as treatment-related, compared to patients in the Atezo+Bev arm (83.9%). The majority of treatment-related AEs (≥5% difference between treatment arms) were reported at a higher frequency in the sorafenib arm, except for aspartate aminotransferase increased, alanine aminotransferase increased, epistaxis, proteinuria, hypothyroidism, and infusion related reaction, which were reported in a higher proportion in the Atezo+Bev arm.

Table 25: IMbrave150 – adverse events related to study treatment with an incidence rate of at least 5% in any treatment arm by SOC and preferred term (safety-evaluable population)

	Atezo+Bev n=329			Sorafenib n=156
	Atezo	Bev	Any tx	
Total no. of pts with at least one AE	252 (76.6)	241 (73.3)	276 (83.9)	147 (94.2)
Overall total no. of events	1259	1136	1505	790
Skin and subcutaneous tissue disorders				
Total no. of pts with at least one AE	82 (24.9)	42 (12.8)	85 (25.8)	107 (68.6)
Total no. of events	123	53	127	175
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	1 (0.3)	2 (0.6)	75 (48.1)
Pruritus	43 (13.1)	17 (5.2)	43 (13.1)	13 (8.3)
Rash	29 (8.8)	14 (4.3)	29 (8.8)	26 (16.7)
Alopecia	3 (0.9)	2 (0.6)	3 (0.9)	21 (13.5)
Gastrointestinal disorders				
Total no. of pts with at least one AE	83 (25.2)	81 (24.6)	97 (29.5)	91 (58.3)
Total no. of events	153	148	180	178
Diarrhoea	34 (10.3)	22 (6.7)	34 (10.3)	67 (42.9)
Nausea	19 (5.8)	19 (5.8)	21 (6.4)	20 (12.8)
Vomiting	13 (4.0)	13 (4.0)	13 (4.0)	8 (5.1)
Constipation	6 (1.8)	8 (2.4)	8 (2.4)	8 (5.1)
Abdominal pain	3 (0.9)	3 (0.9)	3 (0.9)	8 (5.1)
Investigations				
Total no. of pts with at least one AE	107 (32.5)	88 (26.7)	111 (33.7)	45 (28.8)
Total no. of events	341	266	357	124
Aspartate aminotransferase increased	45 (13.7)	29 (8.8)	46 (14.0)	11 (7.1)
Platelet count decreased	23 (7.0)	24 (7.3)	27 (8.2)	15 (9.6)
Alanine aminotransferase increased	34 (10.3)	18 (5.5)	34 910.3)	4 (2.6)
Blood bilirubin increased	27 (8.2)	20 (6.1)	27 (8.2)	9 (5.8)

Weight decreased	12 (3.6)	12 (3.6)	13 (4.0)	8 (5.1)
General disorder and administration site conditions				
Total no. of pts with at least one AE	91 (27.7)	80 (24.3)	97 (29.5)	58 (37.2)
Total no. of events	121	105	132	71
Fatigue	49 (14.9)	40 (12.2)	50 (15.2)	24 (15.4)
Pyrexia	27 (8.2)	25 (7.6)	30 (9.1)	8 (5.1)
Asthenia	10 (3.0)	8 (2.4)	11 (3.3)	16 (10.3)
Vascular disorders				
Total no. of pts with at least one AE	21 (6.4)	81 (24.6)	84 (25.5)	32 (20.5)
Total no. of events	31	102	105	35
Hypertension	17 (5.2)	78 (23.7)	78 (23.7)	31 (19.9)
Metabolism and nutrition disorders				
Total no. of pts with at least one AE	58 (17.6)	50 (15.2)	63 (19.1)	45 (28.8)
Total no. of events	86	74	92	69
Decreased appetite	29 (8.8)	26 (7.9)	33 (10.0)	31 (19.9)
Respiratory, thoracic and mediastinal disorders				
Total no. of pts with at least one AE	42 (12.8)	58 (17.6)	65 (19.8)	25 (16.0)
Total no. of events	51	73	85	29
Dysphonia	15 (4.6)	20 (6.1)	22 (6.7)	10 (6.4)
Epistaxis	4 (1.2)	24 (7.3)	24 (7.3)	3 (1.9)
Renal and urinary disorders				
Total no. of pts with at least one AE	33 (10.0)	68 (20.7)	69 (21.0)	8 (5.1)
Total no. of events	49	95	96	8
Proteinuria	27 (8.2)	62 (18.8)	62 (18.8)	7 (4.5)
Blood and lymphatic system disorders				
Total no. of pts with at least one AE	41 (12.5)	35 (10.6)	43 913.1)	18 (11.5)
Total no. of events	89	78	92	32
Anaemia	9 (2.7)	8 (2.4)	9 (2.7)	8 (5.1)
Endocrine disorders				
Total no. of pts with at least one AE	35 (10.6)	15 (4.6)	36 (10.9)	4 (2.6)
Total no. of events	42	17	43	4
Hypothyroidism	25 (7.6)	14 (4.3)	26 (7.9)	2 (1.3)
Injury, poisoning and procedural complications				
Total no. of pts with at least one AE	33 (10.0)	10 (3.0)	37 (11.2)	0
Total no. of events	40	13	46	0
Infusion-related reaction	32 (9.7)	10 (3.0)	36 (10.9)	0

AE, adverse event
CCOD: 29 August 2019

Adverse events by intensity

The proportion of patients who experienced an AE of any grade was comparable between the two treatment arms (sorafenib arm: 98.7%; Atezo+Bev arm: 98.2%). The proportion of patients who experienced Grade 3–4 AEs (maximum grade) was comparable between the sorafenib (55.1%) and Atezo+Bev (56.5%) arms.

A summary of all AEs with NCI CTCAE Grade 3 and above is provided below.

Table 26: Adverse events by highest NCI CTCAE Grade categories 3–4 and 5 with a difference of at least 2% between treatment arms by system organ class and preferred term (safety-evaluable population)

n, (%)	Atezo+Bev n=329		Sorafenib n=156	
	Grade 3–4	Grade 5	Grade 3–4	Grade 5
Total number of patients with at least one AE	186 (56.5)	15 (4.6)	86 (55.1)	9 (5.8)
Investigations				
Total no. of pts with at least one AE	61 (18.5)	0	25 (16.0)	0
Blood bilirubin increased	8 (2.4)	0	10 (6.4)	0
Alanine aminotransferase increased	12 (3.6)	0	2 (1.3)	0
Platelet count decreased	11 (3.3)	0	2 (1.3)	0
Gastrointestinal disorders				
Total no. of pts with at least one AE	48 (14.6)	5 (1.5)	27 (17.3)	1 (0.6)
Diarrhoea	6 (1.8)	0	8 (5.1)	0
Vascular disorders				
Total no. of pts with at least one AE	53 (16.1)	0	21 (13.5)	0
Hypertension	50 (15.2)	0	19 (12.2)	0
Metabolism and nutrition disorders				
Total no. of pts with at least one AE	30 (9.1)	0	21 (13.5)	0
Decreased appetite	4 (1.2)	0	6 (3.8)	0
Hypophosphataemia	2 (0.6)	0	6 (3.8)	0
General disorder and administration site conditions				
Total no. of pts with at least one AE	14 (4.3)	1 (0.3)	12 (7.7)	3 (1.9)
Asthenia	1 (0.3)	0	4 (2.6)	0
Skin and subcutaneous disorder				
Total no. of pts with at least one AE	2 (0.6)	0	21 (13.5)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	13 (8.3)	0
Rash	0	0	4 (2.6)	0
Renal and urinary disorders				
Total no. of pts with at least one AE	14 (4.3)	0	6 (3.8)	0
Proteinuria	10 (3.0)	0	1 (0.6)	0
Injury, poisoning and procedural complications				
Total no. of pts with at least one AE	13 (4.0)	0	2 (1.3)	0
Infusion-related reaction	8 (2.4)	0	0	0

Overall, a higher proportion of patients in the sorafenib arm (45.5%) experienced at least one Grade 3–4 AE that was considered by the investigator to be treatment-related compared to patients in the Atezo+Bev arm (35.6%).

The treatment-related Grade 3–4 AEs reported with higher incidences (≥2% difference) in the sorafenib arm were palmar-plantar erythrodysaesthesia syndrome, rash, blood bilirubin increased, diarrhoea, hypophosphatemia, and decreased appetite, whereas the AEs reported with higher incidences (≥2% difference) in the Atezo+Bev arm were alanine aminotransferase increased, proteinuria, and infusion-related reaction.

Table 27: IMbrave150 – AEs related to study treatment with an incidence rate ≥1% in any treatment arm by highest NCI CTCAE Grade categories 3–4 and 5 and by SOC and preferred term (safety-evaluable population)

MedDRA SOC MedDRA Preferred Term	Atezo+Bev n=329						Sorafenib n=156	
	Atezo		Bev		Any Treatment		Sorafenib	
	Grade 3–4	Grade 5	Grade 3–4	Grade 5	Grade 3–4	Grade 5	Grade 3–4	Grade 5
Total no. of pts with at least one AE	90 (27.4)	1 (0.6)	97 (29.5)	4 (1.2)	117 (35.6)	6 (1.8)	71 (45.5)	1 (0.6)
Investigations								
Total no. of pts with at least one AE	41 (12.5)	0	27 (8.2)	0	41 (12.5)	0	17 (10.9)	0
Aspartate aminotransferase increased	14 (4.3)	0	6 (1.8)	0	14 (4.3)	0	4 (2.6)	0
Platelet count decreased	7 (2.1)	0	7 92.1)	0	8 (2.4)	0	1 (0.6)	0
Alanine aminotransferase increased	7 (2.1)	0	3 (0.9)	0	7 (2.1)	0	0	0
Gamma-glutamyltransferase increased	4 (1.2)	0	3 (0.9)	0	4 (1.2)	0	3 (1.9)	0
Blood bilirubin increased	2 (0.6)	0	0	0	2 (0.6)	0	4 (2.6)	0
Neutrophil count decreased	3 (0.9)	0	4 (1.2)	0	4 (1.2)	0	1 (0.6)	0
Lymphocyte decreased	4 (1.2)	0	3 (0.9)	0	4 (1.2)	0	0	0
Amylase increased	1 (0.3)	0	1 (0.3)	0	1 (0.3)	0	2 (1.3)	0
Vascular disorders								
Total no. of pts with at least one AE	8 (2.4)	0	38 (11.6)	0	39 (11.9)	0	15 (9.6)	0
Hypertension	7 (2.1)	0	34 (10.3)	0	34 (10.3)	0	14 (9.0)	0
Gastrointestinal disorders								
Total no. of pts with at least one AE	17 (10.9)	0	14 (4.3)	1 (0.3)	17 (5.2)	2 (0.6)	17 (10.9)	0
Diarrhoea	6 (3.8)	0	0	0	1 (0.3)	0	6 (3.8)	0
Gastrointestinal haemorrhage	2 (1.3)	0	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	2 (1.3)	0
Upper gastrointestinal haemorrhage	2 (0.6)	0	2 (0.6)	0	2 (0.6)	0	2 (1.3)	0
Pancreatitis	1 (0.3)	0	1 (0.3)	0	1 (0.3)	0	2 (1.3)	0
Abdominal pain	0	0	0	0	0	0	2 (1.3)	0
Dyspepsia	0	0	0	0	0	0	2 (1.3)	0
Skin and subcutaneous tissue disorders								
Total no. of pts with at least one AE	2 (0.6)	0	0	0	2 (0.6)	0	21 (13.5)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	0	0	13 (8.3)	0
Rash	0	0	0	0	0	0	4 (2.6)	0
Metabolism and nutrition disorders								

Total no. of pts with at least one AE	6 (1.8)	0	6 (1.8)	0	7 (2.1)	0	15 (9.6)	0
Decreased appetite	1 (0.3)	0	2 (0.6)	0	2 (0.6)	0	6 (3.8)	0
Hypophosphataemia	1 (0.3)	0	1 (0.3)	0	1 (0.3)	0	5 (3.2)	0
Hypokalaemia	0	0	0	0	0	0	2 (1.3)	0
General disorder and administration site conditions								
Total no. of pts with at least one AE	6 (1.8)	0	5 (1.5)	0	6 (1.8)	0	11 (7.1)	0
Fatigue	5 (1.5)	0	4 (1.2)	0	5 (1.5)	0	5 (3.2)	0
Asthenia	0	0	0	0	0	0	3 (1.9)	0
Blood and lymphatic system disorders								
Total no. of pts with at least one AE	8 (2.4)	0	8 (2.4)	0	8 (2.4)	0	5 (3.2)	0
Thrombocytopenia	3 (0.9)	0	4 (1.2)	0	4 (1.2)	0	3 (1.9)	0
Anaemia	3 (0.9)	0	3 (0.9)	0	3 (0.9)	0	2 (1.3)	0
Renal and urinary disorders								
Total no. of pts with at least one AE	6 (1.8)	0	10 (3.0)	0	11 (3.3)	0	2 (1.3)	0
Proteinuria	4 (1.2)	0	9 (2.7)	0	9 (2.7)	0	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders								
Total no. of pts with at least one AE	3 (0.9)	0	4 (1.2)	0	5 (1.5)	0	4 (2.6)	0
Pulmonary embolism	0	0	1 (0.3)	0	1 (0.3)	0	2 (1.3)	0
Injury, poisoning and procedural complications								
Total no. of pts with at least one AE	7 (2.1)	0	2 (0.6)	0	8 (2.4)	0	0	0
Infusion-related reaction	6 (1.8)	0	2 (0.6)	0	7 (2.1)	0	0	0

AE, adverse event
CCOD: 29 August 2019

Deaths

At the clinical cutoff date, 157 deaths had occurred in the safety-evaluable population: 64 deaths (n=156; 41.1%) in the sorafenib arm and 93 deaths (n=329; 28.3%) in the Atezo+Bev arm. In both treatment arms, the majority of deaths occurred more than 30 days after the last dose of study drug. The most common cause of death was progressive disease (PD) in both treatment arms: 79.7% (51/64) in the sorafenib arm and 76.3% (71/93) in the Atezo+Bev arm.

Twenty-four deaths in the overall SE population were due to Grade 5 AEs: 9 deaths (5.8%) in the sorafenib arm and 15 deaths (4.6%) in the Atezo+Bev arm. The most common Grade 5 AEs (>1 patient in any treatment arm) were the events of 'death' (2 patients; 1.3%) and hepatic cirrhosis (2 patients; 1.3%) in the sorafenib arm, and the events of gastrointestinal haemorrhage (3 patients; 0.9%) and pneumonia (2 patients; 0.6%) in the Atezo+Bev arm. All remaining fatal AEs, in both arms, were single occurrences spread across several different SOCs.

Bleeding events including fatalities are known adverse reactions for bevacizumab. Based on review of four case details for Grade 5 GI bleeding events reported with Atezo+Bev, all cases had macrovascular invasion, varices at baseline, hepatic cirrhosis, which are well known risk factors of upper GI bleeding in the HCC setting. Of these, three events were assessed as unrelated to study treatment and occurred almost 5 months after the initial dose of study treatment. These Grade 5 events are consistent with the overall safety profile of bevacizumab and with the underlying disease.

Table 28: IMbrave150 – deaths and causes of death (safety-evaluable population)

	Atezo+Bev n=329	Sorafenib n=156	All patients n=485
All death, n	93	64	157
≤30 days after last dose, n (%)	11 (3.3)	14 (9.0)	25 (5.2)
>30 days after last dose, n (%)	82 (24.9)	50 (32.1)	132 (27.2)
Primary cause of death, n	93	64	157
Adverse event, n (%)	15 (4.6)	9 (5.8)	24 (4.9)
Progressive disease, n (%)	71 (21.6)	51 (32.7)	122 (25.2)
Other*, n (%)	7 (2.1)	4 (2.6)	11 (2.3)
Death due to cardio pulmonary arrest	1 (0.3)	0	1 (0.2)
Death due to GI bleed	0	1 (0.6)	1 (0.2)
Death due to heart attack	0	1 (0.6)	1 (0.2)
Death due to post study reporting of death	4 (1.2)	1 (0.6)	5 (1.0)
Death due to unknown	2 (0.6)	1 (0.6)	3 (0.6)

*all deaths that were not attributed to disease progression and occurred either after the adverse event reporting period or from public records were reported as 'other'
GI, gastrointestinal
CCOD: 29 August 2019

Serious adverse events (SAEs)

The incidence of SAEs was numerically lower in the sorafenib arm (30.8%) compared to the Atezo+Bev arm (38%).

Gastrointestinal haemorrhage (1.9% in sorafenib vs. 2.4% in Atezo+Bev arm), oesophageal varices haemorrhage (0.6% vs. 2.4%), and pyrexia (1.3% vs. 2.1%) were the most common SAEs. All other SAEs occurred in <2% of patients in each treatment arm.

At the preferred term level, SAEs were generally balanced between the two arms. There were no SAEs reported with more than 2% difference between two arms.

The incidence rate of treatment-related SAEs was comparable between the sorafenib (15.4%) and the Atezo+Bev (17.0%) arms. Of the treatment-related SAEs occurring in ≥1% of patients in any treatment arm, higher frequencies of gastrointestinal haemorrhage, pancreatitis, blood bilirubin increased, anaemia, and thrombocytopenia were reported in the sorafenib arm, whereas a higher frequency of infusion related reaction was reported in the Atezo+Bev arm. All remaining treatment-related SAEs occurred in <1% of patients in either treatment arm.

Adverse events that led to withdrawal of study treatment

Overall, sixteen patients (10.3%) in the sorafenib arm and 51 patients (15.5%) in the Atezo+Bev arm had AEs (not necessarily related to study treatment) that led to discontinuation of any study treatment. Twenty-three patients (7.0%) in the Atezo+Bev arm had AEs leading to discontinuation of both atezolizumab and bevacizumab. Oesophageal varices haemorrhage (1.2%) was the most common AE leading to discontinuation in the Atezo+Bev arm. All other AEs leading to discontinuation occurred in <1% of patients in any treatment arm.

Of the patients highlighted above, 15 patients (9.6%) in the sorafenib arm and 42 patients (12.8%) in the Atezo+Bev arm had treatment-related AEs that led to discontinuation of any study treatment.

Adverse events that led to dose modification/interruption

AEs that led to dose reduction were reported in 37.2% of patients in the sorafenib arm.

Dose reductions for any reason were not permitted in the Atezo+Bev arm. A numerically lower proportion of patients in the sorafenib arm (41.0%) experienced AEs that led to dose interruption compared to the Atezo+Bev arm (49.5%).

The most common AEs (≥2% of patients) leading to dose reduction/interruption of sorafenib in the sorafenib arm were palmar-plantar erythrodysaesthesia syndrome (17.3%), diarrhoea

(10.9%), blood bilirubin increased (5.1%), fatigue (4.5%), decreased appetite (4.5%), hypertension (3.8%), platelet count decreased (3.2%), pyrexia (3.2%), vomiting (3.2%), rash (3.2%), aspartate aminotransferase increased (3.2%), ascites (2.6%), nausea (2.6%), abdominal pain (2.6%), alanine aminotransferase increased (2.6%), and asthenia (2.6%).

The most common AEs (≥2% of patients) leading to dose interruption of any treatment in the Atezo+Bev arm were proteinuria (6.7%), hypertension (6.1%), aspartate aminotransferase increased (5.2%), alanine aminotransferase increased (3.3%), hyperthyroidism (2.7%), platelet count decreased (2.4%), and pyrexia (2.4%).

Adverse events of special interest for atezolizumab

Please see Appendix F for a full list of the AESI for atezolizumab. In the overall SE population, a higher proportion of patients in the sorafenib arm (82.1%) versus the Atezo+Bev arm (68.7%) experienced AESIs for atezolizumab. Of the most commonly occurring AESI medical concepts (≥5% in any treatment arm), the incidence of immune-mediated rash was ≥5% higher in the sorafenib arm, whereas the percentage of patients with immune-mediated hypothyroidism was ≥5% higher in the Atezo+Bev arm. The incidence rate of immune-mediated hepatitis was similar between the study arms.

The AESIs unique to Atezo+Bev patients included infusion related reactions (10.9%), immune-mediated hyperthyroidism (4.6%), immune-mediated diabetes mellitus (2.4%), immune-mediated pneumonitis (1.2%), immune-mediated nephritis (0.9%), and autoimmune haemolytic anaemia, immune-mediated adrenal insufficiency, immune-mediated ocular inflammatory toxicity, immune-mediated vasculitis, and systemic immune activation (0.3% each, 1 patient). Immune-mediated severe cutaneous reactions was the only medical concept unique to patients treated with sorafenib, occurring at a rate of 0.6% (1 patient).

In both arms, the majority of the AESIs were Grade 1–2 in intensity. The proportion of Grade 3–4 AESIs was numerically higher in the sorafenib arm (30.1%) compared to the Atezo+Bev arm (25.8%). Two patients (1.3%) in the Sorafenib arm and three patients (0.9%) in the Atezo+Bev arm had Grade 5 AESIs. Of the three Grade 5 AESIs in the Atezo+Bev arm, two were assessed as related to treatment with atezolizumab; one patient with liver injury and one patient with hepatic function abnormal.

A comparable proportion of patients in the sorafenib and Atezo+Bev arms had serious AESIs (10.9% vs. 13.7% [Atezo+Bev]) and treatment-related serious AESIs (8.3% vs. 6.1%). The frequency of AESIs leading to withdrawal from any study treatment was similar between the two study arms (5.8% vs. 6.1%), whereas AESIs leading to study treatment modification/dose interruption were more common in the sorafenib arm (35.9% vs. 20.1%).

Adverse events of special interest for bevacizumab

Please see Appendix F for a full list of the AESI for bevacizumab. A numerically lower proportion of sorafenib patients (48.7%) experienced AESIs for bevacizumab compared to patients in the Atezo+Bev arm (57.8%). Of the most commonly occurring AESI medical concepts (≥5% in any treatment arm), the rates of patients with hypertension, bleeding/haemorrhage, and proteinuria by medical concept were ≥5% higher in the Atezo+Bev arm compared to the sorafenib arm. Fistula/abscess (non GI) was reported only in the sorafenib arm, occurring at a rate of 0.6%.The AESIs reported only in the Atezo+Bev arm included wound healing complications (0.6%) and gastrointestinal perforation (0.3%).

In both arms, more than half of the reported AESIs for bevacizumab were Grade 1–2 in intensity. The proportion of Grade 3–4 AESIs (sorafenib: 18.6%; Atezo+Bev: 23.1%) and treatment-related Grade 3–4 AESIs (sorafenib: 13.5%; Atezo+Bev: 16.1%) were comparable between the two treatment arms. Two patients (1.3%) in the sorafenib and 6 patients (1.8%) in the Atezo+Bev arm had Grade 5 AESIs.

A comparable proportion of patients in the sorafenib and Atezo+Bev arm had AESIs that were serious (9.6% vs. 12.2% [Atezo+Bev]) and treatment-related serious AESIs (3.8% vs. 6.4%). AESIs leading to withdrawal from any study treatment (0.6% vs. 7.9%) and study treatment modification/dose interruption (9.6% vs. 17%) were numerically higher in the Atezo+Bev arm.

B.2.11 Ongoing studies

The IMbrave150 study is currently ongoing, with the final OS analysis planned to be conducted after approximately 312 deaths in the ITT population have been observed. This is expected to occur approximately 33 months after the enrolment of the first patient (expected study completion date June 2022). However, since the primary endpoint of OS has been met, any further analyses will be descriptive only.

B.2.12 Innovation

The treatment of unresectable HCC has remained largely unchanged for over a decade, with the addition of just one new treatment option that did not significantly improve survival. Therefore, there remains an unmet need for more efficacious, better tolerated treatments for patients with unresectable HCC who have not received prior systemic therapies.

[redacted]

[redacted].

Given the lack of advancement in the treatment paradigm for locally advanced or metastatic and/or unresectable HCC, treatment combinations may be appropriate to extend survival for these patients. The combination of anti–PD-L1 and anti-VEGF therapies is an innovative strategy that has shown synergy and positive outcomes in Phase I to III studies, particularly in settings where high VEGF levels are known to play an important role in tumour growth (45).

HCC is a highly vascularised tumour in which several proangiogenic factors play a role in its pathogenesis. In HCC, increased VEGF correlates with vascular density, tumour invasiveness and metastasis, and poor prognosis (82, 83). In addition, VEGF-A signalling is known to activate angiogenesis-independent, inductive angiocrine signals from sinusoidal endothelium that stimulate hepatocyte-mediated liver regeneration (84, 85).

In addition to its role in angiogenesis and liver regeneration, the VEGF-A pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumour microenvironment through several mechanisms. For instance, VEGF-A has been shown to induce Fas ligand (FasL) expression on endothelial cells, which have the ability to kill effector CD8+ T cells, but not T-reg cells (47).

Administration of anti-VEGF-A attenuated tumour endothelial FasL expression and produced a significant increase in the influx of tumour-rejecting CD8+ over FoxP3+ T cells, which was FasL-dependent, and led to CD8-dependent tumour growth suppression (47). Furthermore, bevacizumab can restore and/or maintain the antigen presentation capacity of dendritic cells, leading to enhanced T-cell infiltration in tumours (48, 86). In addition to increased trafficking of T cells into tumours (87), several publications have illustrated that anti-VEGF therapies can also reduce frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on CD8+ T cells in tumours (46, 88). Therefore, the immunomodulatory effect of bevacizumab is expected to increase CD8-positive T-cell recruitment and relieve intratumoural immunosuppression, thereby boosting the effects of atezolizumab.

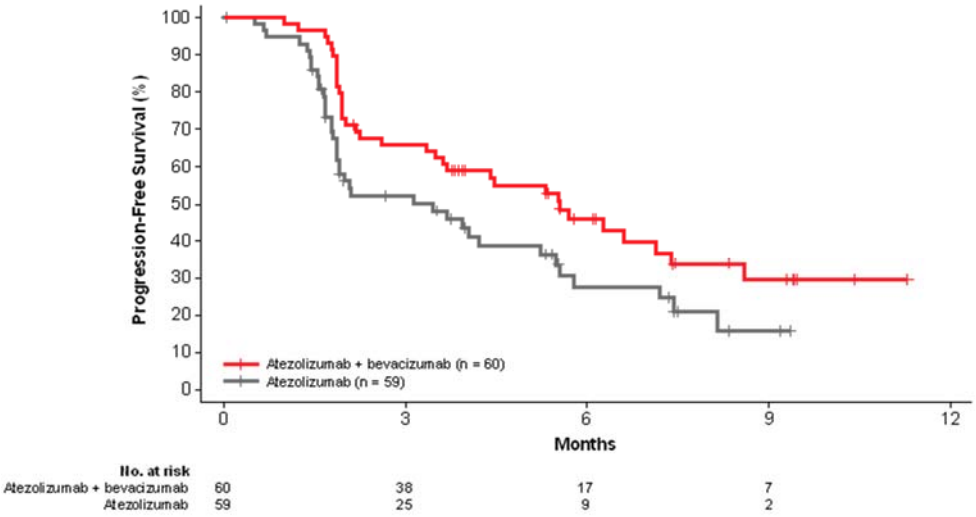
Atezolizumab administered as single-agent for the treatment of HCC has been assessed in PCD4989g and YO29233 multi-cohort Phase I studies that has showed modest clinical activity in first-line and beyond HCC. None of the 15 first-line+ patients with HCC treated with atezolizumab in PCD4989g had a confirmed objective response as assessed by the

investigator per RECIST v1.1. Of the 21 total first-line+ HCC patients in YO29233, two patients had a confirmed partial response. However, due to the small sample sizes, the efficacy data from these studies should be interpreted with caution.

Two published investigator-sponsored bevacizumab monotherapy studies (Boige et al. 2012 [N=48] and Siegel et al. 2008 [N=46]) also provide modest efficacy data for bevacizumab monotherapy in patients with first-line+ HCC (82, 89). Objective response rates were 14% and 13%, and median PFS was 3 months and 6.9 months, respectively, although it should be noted that these studies were conducted in a healthier patient population who did not have MVI, EHS, or greater than 50% tumour involvement in the liver.

Despite the modest efficacy of monotherapy studies, a significantly superior clinical benefit with the combination of Atezo+Bev compared with atezolizumab monotherapy in patients with unresectable HCC was demonstrated in Arm F of the Phase Ib GO30140 study. With a median duration of follow up of 6.6 months, Atezo+Bev extended PFS by 2.2 months compared with atezolizumab monotherapy (median PFS 5.6 months vs 3.4 months; stratified HR=0.55 (0.40–0.74), p=0.0108) (90).

Figure 8: GO30140 (Arm F) – Progression-free survival



Taken together, the findings of atezolizumab and bevacizumab monotherapy studies, along with the data from Arm F of GO30140 support the conclusion that combining atezolizumab with bevacizumab is necessary to improve clinical outcomes in HCC

The need for a combination approach for the treatment of patients with unresectable HCC was further confirmed when the Phase III CheckMate 459 study of nivolumab vs. sorafenib recently failed to meet its primary endpoint of OS (HR=0.85 [95% CI: 0.72-1.02]; p=0.0752) with a marginal improvement in median OS of 16.4 months vs. 14.7 months (29). Keynote-240, a Phase III study evaluating pembrolizumab monotherapy vs. placebo in the second-

line HCC setting also failed to meet its co-primary endpoint of OS (HR=0.78 [95% CI: 0.611-0.998]; p=0.0238) and PFS (HR=0.78 [95% CI, 0.61-0.99]; p=0.0209) though numerical improvements in OS were reported with a median OS of 13.9 months in the pembrolizumab arm vs. 10.6 months in the placebo arm (91).

The IMbrave150 study is the first phase III trial to show a statistically significant and clinically meaningful survival benefit over the standard of care, sorafenib. With an OS HR of 0.58, Atezo+Bev has demonstrated it offers prolonged survival for patients with unresectable HCC and although only 161 OS events (32%) had been reported at the cutoff date, the magnitude of benefit is already large enough to demonstrate statistical significance as the pre-specified boundary for significance (0.0033) was crossed with a p value of 0.0006. Taken together with the manageable toxicity profile, these data suggest that the combination of Atezo+Bev provides an innovative first-line treatment option that addresses the unmet need for patients with unresectable HCC who currently do not have access to cancer immunotherapy.

B.2.13 Interpretation of clinical effectiveness and safety evidence

There remains a high unmet medical need for patients with HCC for whom the overall survival has not been improved upon by new approved therapies in over a decade. The current standard of care for unresectable HCC is sorafenib, which has a modest benefit-risk ratio given the known toxicity and limited efficacy (26, 27). In the REFLECT trial, treatment with lenvatinib was shown to be non-inferior to sorafenib in terms of OS (13.6 months vs. 12.3 months for lenvatinib vs. sorafenib, respectively), with a difference in median PFS over sorafenib of 3.7 months (7.4 months vs. 3.7 months for lenvatinib vs. sorafenib, respectively) per IRF RECIST v1.1, and is considered an alternative standard of care for unresectable HCC patients.

IMbrave150 is an ongoing Phase III, randomised, multicentre, open-label study designed to evaluate the efficacy and safety of Atezo+Bev versus sorafenib in patients with locally advanced or metastatic and/or unresectable HCC who had not received prior systemic treatment. The study was designed to capture endpoints which are relevant to UK clinical practice and address the unmet medical need for this patient population, in particular OS and PFS, response rates and duration of response, as well as the safety and tolerability of the combination and patient-reported outcomes. The open-label design of this study was used to spare patients from two placebo infusions; however, to minimise the potential bias associated with the open-label design, a blinded independent review of imaging for PFS was selected for the co-primary endpoint

Patients eligible for enrolment into IMbrave150 (and the supporting Phase Ib study GO30140) included those who had locally advanced or metastatic and/or unresectable HCC, with diagnosis confirmed by histology/cytology or clinically by AASLD criteria in cirrhotic patients, whose disease was not amenable to curative surgical and/or locoregional therapies. Clinically, patients with locally advanced or metastatic disease not amenable to curative surgical treatment are by definition considered to be unresectable. This may also include patients with intermediate stage HCC who are not amenable to locoregional therapy and/or those with progressive disease, providing they are deemed fit enough for systemic therapy. UK clinical experts estimated that 15–20% of unresectable, BCLC B patients would be referred for systemic treatments (following an average of two rounds of TACE), which is in line with the proportion of BCLC B patients enrolled in the IMbrave150 trial (16%). It is important to note that IMbrave150 allowed for the enrolment of high-risk patients, with approximately 40% of patients with macrovascular invasion. UK clinical experts confirmed to Roche that the baseline characteristics of patients enrolled in IMbrave150 are broadly reflective of unresectable HCC patients seen in UK clinical practice.

The IMbrave150 data demonstrated a statistically significant and clinically meaningful improvement in the co-primary endpoints of OS and PFS by IRF per RECIST v1.1 with Atezo+Bev over sorafenib. The observed OS HR translated into a reduction in the risk of death by 42% with the Atezo+Bev arm compared with the sorafenib arm. With a median duration of survival follow-up of 8.6 months for all patients, the OS results are statistically significant with the pre-specified efficacy boundary crossed, representing the first study in over a decade to demonstrate superior OS over sorafenib, the standard of care in unresectable HCC. Furthermore, a clear separation of the OS Kaplan-Meier curves between the two treatment arms occurred early (approximately 1 month post-randomisation) and remained over time despite a higher proportion of patients in the sorafenib arm having received subsequent systemic therapy, including immunotherapy.

It should also be noted that in previous clinical trials, the median OS for sorafenib has ranged from 12 to 14.7 months (27, 29, 41); therefore, based on the available evidence, the median OS of 13.2 months with sorafenib in the IMbrave150 study is in line with expectations. Furthermore, UK clinical experts stated that they were reassured that the comparator arm in IMbrave150 did not underperform and cited that a UK audit of sorafenib yielded a median survival of 8.5 months (92)

The observed PFS HR translated into a reduction in the risk of disease progression or death by 41% with the Atezo+Bev arm compared with sorafenib. The PFS Kaplan-Meier curves showed an early separation at the time of the first tumour assessment in favour of

Atezo+Bev compared with sorafenib. Taken together, the IMbrave150 data signify a pronounced improvement in OS and PFS with Atezo+Bev over the current standard of care.

In comparison to REFLECT, the IMbrave150 study was conducted in a patient population with more prognostically unfavourable baseline characteristics (41); the REFLECT study excluded patients with MVI of main portal trunk, greater than 50% hepatic involvement, or bile duct invasion. Despite the inclusion of these patients with poorer prognosis, IMbrave150 still demonstrated statistically significant and clinically meaningful improvement of OS and PFS with Atezo+Bev versus sorafenib in the ITT population.

A statistically significant and clinically meaningful improvement in ORR by IRF per RECIST v1.1 and HCC mRECIST was also observed with Atezo+Bev over sorafenib. The clinical benefit was highlighted by the high rate of patients who experienced a CR in the Atezo + Bev arm compared with the Sorafenib arm. While the median DOR of the combination arm has not been reached yet, there was a higher percentage of responders having a DOR ≥6 months (per IRF RECIST v1.1) in the Atezo+Bev arm compared with the sorafenib arm.

Results for secondary endpoints of PFS, ORR, and DOR by IRF per HCC mRECIST and by investigator per RECIST v1.1 were generally consistent to those of the IRF RECIST v1.1 analyses. OS, PFS, and ORR benefits were generally consistent across all pre-defined subgroups.

Pre-specified secondary analyses of robust PRO data using psychometrically valid questionnaires indicated that, compared with sorafenib, treatment with Atezo+Bev resulted in a clinically meaningful delay in deterioration of patient-reported functioning and quality of life. These results are complemented by the clinically meaningful delay in deterioration of patient-reported symptoms (including appetite loss, diarrhoea, fatigue, pain, and jaundice) observed with Atezo+Bev versus sorafenib. All of these results are substantiated by additional pre-specified exploratory PRO analyses, which showed consistent and large treatment benefits in favour of Atezo+Bev versus Sorafenib.

To our knowledge, IMbrave150 is the first positive study of a checkpoint inhibitor and anti-VEGF inhibitor combination in HCC. This study did not test the single-agent contribution of each drug to the combination, therefore it cannot be determined whether the observed efficacy is additive or synergistic. While both atezolizumab and bevacizumab monotherapy studies have shown modest efficacy in HCC in previous studies, Arm F of the Phase Ib GO30140 study met its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful improvement in PFS as assessed by IRF per RECIST v1.1 with Atezo + Bev over atezolizumab monotherapy (90). The totality of Arm F results demonstrate that both atezolizumab and bevacizumab contribute to the overall treatment effect of the

combination of Atezo + Bev. Those conclusions are further substantiated by recent negative Phase III studies of anti-PD-L1 agents used in monotherapy for the treatment of HCC (29, 91). Taken together, the findings of these studies suggest that although checkpoint inhibitors have activity in HCC, a monotherapy approach is insufficient and therefore combining atezolizumab with bevacizumab is necessary to improve clinical outcomes in HCC.

In terms of safety and tolerability, the Atezo+Bev combination in HCC was generally well-tolerated with manageable toxicities. The incidence of the safety events should be interpreted in context of the considerably longer duration of treatment with Atezo+Bev compared with sorafenib. While the spectrum of AEs differed between sorafenib and Atezo+Bev, the safety profile observed in both HCC populations was consistent with the known risks of the individual study treatments and the underlying disease.

The incidences of AEs, Grade 3–4 AEs, and AEs leading to any treatment withdrawal were comparable between the sorafenib and the Atezo+Bev populations. From a clinical perspective, the two most common AEs of hypertension and proteinuria with Atezo+Bev are generally not associated with symptoms and therefore, have less detrimental impact on the patients' quality of life compared with the most common AEs observed in the sorafenib arm; diarrhoea and palmar-plantar erythrodysaesthesia syndrome.

The proportion of patients with SAEs was numerically higher in the Atezo+Bev population compared with the sorafenib population, with no particular pattern of certain events driving the numerical increase observed between the two populations. However, the incidence of treatment-related SAEs was comparable between the two arms. The incidence of AEs leading to dose modification/interruption of any study treatment was lower in the Atezo + Bev population compared with the sorafenib population.

The incidence of atezolizumab-specific AESIs in the Atezo+Bev population was consistent with the known safety profile of atezolizumab and the underlying disease. No new atezolizumab AESIs were identified in the Atezo+Bev population. The spectrum, frequency, and severity of bevacizumab AESIs were in line with the safety profile of bevacizumab and with the underlying disease. No new bevacizumab AESIs were identified in the Atezo+Bev population.

Conclusions

IMbrave150 is the first randomised phase III study in over ten years to show a significant improvement in overall survival over sorafenib, with a 42% reduction in the risk of death and is the first positive phase III study of a cancer immunotherapy in patients with locally advanced or metastatic and/or unresectable HCC. The significantly longer overall survival versus sorafenib achieved with Atezo+Bev is underpinned by a 2.5-month increase in PFS,

a response rate of 27.3%, and a median duration of response that still has not been reached.

These clinically meaningful outcomes, combined with the safety and patient-reported outcome findings, demonstrate a favourable benefit-risk profile and therefore the combination of Atezo+Bev addresses the unmet need for patients with unresectable HCC who have not received prior systemic therapy.

Table 29: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	HCC patients with unresectable, advanced disease have few approved systemic treatments and most have significant liver damage which can further limit therapy options. Their prognosis is dismal, with rapid progression and short OS. Median survival is still less than one year; 4–8 months if untreated and 6–15 months with sorafenib treatment (26-29).	B.1.3.1, page 15
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	There was a statistically significant and clinically meaningful improvement in OS (stratified HR: 0.58 [95% CI: 0.42, 0.79], log-rank p-value= 0.0006) with Atezo+Bev over sorafenib in the ITT population. The Kaplan-Meier (KM) estimated median OS was 13.2 (95% CI: 10.4, NE) months in the sorafenib arm and was not reached in the Atezo+Bev arm.	B.2.6.1, page 34

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify published cost-effectiveness studies in the first-line treatment of patients with unresectable HCC.

An overview of the identified studies is provided below. Descriptions of the eligibility (inclusion/exclusion) criteria, search strategy, extraction methods, results extracted from included publications and PRISMA flow are provided in Appendix G.

B.3.1.1 Summary of identified studies and results

Overall, 57 eligible economic evaluations were identified assessing the cost-effectiveness of treatment for locally advanced or metastatic and/or unresectable HCC in the first-line setting. Of these studies, 27 were presented as full publications, 22 were presented as conference abstracts and eight were previous HTA submissions.

Due to the large volume of evidence identified by the review as well as the limited reporting of methodology and results in conference abstracts, the SLR focuses on studies published as full publications only (N=27).

The majority of studies were cost-utility analyses (CUAs) reporting incremental costs per quality adjusted life year (QALY) gained (n=13). Six studies were cost-effectiveness analyses (CEAs) (include refs), six were combined CUA/CEA and one cost-minimisation analysis (CMA). Finally, one study was a combined cost-utility/cost-benefit analysis reporting cost per quality adjusted life day (QALD) and net health benefit (NHB).

The most common approach to modelling was the Markov approach (n=17) (of which ten used a traditional three state model structure [progression free; progressed disease; death]. three studies were partitioned survival models (PSM), one was a decision tree and one analysis combined the Markov/decision tree model. In the remaining five studies, the model type was either not reported or non-applicable (e.g. database analyses).

A summary of the included economic evaluations is provided in Table 30.

Table 30: Summary list of published cost-effectiveness studies (n=27)

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Camma et al 2013 (93) Italy EUR (2012)	Partitioned survival model (assumed; reported as Markov model): • BCLC B HCC • BCLC C HCC • Death	Patients with HCC who have failed or are unfit for locoregional therapies; BCLC stage B or C, well compensated cirrhosis, ECOG PS 0-1	• Sorafenib (full/dose-adjusted): BCLC B and C together • Sorafenib (full/dose-adjusted): BCLC B • Sorafenib (full/dose-adjusted): BCLC C • BSC	**Clinical:** survival curves from SOFIA study (time-dependent transition rates obtained by assuming a Weibull distribution) **Cost:** published literature (DRG tariffs and national ambulance fees) **QOL:** utility weights derived from NICE TA178	BSC: NR Sorafenib: • Full dose, BCLC B and C: 0.16 • Adjusted-dose, BCLC B and C: 0.44 • Full dose, BCLC B: 0.32 • Adjusted-dose, BCLC B: 0.38 • Full dose, BCLC C: 0.16 • Adjusted-dose, BCLC C: 0.44	BSC: €4,142 Sorafenib: • Full dose, BCLC B and C: €16,081 • Adjusted-dose, BCLC B and C: €19,944 • Full dose, BCLC B: €24,224 • Adjusted-dose, BCLC B: €26,914 • Full dose, BCLC C: €14,841 • Adjusted-dose, BCLC C: €16,625	Sorafenib vs BSC ICER/QALY: • Full dose, BCLC B and C: €69,344 • Adjusted-dose, BCLC B and C: €34,534 • Full dose, BCLC B: €57,385 • Adjusted-dose, BCLC B: €54,881 • Full dose, BCLC C: €65,551 • Adjusted-dose, BCLC C: €27,916
Carr et al 2010 (94) US USD	Markov model: • First-line/no progression • First-line post-progression	Patients with advanced HCC with ≥1 tumour lesion that had not been previously	• Sorafenib • BSC	**Clinical:** transition probabilities from SHARP trial (OS and TTP extrapolated using lognormal	Total LYG: Sorafenib: 1.58 BSC: 1.05	Sorafenib: $40,639 BSC: $7,847	Sorafenib vs BSC ICER/LYG: $62,473

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
(2007)	• BSC/post-progression • Death	treated with local therapy; ECOG PS 0-2		distribution) **Cost:** Red Book, US expert opinion, Physicians' Fee and Coding Guide 2007, DRG tariffs, Medicaid laboratory fee schedule 2010 **QOL:** NA			
Chen et al 2018 (95) China/US USD (2016)	Markov model: • Decompensated cirrhosis • Compensated cirrhosis without progression • Compensated cirrhosis with progression • Death	Patients with advanced HCC; BCLC stage C, Child-Pugh class A or B, ECOG PS 1-2	• Sorafenib o Full dose o Adjusted dose • TACE	**Clinical:** transition probabilities from published literature (various) **Cost:** Medidata database, previously published study (96) **QOL:** NICE TA189(38) and previously published study (97)	Total QALYS China: • Full-dose sorafenib: 0.435 • Adjusted-dose sorafenib: 0.482 • TACE: 0.375 US: • Full-dose sorafenib: 0.435 • Adjusted-dose sorafenib: 0.482 • TACE: 0.375 Total LYG China: • Full-dose sorafenib: 7.236 • Adjusted-dose	China: • Full-dose sorafenib: $16,703.95 • Adjusted-dose sorafenib: $10,488.72 • TACE: $10,642.22 US: • Full-dose sorafenib: $34,190.70 • Adjusted-dose sorafenib: $23,377.97 • TACE: $95,061.13	ICER/LYG: China: • Full-dose sorafenib vs TACE: $101,028.8 • Adjusted-dose vs full-dose sorafenib: dose-adjusted sorafenib dominates US: • Full-dose sorafenib vs TACE: sorafenib

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					sorafenib: 7.898 • TACE: 6.357 US: • Full-dose sorafenib: 7.236 • Adjusted-dose sorafenib: 7.898 • TACE: 6.357		dominates • Dose-adjusted vs full-dose sorafenib: dose-adjusted sorafenib dominates
Clouet et al 2014 (98) France EUR (NR)	NA (CMA)	Patients with unresectable, non-metastatic HCC	• DEB-TACE • TACE	**Clinical:** NR **Cost:** DRGs used to estimate costs from PMSI data and ENCC **QOL:** NA	NA (CMA)	DEB-TACE: €3,960.10 TACE: €2,869.05 Incremental: €1,091.05	NA (CMA)
Cucchetti et al 2016 (99) Italy EUR (2014)	Markov model: • TACE • SAE • Post-TACE syndrome • In-hospital stay • Radiological evaluation 1 month post-TACE • Need for re-	Patients with unresectable HCC	• DEB-TACE • TACE	**Clinical:** transition probabilities from within study meta-analysis **Cost:** published literature, Italian Ministry of Health, Italian NHS **QOL:** published literature (97, 100, 101)	Total QALYs: DEB-TACE: 2.4 TACE: 2.0	DEB-TACE: €10,460 TACE: €9,435	Cost/QALY: DEB-TACE: €4,705 TACE: €4,821

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	TACE • Death						
Gupta et al 2019 (102) India USD (2017)	Markov model: • Progression free • Progressive disease • Death	Patients with advanced unresectable HCC; BCLC stage C	• Sorafenib • BSC	**Clinical:** transition probabilities from Asia-Pacific trial **Cost:** INASL, Central Government Health Scheme, Haryana/Tamil Nadu Medical Services, previously published study (103) **QOL:** NICE TA474 (38)	QALYs: Sorafenib: 0.50 BSC: 0.31 LYG: Sorafenib: 0.68 BSC: 0.43	Sorafenib: $293,978 BSC: $199,796	Sorafenib vs BSC ICER/QALY: $507,520 ICER/LYG: $382,796
Hamdy Elsisi et al 2019 (104) Egypt USD (2017)	Markov model: • Progression free • Progressive disease • Death	Patients with advanced HCC	• Sorafenib • BSC	**Clinical:** transition probabilities from published literature and RWD in Egypt (105) (106) **Cost:** Maadi Oncology and Hematology Military Hospital **QOL:** mapped utilities from NICE TA189 (38)	Total QALYs: Sorafenib: 46.24 BSC: 42.27	Sorafenib: $4,229,940 BSC: $3,092,886	Sorafenib vs BSC ICER/QALY: $286,776

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Ho et al 2018 (107) Taiwan NT$ (2014)	Markov model: • Progression free • Progressive disease • Death	Patients with advanced HCC, unresectable or unsuccessful locoregional therapy; Child-Pugh class A liver function	• Sorafenib monotherapy • Sorafenib combination (surgical resection, PEI, TACE, and/or radiotherapy)	**Clinical:** within study transition probabilities, Cancer Registry, Death Registry, NHIRD **Cost:** Cancer Registry, NHIRD **QOL:** mapped utilities from NICE TA189 (38)	QALYs: • Sorafenib combination: 0.5432 • Sorafenib monotherapy: 0.3837 LYG: • Sorafenib combination: 0.7535 • Sorafenib monotherapy: 0.5352	Sorafenib combination: NT$957,483 Sorafenib monotherapy: NT$522,695	Sorafenib combination vs monotherapy ICER/QALY: NT$2,725,943 ICER/LYG: NT$1,991,699
Kobayashi et al 2019 (108) Japan JPY (2017)	Partitioned survival model: • Progression free • Post-progression • Death	Patients with previously untreated, unresectable HCC	• Lenvatinib • Sorafenib	**Clinical:** survival curves from REFLECT trial (extrapolation of OS using log-logistic distribution and PFS using log-normal distribution) **Cost:** Delphi panel for resource use, NHI Drug Price List 2017, NHI Reimbursement Schedule	QALYs: • Lenvatinib: 1.46 • Sorafenib: 1.23 LYG: • Lenvatinib: 1.88 • Sorafenib: 1.62	Lenvatinib: JPY 5,088,957 Sorafenib: JPY 5,495,264	Lenvatinib vs sorafenib ICER/QALY: Lenvatinib dominates ICER/LYG: Lenvatinib dominates

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				QOL: EQ-5D-3L data from REFLECT trial			
Leung et al 2016 (109) Taiwan NT$ (2015)	Markov model: • Progression free • Progressive disease • Death	Patients with advanced, unresectable HCC	• Sorafenib • SBRT	**Clinical:** transition probabilities from SHARP trial (assumed beta distributions for PFS and progressed disease) **Cost:** NHIRD **QOL:** published literature (93, 110)	Total QALYs: • Sorafenib: 3.07 • SBRT: 2.81	Sorafenib: NT$2,166,079.70 SBRT: NT$1,197,039.20	Sorafenib vs SBRT ICER/QALY: NT$3,788,238
Leung et al 2017 (111) Taiwan NT$ (NR)	Markov model: • Stable disease • Progressive disease • Death	Patients with advanced, unresectable HCC	• Proton beam therapy • SBRT	**Clinical:** transition probabilities from phase I/II trial (112, 113) **Cost:** BNHI database 2016 **QOL:** derived from phase I/II trial (112, 113)	Incremental QALYs: Proton beam therapy vs SBRT: 2.61	Incremental costs: Proton beam therapy vs SBRT: NT$557,907	Proton beam therapy vs SBRT ICER/QALY: NT$213,354
Muszbek et al 2008 (114) Canada	Markov model: • First-line/no progression • First-line continued/post-	Patients aged >18 years with HCC who are unsuitable for surgical or locoregional	• Sorafenib • BSC	**Clinical:** transition probabilities from SHARP trial (extrapolation of OS using lognormal	Total LYG: • Sorafenib: 1.51 • BSC: 1.02	Sorafenib: $47,272 BSC: $10,309	Sorafenib vs BSC ICER/LYG: $75,759

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
CAD (2007)	progression • BSC • Death	therapies; life expectancy ≥12 weeks, ECOG PS 0-2		distribution) **Cost:** expert opinion for resource use, unit costs from Ontario Schedule of Benefits for Insured Services, Ontario Case Costing Project, British Colombia Medical Fee Services, University Health Network (Toronto) **QOL:** NA			
Naugler et al 2010 (115) US USD (NR)	Markov model: • HCC therapy or monitoring • Liver decompensation • Inside/outside Milan criteria • Orthotopic liver transplantati	Patients with unresectable HCC <2cm; compensated cirrhosis, potential transplant candidates	• Immediate treatment: TACE or RFA • Monitoring (every 3 months without treatment)	**Clinical:** transition probabilities from published literature (various) **Cost:** SEER database **QOL:** NA	Total life expectancy (years): Immediate treatment: • TACE: 4.269 • RFA: 5.273 Monitoring: • Vs TACE: 4.324 • Vs RFA: 5.236	Immediate treatment: • TACE: $142,869 • RFA: $92,094 Monitoring: • Vs TACE: $183,105 • Vs RFA: $144,427	TACE vs monitoring ICER/LYS: NR RFA vs monitoring: RFA dominates

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	on • Death						
Parikh et al 2017 (116) US USD (2015)	NA	Patients with advanced (AJCC stage III and IV) HCC	• Sorafenib • No therapy	**Clinical:** SEER-Medicare database **Cost:** Medicare data files **QOL:** NA	Median survival (years): All patients: • Sorafenib: 0.41 • No therapy: 0.17 Decompensated patients: • Sorafenib: 0.25 • No therapy: 0.17	All patients: • Sorafenib: $31,364 • No therapy: $10,950 Decompensated patients: • Sorafenib: $32,519 • No therapy: $13,922	Sorafenib vs no therapy ICER/LYG: All patients: $84,250 Decompensated patients: $224,914
Pollom et al 2017 (117) US USD (2015)	Combined decision tree/Markov model: • Local progression • Treatment for local progression • Post-treatment no evidence of disease • Post-local progression, no evidence	Patients with unresectable localised HCC eligible for both RFA and SBRT	• RFA-SBRT • RFA-RFA • SBRT-SBRT • SBRT-RFA	**Clinical:** transition probabilities from published study (118) **Cost:** Medicare Physician Fee Schedule 2015, SEER-Medicare database, Agency for Healthcare Research and Quality **QOL:** published literature (119) (97, 120)	Total QALYs: • RFA-SBRT: 1.558 • RFA-RFA: 1.546 • SBRT-SBRT: 1.565 • SBRT-RFA: 1.560	• RFA-SBRT: $193,288 • RFA-RFA: $193,571 • SBRT-SBRT: $197,557 • SBRT-RFA: $197,682	ICER/QALY: RFA-SBRT: reference RFA-RFA: dominated SBRT-SBRT: $558,679 SBRT-RFA: dominated

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	of disease • Distant/regional progression • Death						
Qin et al 2018 (121) China USD (NR)	Partitioned survival model (assumed; reported as Markov model): • Progression free • Progressed disease • Death	Patients with advanced or metastatic HCC who were ineligible for curative resection or local treatment	• FOLFOX4 • Sorafenib	**Clinical:** survival curves from EACH trial for FOLFOX4 and ORIENTAL trial for sorafenib **Cost:** clinician interviews, China Hospital Pharmaceutical Audit database **QOL:** published literature (122)	Total QALYs: • FOLFOX4: 0.42 • Sorafenib: 0.38	FOLFOX4: $8,428 Sorafenib: $12,798	FOLFOX4 vs sorafenib ICER/QALY: FOLFOX4 dominates
Rognoni et al 2017 (123) Italy EUR (2015)	Markov model: • Stable disease • Disease progression • Disease-related death • Death for other causes	Patients with intermediate or advanced HCC	• TARE • Sorafenib	**Clinical:** transition probabilities estimated from PLD collected at three oncology (PLD used to fit survival curves using exponential, Gompertz, and Weibull distributions) centres in Italy	QALYs: Intermediate: • TARE: 1.178 • Sorafenib: 0.638 Advanced: • TARE: 0.639 • Sorafenib: 0.568 LYG: Intermediate: • TARE: 2.531	Intermediate: • TARE: €31,071 • Sorafenib: €29,289 Advanced: • TARE: €21,961 • Sorafenib: €30,750	TARE vs sorafenib ICER/QALY: Intermediate: €3,302 Advanced: TARE dominates ICER/LYG:

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				Cost: Regional Healthcare Service price list, Regional DRG Reimbursement **QOL:** CEA Registry	• Sorafenib: 1.575 Advanced: • TARE: 1.445 • Sorafenib: 1.306		Intermediate: €1,865 Advanced: TARE dominates
Rognoni et al 2018 (124) Italy EUR (2016)	Markov model: • Stable disease • Disease progression • Disease-related death • Death for other causes	Patients with intermediate stage HCC	• TARE/TACE + sorafenib • TARE + sorafenib	**Clinical:** transition probabilities estimated from PLD collected at three oncology centres in Italy (PLD used to fit survival curves using exponential and Weibull distributions) **Cost:** Regional Healthcare Service price list, Regional DRG Reimbursement **QOL:** NR	QALYs: • TARE/TACE + sorafenib: 1.385 • TARE + sorafenib: 0.937 LYG: • TARE/TACE + sorafenib: 3.494 • TARE + sorafenib: 2.361	TARE/TACE + sorafenib: €36,509 TARE + sorafenib: €42,812	TARE/TACE + sorafenib vs TARE + sorafenib ICER/QALY: TARE/TACE + sorafenib dominates ICER/LYG: TARE/TACE + sorafenib dominates
Rostambeigi et al 2014 (125)	Decision tree: • Pathway 1: survival (wait-list/transplant, recurrence	Patients with HCC; BCLC stage A, B, or C	• TARE • TACE	**Clinical:** published literature (various) **Cost:** NR **QOL:** NA	Mean survival (months): Simulation up to 5 years: BCLC A:	Simulation up to 5 years: BCLC A: • TACE: $17,000 • TARE: $31,000	ICER/month survival, TARE vs TACE: Simulation up to

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
US USD (NR)	rate at 40%, 60%, or 80%) • Pathway 2: death				• TACE: 39.5 • TARE: 29.7 BCLC B • TACE: 22.9 • TARE: 16 BCLC C: • TACE: 13.3 • TARE: 17.1 Simulation up to 3 years: BCLC A: • TACE: 27.8 • TARE: 23.1 BCLC B: • TACE: 19.3 • TARE: 14.7 BCLC C: • TACE: 12.6 • TARE: 15.5	BCLC B: • TACE: $17,000 • TARE: $31,000 BCLC C: • TACE: $17,000 • TARE: $31,000 Simulation up to 3 years: BCLC A: • TACE: $17,000 • TARE: $31,000 BCLC B: • TACE: $17,000 • TARE: $31,000 BCLC C: • TACE: $17,000 • TARE: $31,000	5 years: • BCLC A: TACE dominates • BCLC B: TACE dominates • BCLC C: $356 Simulation up to 3 years: • BCLC A: TACE dominates • BCLC B: TACE dominates • BCLC C: $366
Shaya et al 2014 (126) US USD (2011)	NA – database analysis	Patients with primary (stage I-IV) HCC enrolled in Medicare	• No treatment • Chemotherapy • Radiation • Liver directed • Resection • Transplant	**Clinical:** SEER-Medicare database **Cost:** SEER-Medicare database **QOL:** NA	Mean survival (years): Stage I: • No treatment: 1.06 • Chemotherapy: 1.29 • Radiation: 1.47 • Liver directed:	Stage I: • No treatment: $35,390 • Chemotherapy: $68,824 • Radiation: $65,098 • Liver directed: $95,566	ICER/LYG, vs no treatment: Stage I: • No treatment: - • Chemotherapy: NR • Radiation: $74,404

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					2.67 • Resection: 4.51 • Transplant: 5.98 Stage II: • No treatment: 1.04 • Chemotherapy: 1.27 • Radiation: 1.39 • Liver directed: 2.14 • Resection: 3.08 • Transplant: 5.85 Stage III: • No treatment: 0.56 • Chemotherapy: 0.95 • Radiation: 1.02 • Liver directed: 1.48 • Resection: 2.81 Stage IV: • No treatment: 0.38 • Chemotherapy: 0.71 • Radiation: 0.62 • Liver directed:	• Resection: $123,807 • Transplant: $207,473 Stage II: • No treatment: $38,265 • Chemotherapy: $61,949 • Radiation: $78,333 • Liver directed: $97,422 • Resection: $125,378 • Transplant: $231,774 Stage III: • No treatment: $27,887 • Chemotherapy: $54,101 • Radiation: $54,115 • Liver directed: $77,069 • Resection: $126,738 Stage IV:	• Liver directed: $25,345 • Resection: $15,303 • Transplant: $55,066 Stage II: • No treatment: - • Chemotherapy: NR • Radiation: NR • Liver directed: $25,657 • Resection: $29,736 • Transplant: $38,337 Stage III: • No treatment: - • Chemotherapy: $68,129 • Radiation: $56,715 • Liver

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					1.32 • Unstaged: No treatment: 0.57 • Chemotherapy: 0.93 • Radiation: 1.14 • Liver directed: 2.18 • Resection: 3.9 • Transplant: 3.82	• No treatment: $23,791 • Chemotherapy: $48,148 • Radiation: $49,638 • Liver directed: $69,084 Unstaged: • No treatment: $23,627 o Chemotherapy: $47,890 o Radiation: $55,710 o Liver directed: $87,859 o Resection: $124,060 o Transplant: $244,442	directed: $49,866 • Resection: $37,366 Stage IV: • No treatment: - • Chemotherapy: $74,037 • Radiation: $108,928 • Liver directed: $33,940 Unstaged: • No treatment: - • Chemotherapy: $67,533 • Radiation: $56,102 • Liver directed: $30,964 • Resection: $20,721 • Transplant: $95,351
Thein et al	NA – database	Patients aged	• No treatment	**Clinical:** Ontario	QALYs lost:	No treatment:	ICER, vs no

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
2017a (127) Canada USD (2013)	analysis	≥18 years with HCC	• TACE + RFA • RFA alone • RFA + resection • Resection • TACE + resection • RFA + transplant • TACE + transplant • RFA + resection + transplant • Transplant • Resection + transplant	Cancer Registry (OCR) **Cost:** Physician Claims History Database for OHIP, National Ambulatory Care Reporting System database, Ontario Drug Benefit Program **QOL:** NR	• No treatment: 10.1149 • TACE + RFA: 9.3606 • RFA: 9.8759 • RFA + resection: 9.1399 • Resection: 9.9144 • TACE + resection: 10.999 • RFA + transplant: 11.8248 • TACE + transplant: 11.4621 • RFA + resection + transplant: 11.2472 • Transplant: 11.8696 • Resection + transplant: 10.8734 PYLL: • No treatment:	$38,472 TACE + RFA: $48,485 RFA: $55,925 RFA + resection: $109,927 Resection: $119,032 TACE + resection: $126,514 RFA + transplant: $155,898 TACE + transplant: $178,354 RFA + resection + transplant: $208,484 Transplant: $211,286 Resection + transplant: $222,275	treatment **ICER/QALY:** • TACE + RFA: $2,465 • RFA: $15,553 • RFA + resection: $48,761 • Resection: $79,495 • TACE + resection: $217,932 • RFA + transplant: $59,642 • TACE + transplant: $72,941 • RFA + resection + transplant: $60,602 • Transplant: $76,738 • Resection + transplant: $71,972

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					11.2251 • TACE + RFA: 9.6379 • RFA: 10.2246 • RFA + resection: 9.0966 • Resection: 10.0818 • TACE + resection: 11.4624 • RFA + transplant: 12.0635 • TACE + transplant: 11,4675 • RFA + resection + transplant: 11.1088 • Transplant: 11.9376 • Resection + transplant: 10.756		**ICER/LYG:** • TACE + RFA:$1,261 • RFA: $7,919 • RFA + resection: $27,143 • Resection: $41,301 • TACE + resection: $87,759 • RFA + transplant: $37,226 • TACE + transplant: $43,392 • RFA + resection + transplant: $40,069 • Transplant: $47,930 • Resection + transplant: $46,157
Thein et al 2017b	NA – database analysis	Patients aged ≥18 years with	• TACE or TACE + sorafenib	**Clinical:** Ontario Cancer Registry	QALYs: • No treatment:	No treatment: $36,415	ICER, vs no treatment/BSC

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
(128) Canada USD (2013)		HCC	• Sorafenib • Non-sorafenib chemotherapy • No treatment/ BSC	(OCR) **Cost:** Physician Claims History Database for OHIP, National Ambulatory Care Reporting System database, ODB Program **QOL:** NR	0.5422 • TACE or TACE + sorafenib: 1.2828 • Non-sorafenib chemotherapy: 0.9628 • Sorafenib: 0.9474 LYG: • No treatment: 0.7034 • TACE or TACE + sorafenib: 1.6715 • Non-sorafenib chemotherapy: 1.3314 • Sorafenib: 1.3370	TACE or TACE + sorafenib: $45,638 Non-sorafenib chemotherapy: $51,657 Sorafenib: $53,198	**ICER/QALY:** • TACE or TACE + sorafenib: $6,665 • Non-sorafenib chemotherapy: $47,557 • Sorafenib: $99,032 **ICER/LYG:** • TACE or TACE + sorafenib: $4,569 • Non-sorafenib chemotherapy: $31,367 • Sorafenib: $59,799
Vitale et al 2010 (129) Italy EUR	Markov model: • Compensated cirrhosis • Decompensated cirrhosis • Liver	Patients with HCC meeting the Milan criteria who are candidates for transplantation	• Sorafenib before liver transplant • No bridging therapy before liver transplant	**Clinical:** transition probabilities from published literature (various, including SHARP trial) **Cost:** author's institution	NR	NR	Sorafenib vs no bridging therapy ICER/QALD: €197 *[NHB reported in graph format]*

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
(2008)	transplant • Post-liver transplant follow up • Death			**QOL:** previous systematic review (not referenced)			
Zhang et al 2015 (96) China USD (NR)	Markov model: • Progression free • Progressed disease • Death	Patients aged ≥18 years with previously untreated advanced HCC; ECOG PS 0-2, Child-Pugh class A or B liver function	• Sorafenib • BSC	**Clinical:** transition probabilities from Asia-Pacific study (not referenced) and medical records **Cost:** national drug prices **QOL:** Asia-Pacific study (not referenced)	Total QALYs: Sorafenib: 0.45 BSC: 0.27	Sorafenib: $19,149.05 BSC: $897.21	Sorafenib vs BSC ICER/QALY: $101,399.11
Zhang et al 2016a (130) China USD (NR)	Markov model: • Progression free • Progressed disease • Death	Patients with previously untreated advanced HCC	• FOLFOX4 • Sorafenib	**Clinical:** EACH trial for FOLFOX4, ORIENTAL trial for sorafenib (reference to previous study for estimation of transition probabilities (131)) **Cost:** national drug prices, West China Hospital **QOL:** NR	Total QALYs: FOLFOX4: 0.3808 Sorafenib: 0.3935	FOLFOX4: $6,876.02 Sorafenib: $18,748.00	FOLFOX4 vs sorafenib ICER/QALY: $934,801.57

Study, country, currency (ref year)	Summary of model	Patient population	Interventions	Model inputs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Zhang et al 2016b (132) China USD (NR)	Markov model: • Progression free • Progressed disease • Death	Patients with advanced HCC; ECOG PS 0-2, Child-Pugh Class A or B liver function, detectable HBsAg	• Sorafenib + antiviral therapy • Sorafenib alone	**Clinical:** transition probabilities estimated from medical records of patients at West China Hospital and a previously defined formula (131) **Cost:** national drug prices, West China Hospital **QOL:** published literature (93)	Total QALYs: Sorafenib + antivirals: 0.68 Sorafenib alone: 0.42	Sorafenib + antivirals: $25,026.04 Sorafenib alone: $20,249.64	Sorafenib + antivirals vs sorafenib alone ICER/QALY: $18,370.77
Zhao et al 2017 (133) China USD (2015)	Markov model: • Post-therapy, stable • Post-therapy, progression • Death	Patients with unresectable HCC; BCLC stage B or C, Child-Pugh class A or B liver function, ECOG PS 0-2	• TACE • TACE-sorafenib	**Clinical:** transition probabilities from published literature (various) **Cost:** NR **QOL:** published literature (93, 119)	Total QALYs: TACE-sorafenib: 1.02 TACE: 0.71	TACE-sorafenib: $44,542 TACE: $26,951	TACE-sorafenib vs TACE ICER/QALY: $56,745

AJCC, American Joint Committee on Cancer; AUD, Australian dollar; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CAD, Canadian dollar; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; DEB-TACE, drug eluting beads-transarterial chemoembolisation; DRG, Diagnosis Related Group; ECOG, Eastern Cooperative Oncology Group; ENCC, French National Scale for Common Methodology Costs; EQ-5D-3L, European Quality of Life-5 Dimensions; EUR, euro; FOLFOX4, oxaliplatin, leucovorin, and 5-fluorouracil; GBP, Great British pound; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; INASL, Indian National Association for the Study of the Liver; LYG, life year gained; LYS, life year saved; NA, not applicable; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; NICE, National Institute for Health and Care Excellence; NR, not reported; NT$, New Taiwanese dollar; OHIP, Ontario Health Insurance Plan; OS, overall survival; PEI, percutaneous ethanol injection; PFS, progression free survival; PLD, patient level data; PYLL, potential years of life lost; QALD, quality adjusted life day; QALY, quality adjusted life year; QOL, quality of life; RFA, radiofrequency ablation; RWD, real-world data; SBRT, stereotactic body radiation therapy; SEER, Surveillance, Epidemiology, and End Results; SMC, Scottish Medicines Consortium; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; TTP, time to progression; UK, United Kingdom; US, United States; USD, United States dollar.

B.3.2 Economic analysis

The cost-effectiveness studies identified in Section B.3.1, as well as previous NICE technology appraisals, were utilised to inform the structure for the model used in the economic analysis. However, none of the identified literature appraised Atezo+Bev for the first-line treatment of adult patients with unresectable HCC. Therefore, a de novo economic model was built to inform decision making.

B.3.2.1 Patient population

The de novo analysis assesses Atezo+Bev in adult patients with locally advanced or metastatic and/or unresectable HCC who had not received prior systemic treatment, in comparison to sorafenib and lenvatinib. This population is consistent with the ITT population of study IMbrave150, the NICE final scope for this appraisal, the decision problem and the anticipated marketing authorisation for Atezo+Bev.

B.3.2.2 Model Structure

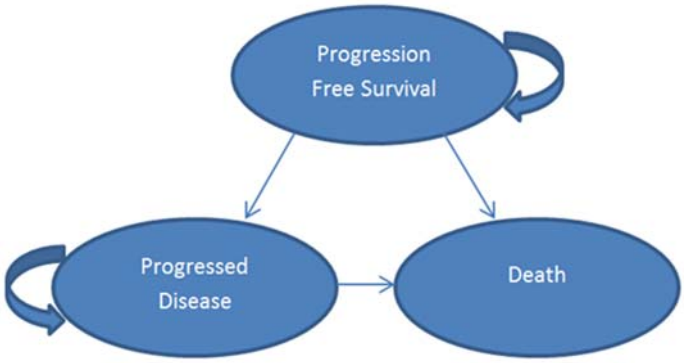
The economic evaluation was developed in Microsoft Excel and is an Area-Under-the-Curve (AUC) or partitioned survival model and is composed of 3-mutually exclusive health states, “progression-free survival (PFS)”, “progressed disease (PD)” and “death”. This approach is consistent with previous appraisals accepted by NICE for HCC, TA474, TA551 and TA555 (38, 42, 43).

Within the AUC model, health states are based on the partitioning of the proportion of patients alive into “PFS” and “PD” at discrete time points, based on the PFS and OS curves from IMbrave150 and the relative treatment effect derived from the ITC. The proportion of patients in the “PD” health state is assumed to be the difference between the OS and PFS health states. The three health states in the model represent the primary stages of disease in unresectable HCC.

The AUC model structure was selected because the three health states in the model represent the primary stages of disease in unresectable HCC, and is fully aligned with two of the primary objectives of treatment in HCC; avoiding disease progression and prolonging life. PFS, PD and death are the most relevant disease related health states from a patient, clinician and NHS perspective. Further, the direct correspondence between the primary endpoints of the IMbrave150 trial (i.e. PFS and OS) and the survival functions required to determine state occupancy allows for full use of the IMbrave150 data. The model structure and health states selected are typical of modelling in oncology and were used in all previous HCC NICE submissions (38, 42, 43). As demonstrated below, the partitioned survival model

was able to accurately represent the available data and known long-term outcomes for PFS and OS. As such, a partitioned survival model was well justified. The resulting structure can be found in Figure 9.

Figure 9: Economic model structure



The health economic model was developed to compare the cost-effectiveness of Atezo+Bev vs. the UK standard of care therapies in patients with locally advanced or metastatic and/or unresectable HCC who had not received prior systemic treatment (i.e. sorafenib and lenvatinib). More details and further justification for the comparisons to UK standard of care therapies within our submission are provided in Sections B.1.1 and B.3.2.3.

All patients enter the model in the PFS health state and remain in this health state until they progress. At progression, patients either transition into the PD health state or enter the absorbing health state of death. Patients in the PD health state remain there until death. Patients cannot transition to an improved health state (i.e. back to PFS), a restriction that is consistent with the clinical course of HCC and previous economic modelling in oncology.

Due to the structural form of the model, patient transitions between the health states were not explicitly modelled. Instead, the proportion of patients in each health state was based on its respective survival curve from IMbrave150 for Atezo+Bev and sorafenib. For lenvatinib, this was based on the relative treatment effects derived from the ITC. The partitioned survival approach allows for the modelling of OS and PFS based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with Atezo+Bev and sorafenib. However, the primary limitation of this approach is that as transitions are not explicitly modelled, the model structure is rigid and does not allow exploratory or sensitivity analyses to be explored that require changing the transition probability between different health states.

The model inputs (efficacy, safety and tolerability) for the intervention arm and sorafenib are based on the results of the phase III IMbrave150 trial for Atezo+Bev vs sorafenib. Model inputs for lenvatinib are generated from the indirect treatment comparison (ITC) outlined in

Section B.2.9. Model results are reported in terms of cost per life years gained (LYG) and costs per quality adjusted life years (QALY) gained. This appropriately reflects the decision problem.

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle.

The economic model base case uses a time horizon of 20 years, which is considered sufficiently long enough to reflect all important differences in costs or outcomes between the technologies being compared. This takes into consideration: 1) prognosis of patients treated in this setting; 2) expected survival times following present NHS treatment in this setting and 3) the maximum plausible impact of improved outcomes following treatment with Atezo+Bev. Scenario analyses are provided that consider both shorter and longer time horizons. The 20-year time horizon is also consistent with TA551, the recent lenvatinib appraisal in first-line advanced or metastatic HCC (42).

Costs and health outcomes are discounted at 3.5 % and the perspective of the NHS and personal social services (PSS) is assumed, as per the NICE reference case (134).

The model has been designed to use a weekly cycle, with the proportion of patients in each health state calculated each week. Transition between health states can occur at any time within the cycle. To account for the over or under estimation of transitions occurring at the beginning or end of the cycle, a half-cycle correction was applied, in line with previous NICE technology appraisals in this disease area (38, 42, 43)

Table 31 details the main features of this economic analysis as compared with previous NICE appraisals in first line unresectable HCC.

Table 31: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA474 Sorafenib (38)	TA551 Lenvatinib (42)	Base Case	Justification
Time horizon	Lifetime	Lifetime	Lifetime	Atezo+Bev is associated with improved OS and PFS versus sorafenib and lenvatinib over the lifetime of individuals
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Yes	NICE reference case (134) Only direct health effects related to patients were considered, and no wider societal impact or impact on carers

Discount of 3.5% for utilities and costs	Yes	Yes	Yes	NICE reference case (134)
Perspective (NHS/PSS)	Yes	Yes	Yes	NICE reference case (134)
Treatment waning effect?	None	None	None	Clinical experts explained that the duration of treatment effect is very hard to quantify. This is explored in the model, and the impact of modelling a waning treatment effect is minimal
Source of utilities	Mapping from FACT-G to a set of time trade-off utility values using an algorithm developed by Dobrez et al	REFLECT	IMbrave150	Utility values and efficacy data are taken from the same source for consistency. The appraisal committee considered utility values in TA474 implausible, as the utility value for the progressed state was higher than that for the progression-free state. The committee accepted the utility values in TA551 from the REFLECT trial.
Source of costs	NHS reference costs; PSSRU; NHS Health and Social Care Information Centre; Newcastle Upon Tyne 2006/07 tariffs*; Plymouth Hospital NHS Trust 2008*; UCL lab tariff 2007*; Mullhaven Medical Laboratory 2008*; BNF	NHS reference costs; PSSRU; BNF; Sorafenib submission to NICE (2016); Nuffield Trust; Marie Curie Cancer Care	NHS reference costs; PSSRU; BNF; Sorafenib submission to NICE (2016); Nuffield Trust; Marie Curie Cancer Care	An SLR was conducted to identify studies reporting cost and resource use data (see Appendix I). None of the identified studies were conducted in the UK and therefore they were not considered to be relevant to clinical practice in England

* These references provided in the TA474 submission (38) are no longer available.
Abbreviations: BNF: British National Formulary; FACT-G: Functional Assessment of Cancer Therapy - General; NHS: National Health Service; OS: overall survival; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; SLR: systematic literature review; UCL: University College London.

B.3.2.3 Intervention technology and comparators

The final scope intervention is Atezo+Bev. In line with the UK standard of care for patients with unresectable HCC, the comparators included in the economic model include sorafenib and lenvatinib.

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the economic model

The primary source for clinical data in the economic model for the intervention is the Phase III pivotal randomised controlled trial, IMbrave150, comparing Atezo+Bev to sorafenib. This study is also the data source for adverse events and quality of life (utilities) for Atezo+Bev and sorafenib.

As lenvatinib was not included in IMbrave150, and there were no head-to-head trials comparing it to Atezo+Bev, an ITC was conducted to estimate its relative effectiveness. Survival estimates for lenvatinib were then generated by applying the hazard ratios generated by the ITC to survival data from the IMbrave150 study in the economic model (Section in B.2.9).

PFS and OS results from IMbrave150 were extrapolated to the 20-year time-horizon of the model, as lifetime results are not available for patients in the IMbrave150 study. The maximum follow-up from IMbrave150 was 16 months, and at the time of the clinical cutoff date of 29 August 2019, only 161 OS events (32%) had occurred, 28.6% in the Atezo+Bev arm and 39.4% in the sorafenib arm.

Guidance from the NICE DSU was followed to identify base case parametric survival models for OS, PFS and time to treatment discontinuation (TTD) (134).

All parametric models were assessed against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for statistical fit to the observed data. Curves were visually inspected and validated against relevant long-term data sources available to help identify the most plausible survival model. Clinical expert opinion was also utilised to validate the extrapolation approach taken.

B.3.3.1.1 Proportional hazards assessment

The validity of the PH assumption between treatments was assessed. This was tested using the PH Schoenfeld residual test and via visual inspection of the log-cumulative hazard plots.

B.3.3.1.1.1 Overall Survival

The log-cumulative hazard plot for OS is presented in Figure 10. Based on this graphical assessment, the OS curves could be considered parallel, hence PH assumption seems to hold. However, independent parametric models for each treatment arm were also fit for OS allowing for both PH and non-PH within the model. Additionally, the PH global Schoenfeld residual test yielded a p-value of 0.5097, which indicates no statistically significant deviation to the PH assumption (Figure 11).

Figure 10: Log-cumulative hazard plot – OS data

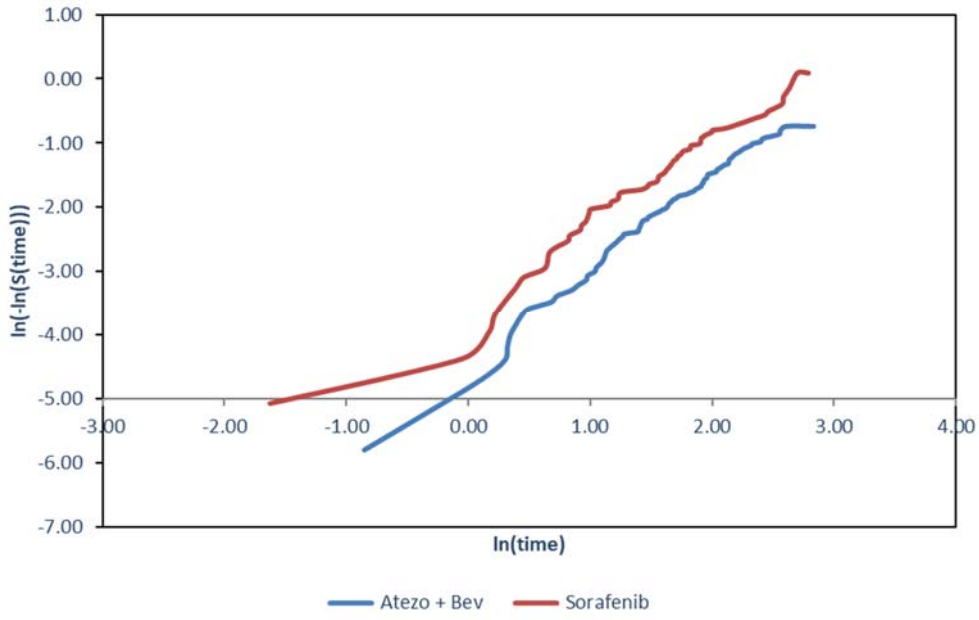
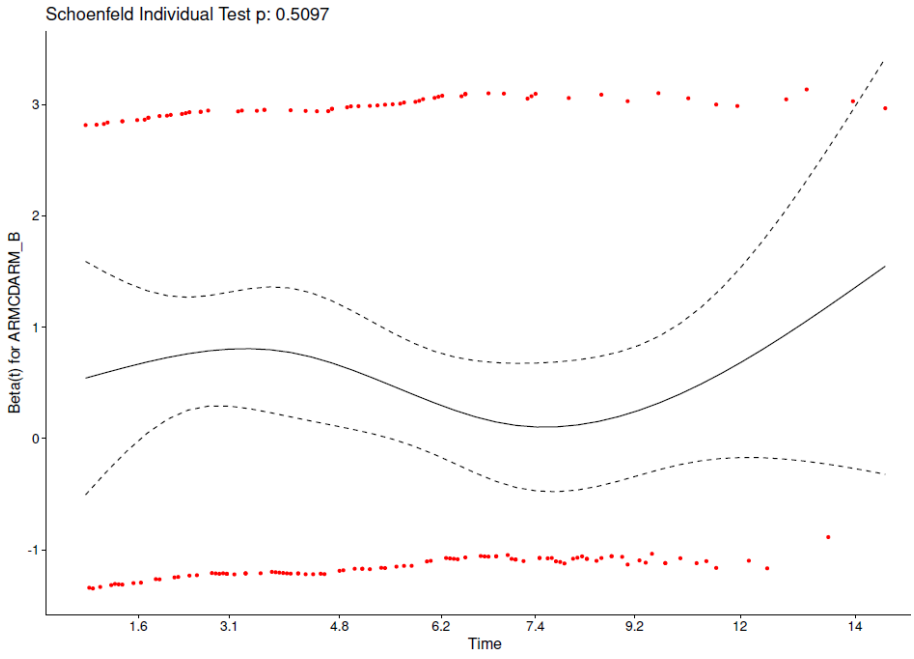


Figure 11: Overall survival PH Schoenfeld residual test



B.3.3.1.1.2 Progression-free Survival

The log-cumulative hazard plot for PFS is presented in Figure 12. Based on visual inspection of the log cumulative hazard plot, it was determined that the PH assumption does not hold for PFS, given the curves cross at a couple of time points and are not entirely parallel, suggesting a change in the trend of the hazard. However, the PH global test yielded a p-value of 0.3324 (Figure 13), which indicates no statistically significant deviation to the PH assumption. To capture a potential change of the hazard ratio over time, independent parametric models for each treatment arm have been used in the model for both PFS and OS.

Figure 12: Log-cumulative hazard plot – PFS data

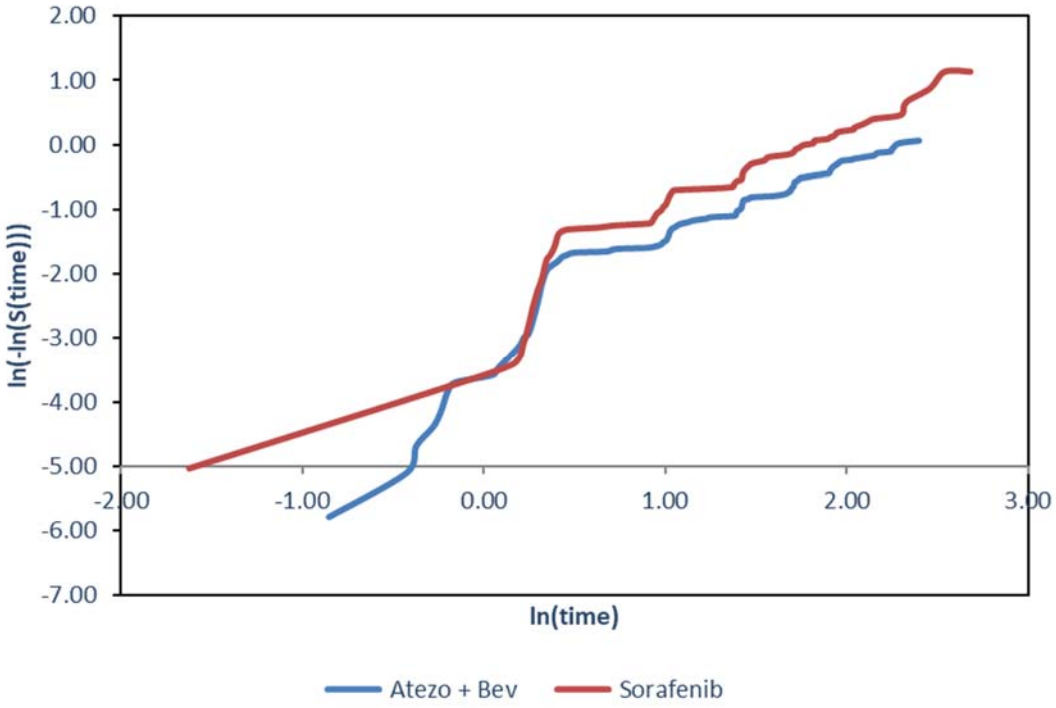
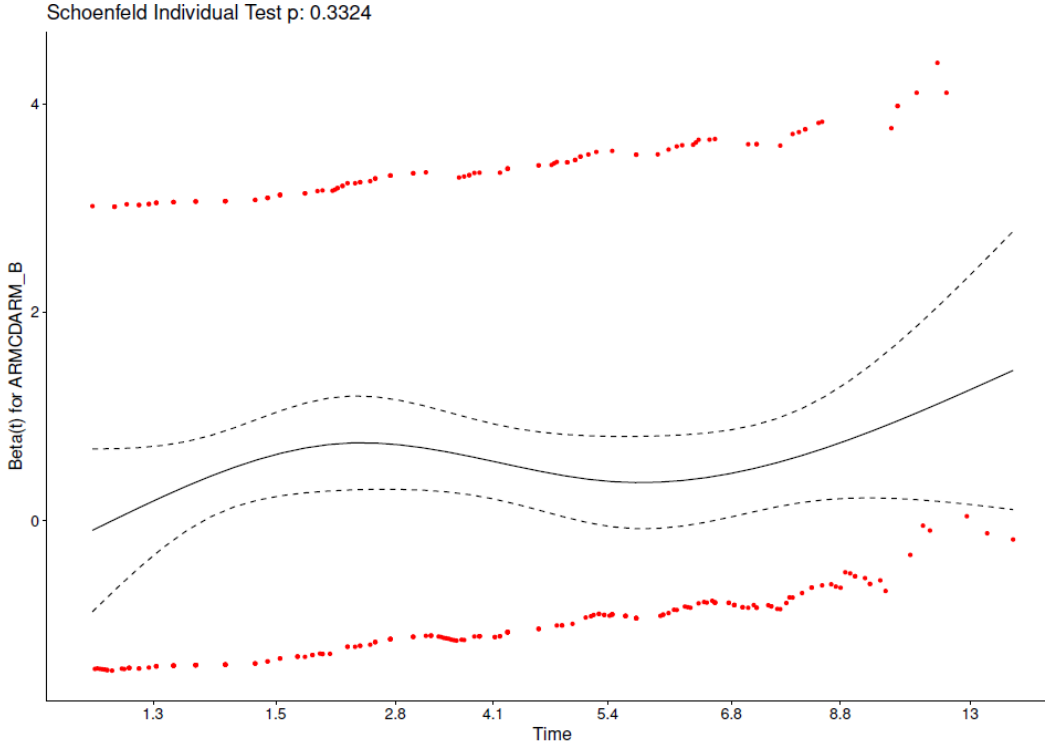


Figure 13: Progression-free survival PH Schoenfeld residual test



B.3.3.2 OS extrapolation

To determine which distribution was the most appropriate fit to the observed data, six parametric distributions (Exponential, Weibull, Log-normal, Generalised Gamma, Log-logistic, and Gompertz) were fitted to the observed data and assessed for goodness of fit using AIC and BIC tests, and visual inspection. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered important. Thus when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility becomes paramount.

Table 32 provides the AIC and BIC statistics for Atezo+Bev and Table 33 provides the AIC and BIC statistics for sorafenib.

Table 32: Summary of goodness of fit for OS – Atezo+Bev

	Overall Survival – goodness of fit statistics Atezo + Bev	
Parametric distribution	**AIC**	**BIC**
Exponential	547.24 (6)	551.06 (5)
Weibull	538.43 (4)	546.06 (4)
Log-normal	534.56 (2)	542.19 (2)
Generalised Gamma	534.55 (1)	542.19 (1)
Log-logistic	536.30 (3)	543.93 (3)
Gompertz	544.90 (5)	552.53 (6)

Table 33: Summary of goodness of fit for OS – Sorafenib

	Overall Survival – goodness of fit statistics - sorafenib	
Parametric distribution	**AIC**	**BIC**
Exponential	325.09 (5)	328.20 (5)
Weibull	322.36 (4)	328.57 (4)
Log-normal	320.63 (1)	326.84 (1)
Generalised Gamma	322.26 (3)	331.57 (3)
Log-logistic	320.88 (2)	327.09 (2)
Gompertz	325.28 (6)	331.49 (6)

Based on the AIC and BIC values for Atezo+Bev, the best fitting function for OS would be the Generalised Gamma. However, given that parametric models with a difference in AIC / BIC of less than five are considered similar, all models apart from Exponential and Gompertz appear to have similar statistical fit for OS. Based on the AIC and BIC values for sorafenib, the best fitting function for OS would be the log-normal. However, all models appear to have similar statistical fit for OS. It should be noted that AIC and BIC tests are based only upon the relative fit of parametric models to the observed data. While these tests are useful to determine which models fit the observed data best, they cannot provide information on how suitable a parametric model is for the time period beyond the final trial follow-up. In other words, the AIC and BIC tests address only the internal validity of fitted models, but not their external validity.

All parametric distributions were assessed for visual fit to the Kaplan Meier data (Figure 14 and Figure 15).

Figure 14: Visual fit of OS distributions to IMbrave150 KM data (Atezo+Bev)

Figure 15: Visual fit of OS distributions to IMbrave150 KM data (sorafenib)

As demonstrated above, the curves seem to follow a similar trend for both arms of the model. The exponential model seems to underestimate survival in the first 6 months. The Gompertz and Weibull are generally a poor fit for both curves, across different stages of the KM: frequently over and underestimating survival. In line with the AIC/BIC statistical fit, the log-logistic, log-normal and Generalised Gamma curves appear as the best visual fits.

The resulting tails of the distributions were assessed for their clinical plausibility (Figure 16 and Figure 17).

Figure 16: Atezo+Bev OS extrapolation curves

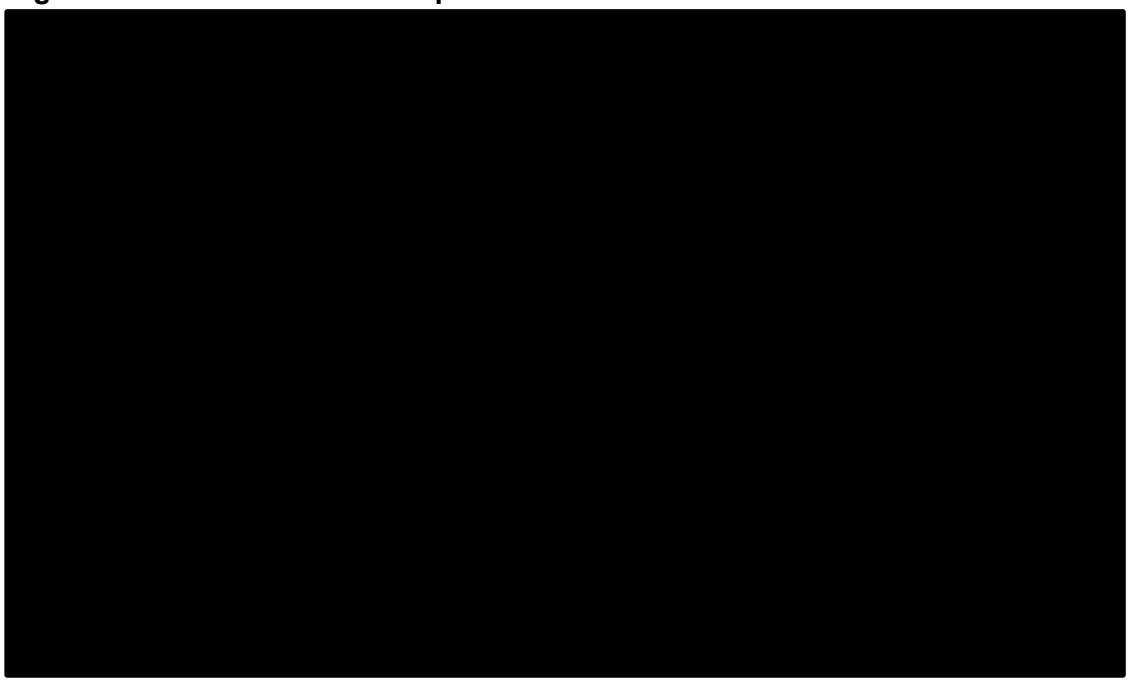


Figure 17: Sorafenib OS extrapolation curves

Initially, the log-logistic distribution was the preferred distribution based on statistical fit and visual inspection alone. Furthermore, the log-logistic curve was considered the most suitable model in the lenvatinib NICE submission and the reconsideration of sorafenib (38, 42).

However, before determining the correct distribution to extrapolate OS, expert opinion from six UK clinicians was was collected, as part of an advisory board organised by Roche (36). This was to ensure the curves represented outcomes seen in UK clinical practice. The survival curves of Atezo+Bev, sorafenib and lenvatinib were presented using all six

distributions. It was a unanimous decision that only the exponential model and the Generalised Gamma model represented clinically plausible estimates, as the remaining four models projected a higher OS for sorafenib than lenvatinib, which is not aligned with the REFLECT trial clinical data which showed lenvatinib OS to be non-inferior to sorafenib (61).

Table 34 provides the proportion of patients expected to be alive at set time points, comparing the exponential and Generalised Gamma models with the IMbrave150 trial-based survival/REFLECT trial, and REFLECT KM data. The exponential and Generalised Gamma proportions were presented at the advisory board in order to validate the resulting long-term survival estimates. The clinical experts unanimously agreed that the exponential curve represented the most realistic survival rates for both sorafenib and lenvatinib.

Table 34: Proportion of patients expected to be alive at set time points based on parametric distributions, compared with IMbrave150/REFLECT trial data

	12 months			24 months			36 months			48 months			60 months		
	Atezo+ Bev	Sora	Lenva	Atezo+ Bev	Sora	Lenva	Atezo+ Bev	Sora	Lenva	Atezo+ Bev	Sora	Lenva	Atezo+ Bev	Sora	Lenva
IMbrave150 analysis/ REFLECT	[redacted]	54.6%	56.6%	-	-	-	-	-	-	-	-	-	-	-	-
REFLECT (based on KM data)	-	50%	55%	-	26%	30%	-	15%	15%	-	-	-	-	-	-
Exponential	[redacted]	53%	54%	[redacted]	28%	29%	[redacted]	15%	16%	[redacted]	8%	9%	[redacted]	4%	5%
Generalised Gamma	[redacted]	52%	53%	[redacted]	27%	28%	[redacted]	16%	16%	[redacted]	10%	10%	[redacted]	7%	7%

However, the exponential curve doesn't account for the potential long-term survivors on immunotherapy which could lead to a change in the hazard due to a decrease in the number of deaths. Thus it may be a conservative choice and potentially under-estimates the long-term survival benefit of Atezo+Bev.

Figure 18 demonstrates the resulting long-term exponential OS curves, and Figure 19**Error! Reference source not found.** illustrates the fit of the exponential extrapolation to the REFLECT trial lenvatinib and sorafenib KM data.

Figure 18: Long-term exponential overall survival curves

Figure 19: REFLECT KM fit to long-term exponential overall survival curves

B.3.3.3 PFS extrapolation

Similar to the approach taken to incorporate OS in to the economic model, alternative parametric distributions fitted the observed KM PFS data from the trial. Candidate curves were checked for fit to the observed data and clinical plausibility of long-term extrapolations.

Based on the AIC and BIC values as demonstrated in Table 35 and Table 36, the Generalised Gamma and Log-normal models appear to be the best statistical fit to the PFS KM data for both treatment arms. In the Atezo+Bev arm, the log-logistic is greater than 10 points difference, and the Weibull, Gompertz and Exponential have a much poorer fit (>15 points difference). In the sorafenib arm, the log-logistic has a similar statistical fit to the log-normal and Generalised Gamma, but the remaining models are greater than 10 points difference.

Table 35: Summary of goodness of fit: PFS - Atezo+Bev

	PFS – goodness of fit statistics Atezolizumab + Bev	
Parametric distribution	**AIC**	**BIC**
Exponential	841.34 (5)	845.16 (5)
Weibull	836.71 (4)	844.34 (4)
Log-normal	815.65 (2)	823.28 (2)
Generalised Gamma	813.19 (1)	824.64 (1)
Log-logistic	825.06 (3)	832.70 (3)
Gompertz	843.11 (6)	850.75 (6)

Table 36: Summary of goodness of fit: PFS - Sorafenib

	Overall Survival – goodness of fit statistics - sorafenib	
Parametric distribution	**AIC**	**BIC**
Exponential	381.53 (6)	384.64 (6)
Weibull	370.46 (4)	376.67 (4)
Log-normal	360.21 (1)	366.42 (1)
Generalised Gamma	362.19 (2)	371.50 (2)
Log-logistic	364.08 (3)	370.29 (3)
Gompertz	378.92 (5)	385.14 (5)

All parametric distributions were assessed for visual fit to the Kaplan Meier data (Figure 20 and Figure 21Figure 15).

Figure 20: Visual fit of PFS distributions to IMbrave150 KM data (Atezo+Bev)

Figure 21: Visual fit of PFS distributions to IMbrave150 KM data (Sorafenib)

Similarly to OS, the curves seem to follow a similar trend for both arms of the model. The exponential model seems to underestimate progression free survival in the first 6 months. The Gompertz and Weibull are generally a poor fit for both curves, across different stages of

the KM: frequently over and underestimating PFS. In line with the AIC/BIC statistical fit, the log-logistic, log-normal and Generalised Gamma curves appear as the best visual fits.

The resulting tails of the distributions were assessed for their clinical plausibility (Figure 22 and Figure 23).

Figure 22: Atezo+Bev PFS extrapolation curves

Figure 23: Sorafenib PFS extrapolation curves

In line with OS, before determining the correct distribution to extrapolate PFS, clinical plausibility needed to be assessed. Visual assessment of the selected OS exponential distribution compared with the potential PFS distributions highlighted that the Generalised Gamma PFS curve exceeded the OS curve, and therefore was ruled out on the basis of clinical plausibility.

The resulting curves (Log-normal, Log-logistic, Exponential, Weibull and Gompertz) were then assessed against clinical expert opinion, from six UK clinicians as part of the advisory board organised by Roche (36). This was to ensure the curves represented UK clinical practice.

Of the five distributions, only the exponential, the log-normal and the log-logistic produced a lenvatinib PFS curve in line with lenvatinib KM data from the REFLECT trial. The remaining two models were therefore excluded from the selection.

Table 37 demonstrates that the PFS rates are very similar for the log-normal and log-logistic models; the functions with the best statistical fit of the three recommended models. The exponential over-estimates very slightly in the first 12 months, yet becomes the most conservative option of the three in year 2 and 3. The log-normal distribution was used in the lenvatinib submission to extrapolate PFS for both treatment arms (lenvatinib and sorafenib), and was accepted by the ERG and the appraisal committee (42). Additionally as the treatment effects from the ITC are HRs, it was deemed appropriate to apply them to an accelerated failure time (AFT) model. As such, the parametric extrapolation used for PFS in the base case analysis is the log-normal model.

Table 37: Proportion of patients progression-free at set time points based on parametric distributions, compared with IMbrave150/REFLECT trial data

	12 months			24 months			36 months		
	Atezo +Bev	Sora	Lenva	Atezo +Bev	Sora	Lenva	Atezo +Bev	Sora	Lenva
IMbrave150 analysis	[redacted]	9.2%	-	-	-	-	-	-	-
REFLECT (based on KM data)	-	17%	30%	-	7%	8%	-	6%	5%
Exponential	[redacted]	15%	29%	[redacted]	0%	2%	[redacted]	2%	8%
Log-logistic	[redacted]	13%	27%	[redacted]	4%	11%	[redacted]	2%	6%
Log-normal	[redacted]	13%	28%	[redacted]	3%	11%	[redacted]	1%	6%

Figure 24 demonstrates the resulting long-term log-normal PFS curves, and Figure 25 illustrates the fit of the log-normal extrapolation to the lenvatinib and sorafenib KM data from the RELFECT trial.

Figure 24: Extrapolated Log-normal progression-free survival curves

Figure 25: REFLECT KM fit to log-normal progression-free survival curves

B.3.3.4 Treatment duration extrapolation

Atezolizumab is used until loss of clinical benefit or unmanageable toxicity in study IMbrave150, in line with its anticipated license for this indication. Results from the IMbrave150 study, and clinical trial evidence from other indications for atezolizumab, suggest that patients can continue to receive treatment with atezolizumab for a limited time after disease progression. On the other hand, tolerability may result in earlier discontinuation. As such, PFS is only an approximation for treatment duration of Atezo+Bev but not an accurate surrogate.

Data on time to treatment discontinuation (TTD) are available for Atezo+Bev and sorafenib in IMbrave150. 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. As TTD data for lenvatinib was not available, PFS was used as a proxy in the economic model.

Not all patients had discontinued treatment in IMbrave150; approximately 43.5% and 14.5% of patients were still on treatment with Atezo+Bev and sorafenib respectively at the time of

the IMbrave150 data cut (August 2019). As such, it was necessary to extrapolate the study results so that treatment duration could be estimated beyond the trial period.

Similarly to OS and PFS, parametric distributions were fitted to the TTD Kaplan–Meier curves and assessed for their goodness of fit to the data using the AIC/BIC statistics, visual assessment and clinical plausibility of each of the extrapolations.

Table 38 provides the AIC and BIC goodness of fit results for the functions used to model TTD. According to AIC/BIC only, the best function to model TTD would be the Generalised Gamma; however, the resulting extrapolated curves provide implausible tails. The Weibull, Log-Normal and Log-Logistic provided poor fit to the observed data and very long unrealistic tails. The Gompertz and Exponential reported the same values. Therefore, the Exponential parametric distribution is used in the base case for the extrapolation of TTD, because whilst it does not provide the best statistical fit, it does demonstrate the best visual fit out of all potential distributions, as well as clinical validity. Alternative plausible distributions are explored in sensitivity analyses.

Table 38: Summary of goodness of fit for TTD

	TTD – Atezolizumab		TTD – Bev		TTD – Sorafenib	
Parametric distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	993.29	997.08	1011.30	1015.10	483.00	486.05
Weibull	980.51	988.10	1000.00	1007.59	485.00	491.10
Log-normal	1013.53	1021.12	1036.39	1043.99	468.64	474.74
Generalised Gamma	976.55	987.93	996.31	1007.69	470.33	479.48
Log-logistic	992.49	1000.08	1013.17	1020.76	470.44	476.54
Gompertz	995.29	1002.88	1013.30	1020.89	485.00	491.10

Given that the observed TTD data for Atezo+Bev and sorafenib in IMbrave150 are relatively complete, it was deemed appropriate to use the TTD KM curve followed by the Exponential distribution, as this was the parametric model showing the best visual fit to the observed data, for atezolizumab, bevacizumab and sorafenib. The Exponential curve was also used to extrapolate PFS and therefore demonstrates consistent long-term behaviour. The cut-off point for switching from KM to parametric extrapolation is at 14 months, to ensure robustness in terms of patient numbers at risk whilst the KM data is being utilised. The resulting extrapolations in the base case analysis are displayed in Figure 26 below.

Figure 26: TTD extrapolation curves – Atezo, Bev and Sorafenib – Kaplan-Meier plus Exponential parametric extrapolation

B.3.4 Measurement and valuation of health effects

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

Health-related quality of life (HRQoL) data were collected in the IMbrave150 study directly from first line metastatic HCC patients via the EQ-5D-5L questionnaire. Measurement and valuation of HRQoL using EQ-5D-5L directly from patients is consistent with the NICE reference case (134), hence HRQoL from IMbrave150 is used in our base case analysis. The EQ-5D-5L results were mapped to EQ-5D-3L, using the van Hout algorithm (135).

EQ-5D-5L data were collected in IMbrave150 at each scheduled study visit prior to administration of study drug and prior to any other study assessment(s). During survival follow-up the EQ-5D-5L questionnaire was completed every 3 months (for 1 year) following disease progression or treatment discontinuation, unless the patient withdrew consent, whichever occurred first.

The EQ-5D utility weights per visit for each treatment arm were calculated using the UK Tariff from Dolan et al. and the Van Hout Crosswalk (2012) (135, 136) . These estimates are based purely on the average observed utility weights, without any adjustment on baseline

utility; hence such estimates are not appropriate in assessing the relative impact of each treatment in the quality of life of the patients. Such an assessment is demonstrated in the following part of the report.

Four different approaches were considered for the calculation of utility values from IMbrave150: (i) on/off treatment, (ii) the pre- and post-progression approach, (iii) the pre- and post-progression approach and grade 3+ adverse events and, (iv) the proximity to death approach. This section provides further detail on all approaches. The proximity to death approach was used in the base case analysis, as it reflects the known decline in cancer patients' quality of life during the terminal phase of the disease.

To estimate the mean utility scores, repeated measurement models were used initially assuming an unstructured correlation between observations coming from the same subject. Where convergence issues were observed, an exchangeable correlation structure was assumed.

(i) On/off treatment approach

Time on treatment from the IMbrave150 trial was used to anchor the on/off treatment utilities in the model. Using the on/off treatment method, health state utility values varied according to whether patients received Atezo+Bev or sorafenib.

(ii) Pre- and post-progression approach

Two fixed effects models were used, one for the pre-progression period and one for the post-progression period, respectively.

Utilities during the pre-progression period were determined by treatment arm. Since there are fewer observations during the post-progression period, we observed larger variability of the means and broader confidence intervals. As such, we used a pooled post-progression mean utility in the economic model, regardless of treatment arm.

(iii) Pre- and post-progression approach and grade 3+ adverse events

An extension of the previous analysis was performed, by including an additional covariate, grade 3+ adverse events, into the regression. Similar to the previous approach, the pre-progression utility model included as fixed effects the day of assessment, the treatment arm and an indicator binary variable capturing a value = 1 if a patient had a treatment related adverse event grade 3, and zero otherwise. We assumed an exchangeable working correlation. The assessment was made based on whether the patient had an AE before progression or not. The duration of the event is not taken into account.

(iv) Proximity to death approach

As already stated, the proximity to death approach was considered as more relevant, since it reflects the known decline in cancer patients' quality of life during the terminal phase of the disease, and it is also consistent with recent cancer immunotherapy NICE appraisals (137). The proximity to death utilities were analysed for patients who were both on treatment and patients who had discontinued treatment. We considered four intervals for the proximity to death approach:

- Group 1: ≤ 5 weeks before death (BD)
- Group 2: > 5 & ≤ 10 weeks BD
- Group 3: > 10 & ≤ 30 weeks BD
- Group 4: > 30 weeks BD

The proximity to death sub states were further stratified according to whether patients were on or off treatment. A mixed linear model was fitted through restricted maximum likelihood, adjusting for baseline EQ-5D values. The on/off treatment status was an effect modifier in the regression, e.g. a factor or covariate. UK preference-based scores were used for patient data from the trial and the time trade-off (TTO) technique was used to develop the UK scoring functions.

The utility values from IMbrave150 considered in our evidence submission are summarised in Table 40.

B.3.4.2 Mapping

Health related quality of life was evaluated in the IMbrave150 trial using the EuroQoL EQ-5D-5L. Following the NICE position paper on the EQ-5D-5L (138), the scores were mapped to the EQ-5D-3L using the Van Hout algorithm (135).

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

A SLR was conducted to identify HRQoL evidence in the first-line treatment of patients with HCC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix H.

Summary of identified studies and results

Overall, the review identified 23 publications reporting health state utility values associated with first-line advanced or metastatic HCC. Of these 23 studies, 15 were presented as full publications, and eight were presented as conference abstracts only. Utilities were reported for a range of health states for the population of interest, including intervention-specific utilities, progression status (progression free/progressive disease/stable disease), treatment line, disease stage, disutilities associated with adverse events and patient characteristics

such as time since diagnosis, presence or absence of metastatic disease, and recurrence status.

With regard to utility relevance for NICE, of the full publications identified, the majority utilised the EQ-5D to derive utilities in line with the NICE reference case. However, only two studies fully met the NICE requirements; that is, utilities were derived directly from patients using the preferred EQ-5D and health states were valued using UK societal preference elicited using the direct TTO method (139, 140). A summary of the studies and conference abstracts relevant to NICE identified in the systematic review summary and the reported utility data are presented in Appendix H.

B.3.4.4 Adverse reactions

All grade ≥3 adverse events for Atezo+Bev and sorafenib, with an incidence of ≥5% in at least one treatment arm were sourced from the IMbrave150 clinical study. A total of 5 adverse events were captured. The corresponding grade ≥3 adverse events with an incidence of ≥5% for lenvatinib were sourced from the lenvatinib NICE submission (42).

Two approaches could be taken regarding the inclusion of the impact of AEs on HRQoL:

1. The assumption that any disutility has already been incorporated in the base case health state utilities through the trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting;
2. The assumption that averaged trial-derived utilities underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied.

The base case analysis takes the former assumption (disutility has already been incorporated). See Table 39 for the complete list of AEs included in the model.

Table 39: IMbrave150 adverse events included in the economic model (events occurring at Grade 3-5, affecting 5% or more of patients)

n, (%)	Atezo+Bev	Sorafenib	Lenvatinib
Aspartate aminotransferase increased	23 (7)	8 (5)	24 (5)
Blood bilirubin increased	8 (2)	10 (6)	31 (7)
Diarrhoea	6 (2)	8 (5)	20 (4)
Hypertension	50 (15)	19 (12)	111 (23)
Palmar-plantar erythrodysaesthesia syndrome	0 (0)	13 (8)	14 (3)

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

Table 40: Summary of utility values for cost-effectiveness analysis

Category	Utility	95% CI	Reference in submission	Justification
IMbrave150 utilities - Proximity to death approach – Base case				
On treatment				
≤ 5 weeks before death	0.64	0.573, 0.713	Section B.3.4.1	Derived from EQ-5D data collected during IMbrave150 study. Methodology as per NICE reference case (134)
> 5 & ≤ 15 weeks before death	0.73	0.702, 0.759		
> 15 & ≤ 30 weeks before death	0.78	0.750, 0.805		
> 30 weeks before death	0.80	0.763, 0.834		
Off treatment				
≤ 5 weeks before death	0.37	0.303, 0.430	Section B.3.4.1	Derived from EQ-5D data collected during IMbrave150 study. Methodology as per NICE reference case (134)
> 5 & ≤ 15 weeks before death	0.62	0.572, 0.658		
> 15 & ≤ 30 weeks before death	0.66	0.585, 0.722		
> 30 weeks before death	0.71	0.607, 0.816		
IMbrave150 utilities – On/Off treatment - Scenario analysis				
On treatment: Atezo+Bev	0.79	0.777, 0.803	Section B.3.4.1	Derived from EQ-5D data collected during IMbrave150 study.
On treatment: Sorafenib	0.75	0.734, 0.771		
Off treatment: Pooled	0.68	0.666, 0.702		
IMbrave150 utilities - Pre- and post-progression - Scenario analysis				
Pre-progression: Atezo+Bev	0.78	0.765, 0.792	Section B.3.4.1	Derived from EQ-5D data collected during IMbrave150 study.
Pre-progression: Sorafenib	0.77	0.749, 0.786		
Post-progression: Pooled	0.74	0.723, 0.753		
IMbrave150 utilities - Pre- and post-progression with AE3+ - Scenario analysis				
Pre-progression: Atezo+Bev	0.74	0.728, 0.764	Section B.3.4.3	Derived from EQ-5D data collected during IMbrave150 study.
Pre-progression: Sorafenib	0.72	0.695, 0.744		
Post-progression: Pooled	0.72	0.700, 0.735		

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

A SLR was conducted to identify recent studies (published in the last five years) presenting novel cost and resource use data associated with unresectable or metastatic HCC, irrespective of treatment line, relevant to the economic model of Atezo+Bev as a first-line treatment of patients with HCC.

Summary of identified studies and results

A total of 78 full publications met the inclusion criteria of the SLR. Detailed descriptions of the search strategy, search terms and extraction methods, as well as details of the included studies, are provided in Appendix I. Only one study with UK data was identified (139).

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs for the treatments considered in the model are presented in Table 41. Drug costs were sourced from the British national Formulary (BNF) (141). It is also useful to note that sorafenib and lenvatinib are associated with confidential discounts.

The dosing for each of the drugs considered in the model is outlined below:

- Atezolizumab: as per anticipated marketing authorisation for Atezo+Bev and dosing schedule in study IMbrave150 i.e. atezolizumab at a fixed dose of 1200 mg Q3W until loss of clinical benefit or unacceptable toxicity.
- Bevacizumab: as per dosing schedule in study IMbrave150 and anticipated marketing authorisation for Atezo+Bev i.e.15 mg/kg Q3W until disease progression or unacceptable toxicity.
- Sorafenib: in line with its marketing authorisation and use in UK clinical practice, i.e. 400 mg, twice per day
- Lenvatinib: in line with its marketing authorisation and use in UK clinical practice, i.e. 12 mg for patients ≥60 kg and 8 mg for patients <60 kg, once-daily

The average weight (71.7kg) and BSA (1.82m^2 using the Dubois formula) from the IMbrave150 study (Arms A and B) were utilised to estimate the average cost per dose for patients treated with Atezo+Bev.

The base case of the economic model assumes full vial sharing (i.e., no wastage) for the administration of bevacizumab. For completeness, a scenario analysis is provided assuming drug wastage.

Table 41: Drug acquisition costs

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Cost per mg	Source
Atezolizumab	60 mg/ml	20 ml	1200 mg	£3807.69	£3.17	BNF (141)
Bevacizumab	25 mg/ml	4 ml	100 mg	£242.66	£2.43	BNF (141)
Bevacizumab	25 mg/ml	16 ml	400 mg	£924.40	£2.31	BNF (141)
Sorafenib		112 mg	200 mg	£3576.56	£0.16	BNF (141)
Lenvatinib		30 mg	4 mg	£1437	£11.98	BNF (141)

Table 42: Dosing schedule and dose per administration

Drug	Dosing per administration	Frequency of administration	Total dose	Reference for dosing
Atezolizumab	1200 mg fixed	Q3W	1200 mg	SmPC (1) IMbrave50
Bevacizumab	15 mg/kg	Q3W	1079 mg	SmPC (12) IMbrave150
Sorafenib	400 mg	BID	800 mg	SmPC (40) IMbrave150
Lenvatinib	4mg	QD	12 mg	SmPC (142)

Q3W: every three weeks; BID: twice a day; QD: once a day

Table 43: Drug cost per weekly treatment cycle for interventions used in the cost-effectiveness model

Comparator	Method and frequency of administration	Total drug cost per cycle (with vial sharing)	Drug cost per combination partner per cycle
Atezo+Bev	IV, Q3W	£6,423.00*	Atezo: £3,807.69 Bev: £2,615.31
Sorafenib	Oral, BID	£894.14	-
Lenvatinib	Oral, QD	£930.27	-

IV: intravenous; Q3W: every three weeks; BID: twice a day; QD: once a day

*Please note, the Atezo+Bev total drug cost per cycle is applied in the model every 3 weeks.

Subsequent therapies

The costs of subsequent lines of therapy are included in the progressed disease health state of the model. Although data on the treatment and duration of subsequent therapy were collected in the IMbrave150 study after discontinuation from Atezo+Bev and sorafenib, these are not fully representative of UK clinical practice. Currently, the only approved second line therapy for patients with advanced HCC is regorafenib; however, this is only available for patients previously treated with sorafenib. Patients treated with lenvatinib and Atezo+Bev would not be entitled to receive regorafenib, or any other type of therapy. This differs to some extent from the IMbrave150 data, as 21% and 44% of patients treated with Atezo+Bev

and sorafenib respectively, received subsequent cancer immunotherapy, multiple TKIs or chemotherapy.

IMbrave150 subsequent therapy data are presented in Table 44. In the IMbrave150 dataset, lines of treatment were not distinguished; hence subsequent therapies represent second or further-line therapies. Treatment duration was also sourced from IMbrave150.

It is evident from Table 44 that this is not fully aligned with UK clinical practice and there is an imbalance in the proportion of patients who received subsequent therapy (44% in the sorafenib arm vs 21% in the Atezo+Bev arm). The imbalance is consistent with the higher frequency of patients from the sorafenib arm having discontinued study treatment at the time of the clinical cut-off date.

In order to test the significance of the imbalance on overall survival outcomes, a cox regression analysis was carried out to test the post discontinuation therapy coefficient. For the Atezo+Bev arm, there was no statistically significant difference in overall survival between patients receiving post progression therapy versus those who did not.

This suggests that the OS benefit for patients treated with Atezo+Bev in IMbrave150 is predominantly from Atezo+Bev and differences in post progression treatment in UK clinical practice are unlikely to result in differences in OS compared to the IMbrave150 trial.

However, this is not the case in the sorafenib arm as the interaction of sorafenib and post-discontinuation therapy is significant, which would be expected as regorafenib was approved based on improved OS after treatment with sorafenib (43). While this indicated that the inclusion of subsequent therapy improved OS benefit of sorafenib compared to a scenario without post progression treatment, including this effect was appropriate for UK clinical practice and OS results would not need to be adjusted in the sorafenib arm of IMbrave150.

Table 44: Subsequent therapies after discontinuation from Atezo+Bev and Sorafenib in IMbrave150

	Sorafenib n=165	**Atezo+Bev n=336**
Number of patients with at least 1 systemic treatment	[redacted]	[redacted]
Therapy type		
TKIs	[redacted]	[redacted]
Angiogenesis Inhibitors	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Others	[redacted]	[redacted]

In light of the above, multiple options have been included in the model to account for the cost of subsequent therapy. In the model base-case, the proportion who received subsequent therapy in IMbrave150 after sorafenib (44%), are assumed to receive regorafenib second-line. This is reflective of UK clinical practice and in line with the second-line marketing authorisation of regorafenib. Patients treated with Atezo+Bev or lenvatinib are assumed to have received no additional subsequent therapy. Our base-case approach to subsequent therapies is outlined in Table 45.

Table 45: Subsequent therapies after discontinuation: Base-case analysis

Post-discontinuation therapy	Treatments after Atezo+Bev	Treatments after sorafenib	Duration of therapy (weeks)	Source for duration of therapy
Regorafenib	0%	44%	13.3	IMbrave150 (52)

Two other options included in the model as scenario analyses include updating the proportion of patients receiving regorafenib after sorafenib to 20%; a proportion provided by clinical experts during a Roche UK advisory board. The second option includes modelling the IMbrave150 trial data.

Table 46 highlights all options included in the model and Table 47 presents the drug acquisition costs and dosing schedule for subsequent therapies.

Table 46: Subsequent therapy options

Post-discontinuation therapy	Treatments after Atezo+Bev	Duration of therapy (weeks)	Treatments after sorafenib	Duration of therapy (weeks)	Source for duration of therapy
Base Case (sorafenib arm only)					
Regorafenib	0%	-	44%	13.3	IMbrave150
Scenario analysis (sorafenib arm only – clinical expert opinion)					
Regorafenib	0%	-	20%	13.3	IMbrave150
Scenario analysis (IMbrave150 trial data)					
Immunotherapy: Nivolumab	1.2%	28.4	18.8%	18.6	IMbrave150
TKI: Average of Sorafenib, Lenvatinib and Regorafenib	18.8%	13.4	26.1%	13.3	IMbrave150

Table 47: Subsequent therapy drug acquisition costs

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Cost per mg	Source
Nivolumab (large)	10 mg/ml	10 ml	100 mg	£1097	£10.97	BNF (141)
Nivolumab (small)	10 mg/ml	4 ml	40 mg	£439.00	£10.98	BNF (141)
Regorafenib		84 mg	40 mg	£3744	£1.11	BNF (141)
Sorafenib		112 mg	200 mg	£3576.56	£0.16	BNF (141)
Lenvatinib		30 mg	4 mg	£1437	£11.98	BNF (141)

Drug administration costs

Costs associated with treatment administration are summarised in Table 48. The administration cost for Atezo+Bev is assumed to be that of a complex chemotherapy with prolonged infusion treatment as a day case (as described in the NHS reference costs 2018-19) (143) to account for the prolonged infusion time and administration burden. Sorafenib and lenvatinib are oral therapies and therefore do not require hospital administration. However, given that these are oral chemotherapy we have applied a cost of £195 for delivering oral chemotherapy in the first cycle. The administration costs of subsequent therapy has also been included below.

Table 48: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezo+Bev	Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	Day case	SB14Z	£371	NHS reference costs 2018-19
Sorafenib and Lenvatinib	Deliver Exclusively Oral Chemotherapy	Day case	SB11Z	£195	NHS reference costs 2018-19
Subsequent therapy					
Nivolumab	Subsequent Elements of Chemotherapy Cycle	Day case	SB15Z	£332	NHS reference costs 2018-19

B.3.5.2 Health-state unit costs and resource use

Unit costs for supportive care are listed in Table 49 and were sourced from NHS reference costs 2018/2019 and PSSRU 2019 (143, 144).

Resource use estimates in the base case were derived from a questionnaire of 6 UK clinicians currently treating patients with HCC. This was conducted in early 2020 in preparation for this submission, in order to provide current estimates since the literature estimates were based on evidence collected over 10 years ago. Values used in the base case are provided in Table 50.

A scenario analysis has been included utilising the resource use estimates from the lenvatinib NICE submission TA551 (Table 51) (42), whereby resource use estimates were obtained from the original sorafenib submission (38). As TA551 used estimates from the sorafenib submission, which was partly carried out over 10 years ago in 2009 and partly updated in 2016, the values in Table 50 were deemed the most recent and clinically relevant.

Table 49: Resource use costs

Resource required		Unit Cost	Reference
Physician visits	Oncologist	£194.17	NHS reference costs 2018/19. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (medical oncology)
	Hepatologist	£194.79	NHS reference costs 2018/19. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (hepatology)
	Gastroenterologist	£137.88	NHS reference costs 2018/19. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (gastroenterology)
	Macmillan nurse	£36.65	PSSRU, Unit Costs of Health and Social Care 2018/19. Nurse (GP practice). Cost per hour, including qualifications
	Radiologist	£151.85	NHS reference costs 2018/19. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (interventional radiology)
	Clinical nurse specialist	£36.65	PSSRU, Unit Costs of Health and Social Care 2018/19. Nurse (GP practice). Cost per hour, including qualifications
	Palliative care physician/nurse	£36.65	PSSRU, Unit Costs of Health and Social Care 2018/19. Nurse (GP practice). Cost per hour, including qualifications
Laboratory tests	AFP Test	£23.71	NHS reference costs 2018/19. Average of DAPS01 and DAPS02 (cytology, and histopathology and histology)

	Liver Function Test	£23.71	NHS reference costs 2018/19. Average of DAPS01 and DAPS02 (cytology, and histopathology and histology)
	INR	£2.75	NHS reference costs 2018/19. Average of DAPS03, DAPS05 and DAPS08 (integrated blood services, haematology and phlebotomy)
	Complete blood count	£2.75	NHS reference costs 2018/19. Average of DAPS03, DAPS05 and DAPS08 (integrated blood services, haematology and phlebotomy)
	Biochemistry	£1.10	NHS reference costs 2018/19. DAPS04 (clinical biochemistry)
	Endoscopy	£207.82	NHS reference costs 2018/19. FE50A (Wireless Capsule Endoscopy, 19 years and over). Outpatient procedures
Radiological tests	CT scan: abdominal	£104.85	NHS reference costs 2018/19. Average of all CT codes, adult only, weighted by activity (RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z)
	MRI: abdominal	£190.21	NHS reference costs 2018/19. Average of all MRI codes, adult only, excluding cardiac magnetic resonance imaging, weighted by activity (RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z)
Hospitalisation	Hospitalisation	£1,441.38	NHS reference costs 2018/19. Average of all hospitalisations for malignant, hepatobiliary or pancreatic disorders, weighted by activity (Non-elective short stay - GC12C, GC12D, GC12E, GC12F, GC12G, GC12H, GC12J, GC12K)
Hospital follow-up	Specialist	£194.79	NHS reference costs 2018/19. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (hepatology)
	GP	£33.00	PSSRU, Unit Costs of Health and Social Care 2018/19. General practitioner, cost per surgery consultation lasting 9.22 minutes (including direct care staff costs, with qualification costs)
	Nurse	£36.65	PSSRU, Unit Costs of Health and Social Care 2018/19. Nurse (GP practice). Cost per hour, including qualifications

AFP: Alpha-fetoprotein; GP: general practitioner; CT: computerised tomography; INR: international normalised ratio; MRI: Magnetic resonance imaging; NHS: National Health Service; PSSRU: Personal Social Services Research Unit

Table 50: Summary of health state resource use, based on clinical expert opinion

	Progression free			Progressed		
Resource required	**% patients per month**	**Frequency per month**	**Frequency per weekly cycle**	**% patients per month**	**Frequency per month**	**Frequency per weekly cycle**
Oncologist	92%	1.17	0.27	56%	1.05	0.24
Hepatologist	3%	0.33	0.08	22%	0.65	0.15
Gastroenterologist	0%	0.17	0.04	12%	0.63	0.14
Macmillan nurse	20%	0.58	0.13	50%	0.92	0.21
Radiologist	25%	0.22	0.05	2%	0.17	0.04
Clinical nurse specialist	75%	1.83	0.42	56%	1.80	0.41
Palliative care physician/nurse	22%	0.72	0.16	53%	1.25	0.29
AFP Test	100%	1.00	0.23	51%	0.83	0.19
Liver Function Test	100%	1.03	0.24	58%	0.96	0.22
INR	100%	1.03	0.24	58%	0.96	0.22
Complete blood count	100%	1.00	0.23	58%	0.96	0.22
Biochemistry	100%	1.03	0.24	58%	0.96	0.22
Endoscopy	12%	0.36	0.08	7%	0.19	0.04
CT scan: abdominal	90%	0.61	0.14	26%	0.41	0.09
MRI: abdominal	42%	0.61	0.14	14%	0.40	0.09
Hospitalisation	8%	0.75	0.17	23%	0.80	0.18
Specialist	26%	0.38	0.09	27%	0.38	0.09
GP	19%	0.50	0.11	32%	0.63	0.14
Nurse	28%	0.50	0.11	15%	0.50	0.11
Total cost per week	**£129.91**			**£131.07**		

AFP, Alpha-fetoprotein; CT, computerised tomography; GP, general practitioner; INR, international normalised ratio; MRI, Magnetic resonance imaging

Table 51: Summary of health state resource use, based on the Lenvatinib NICE submission TA551

	Progression free			Progressed		
Resource required	**% patients per month**	**Frequency per month**	**Frequency per weekly cycle**	**% patients per month**	**Frequency per month**	**Frequency per weekly cycle**
Oncologist	100%	0.75	0.17	100%	0.38	0.09
Hepatologist	100%	0.17	0.04	100%	0.50	0.11
Gastroenterologist	100%	0.08	0.02	100%	0.00	0.00
Macmillan nurse	100%	0.50	0.11	100%	1.00	0.23
Radiologist	100%	0.08	0.02	100%	0.00	0.00
Clinical nurse specialist	100%	0.50	0.11	100%	0.23	0.05
Palliative care physician/nurse	100%	0.13	0.03	100%	0.75	0.17
AFP Test	75%	0.83	0.19	38%	1.00	0.23
Liver Function Test	50%	0.67	0.15	25%	1.00	0.23
INR	50%	0.67	0.15	0%	0.00	0.00
Complete blood count	75%	1.00	0.23	50%	1.00	0.23
Biochemistry	50%	1.00	0.23	25%	1.00	0.23
Endoscopy	25%	0.33	0.08	0%	0.00	0.00
CT scan: abdominal	73%	0.33	0.08	73%	0.39	0.09
MRI: abdominal	28%	0.33	0.08	28%	0.50	0.11
Hospitalisation	46%	0.16	0.04	48%	0.40	0.09
Specialist	100%	0.25	0.06	100%	3.00	0.69
GP	100%	1.50	0.34	100%	1.50	0.34
Nurse	100%	1.75	0.40	100%	2.00	0.46
Total cost per week	**£137.52**			**£299.14**		

AFP, Alpha-fetoprotein; CT, computerised tomography; GP, general practitioner; INR, international normalised ratio; MRI, Magnetic resonance imaging

Cost of terminal care

In line with TA551, it is assumed that all patients are assigned a standard cost for palliative care before death (42). This is assumed to cover hospital care in the 90 days before dying, based on Georghiou and Bardsley (2014) (145). The costs of terminal care included services such as hospital care costs, local authority funded social care, district-nursing costs and the cost of GP visits. This cost was applied as a one-off cost at the point of death. The total cost is estimated to be £8,186 (Table 52).

Table 52: Cost of palliative care

Cost	Unit cost	Reference	2019 Uplifted cost (PSSRU 2019) (144)
All hospital contacts	£5,890.00	Georghiou and Bardsley (2014) (145)	£6,616.97
Local authority-funded social care	£444.00		£498.80
Nurse visits	£588.00		£660.57
GP visits	£365.00		£410.05
Total			**£8,186.40**

PSSRU, Personal Social Services Research Unit.

B.3.5.3 Adverse reaction unit costs and resource use

Adverse event data used in the model for Atezo+Bev and sorafenib were taken directly from the IMbrave150 study. Adverse events for lenvatinib were sourced from the lenvatinib NICE submission. In order to ensure a more robust assessment of the safety profile of the treatment regimens being compared, all Grade ≥3 treatment-related AEs with an incidence of ≥5% in either the Atezo+Bev or sorafenib arm of the IMbrave150 trial are included in the base case analysis. The resulting adverse events included in the economic model are shown in Table 39.

Please note that there may be a difference in the number of AEs included in the economic model, compared to the AEs reported in the adverse reactions section (Section B.2.10). The reason for this is that in the economic model, we have to account for multiple occurrences of an AE per patient in order to be able to calculate the probability of occurrence for each AE, whilst in the reporting of the clinical study, multiple occurrences of the same AE in an individual are counted once at the highest grade for this patient, as per standard reporting of safety results from clinical studies.

The unit costs related to the management of AEs were mainly derived from the lenvatinib NICE submission (42)), and inflated to 2018/2019 NHS reference costs. When unit costs were not available, an assumption was applied, and when AE management costs were trivial, they were assumed to be zero. Table 53 presents the unit costs per AE for which costing was applied in the cost-effectiveness model.

Table 53: Unit cost per AE used in the economic model

Adverse Event	Unit Cost	Reference
Aspartate aminotransferase increased	£589	NHS reference costs 2018/19. Average cost of non-elective short stay
Blood bilirubin increased	£888	NHS reference costs 2018/19. Average cost of non-elective short stay; WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (medical oncology); Average of all CT codes, adult only, weighted by activity (RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z, RD28Z)
Diarrhoea	£555	NHS reference costs 2018/19. FD10K Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6-10 – non-elective short-stay
Hypertension	£816	NHS reference costs 2018/19. Average cost of non-elective short stay; WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (medical oncology); PSSRU, Unit Costs of Health and Social Care 2018/2019. General practitioner, cost per surgery consultation lasting 9.22 minutes (including direct care staff costs, with qualification costs)
Palmar-plantar erythrodysaesthesia syndrome	£391	NHS reference costs 2018/19 – JD07J Skin Disorders without Interventions, with CC score 2-5 - non-elective short stay

B.3.5.4 Miscellaneous unit costs and resource use

All elements of resource use and cost have been outlined in previous sections.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A table summarising the full list of variables applied in the economic model is presented in Appendix M.

B.3.6.2 Assumptions

Table 54: Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	20 years	Based on IMbrave150 trial data, the average age of patients in the model is [redacted]. The 20 year model horizon is in line with NICE reference case (134) , and also long enough to reflect the difference in costs and outcomes between the interventions being compared in this submission. Also consistent with previous NICE appraisals in this indication (42)

Comparators considered in the economic model	Sorafenib and lenvatinib	See Section B.1.1
Resource use utilisation	Resource use utilisation is assumed to be the same on all arms	In line with assumptions made and accepted in TA551 (42)
Subsequent therapy	Regorafenib cost applied to IMbrave150 proportion of patients who received subsequent therapy after sorafenib (44%)	This is reflective of UK clinical practice and in line with the second-line marketing authorisation of regorafenib. As the inclusion of subsequent therapy improved OS for patient's receiving sorafenib, it is appropriate to apply the corresponding cost. As patients treated with Atezo+Bev or lenvatinib would not receive subsequent therapy, no additional costs have been applied. Therefore the survival and costs reflect UK clinical practice.
Atezo+Bev and Sorafenib: clinical efficacy and safety	IMbrave150 study data were used for Atezo+Bev and sorafenib. Efficacy and safety results from IMbrave150 are transferable to the UK population	Advice from UK clinical experts suggested that the outcomes seen from the study are expected in UK patients despite differences in aetiology between the trial and patients in the UK.
Lenvatinib: clinical efficacy and safety	A hazard ratio ITC was conducted vs. lenvatinib	As per NICE guide to the methods of technology appraisal (134), and based on availability and limitations of published evidence for relevant comparators.
Extrapolation of time-to-event endpoints	Best fit according to combined data on AIC / BIC statistics, visual fit to observed data and long-term clinical plausibility. In order to validate long-term OS for sorafenib and lenvatinib, UK published estimates from NICE committee-preferred assumptions were used, in addition to clinical expert opinion. For Atezo+Bev, UK clinical expert opinion was used to validate long-term OS estimates	Based on NICE DSU recommendation (146)
HRQoL	Based on EQ-5D data collected in IMbrave150. Proximity to death utility approach used in the base-case analysis.	In line with NICE reference case (134)

Safety	Grade ≥3 treatment related adverse events experienced by ≥5% of patients in the both treatment arms of IMbrave150 were included. The same AEs for lenvatinib were sourced from the lenvatinib NICE submission (42). No disutility from AEs considered in base-case analysis.	The threshold of 5% for AE inclusion is conservative as an approach. No disutility from AEs in base-case analysis to avoid double-counting; disutility associated with AEs was assumed to have been captured in the EQ-5D responses in IMbrave150.

AE, adverse event; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DSU, Decision Support Unit; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TA, technology appraisal

B.3.7 Base-case results

In the model base case, discounted model results with a PAS applied to the Atezo+Bev arms are presented in Table 55. The results excluding the PAS are presented in Appendix L. Using a 20-year time horizon, the incremental total LYs gain of Atezo+Bev versus sorafenib and lenvatinib was [redacted] and [redacted] respectively. The discounted incremental costs of £[redacted] and £[redacted] and incremental QALYs of [redacted] and [redacted] resulted in ICERs of £29,524 versus sorafenib and £4,146 versus lenvatinib.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 55: Base case results: Atezo+Bev (with PAS) versus sorafenib and lenvatinib (list price)

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	45,577	1.50	1.05	[redacted]	[redacted]	[redacted]	22,912	29,524
Lenvatinib	63,184	1.54	1.13	[redacted]	[redacted]	[redacted]	2,972	4,146

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. 2,000 iterations were used to ensure convergence. The total costs, LYs and QALYs were recorded for each iteration and averaged.

PSA results for the comparison to sorafenib and lenvatinib are presented in Table 56. The results excluding the PAS are presented in Appendix L. The deterministic ICER for

Atezo+Bev versus sorafenib (£29,524) is in line with the PSA result of £29,714. However, the deterministic ICER for Atezo+Bev versus lenvatinib (£4,146) is slightly less in line with the PSA result of £3,417. This is not overly surprising as the hazard ratios generated in the ITC had very wide credible intervals.

Table 56: Probabilistic sensitivity analysis results: Atezo+Bev (with PAS) versus sorafenib and lenvatinib (list price)

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-		-
Sorafenib	45,689	1.51	1.06	[redacted]	[redacted]	[redacted]	23,097	29,714
Lenvatinib	63,863	1.60	1.17	[redacted]	[redacted]	[redacted]	2,447	3,417

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 27 represents the scatter plot of the incremental costs and QALYs from the PSA results of Atezo+Bev vs sorafenib and lenvatinib, based on 2,000 iterations. Evidently, Atezo+Bev is associated with a clear clinical benefit over sorafenib and lenvatinib. As mentioned previously, the spread of iterations witnessed for lenvatinib is due to the wide confidence intervals. This resulted in clinically implausible probabilistic estimates for lenvatinib, with mean OS estimates exceeding those of sorafenib significantly due to outliers in the simulation. The clinical benefit of Atezo+Bev is further illustrated in the cost-effectiveness acceptability curve (Figure 28).

Figure 27: Cost-Effectiveness Plane – Atezo+Bev (with PAS) vs sorafenib and lenvatinib (list price)

Figure 28: Cost-effectiveness acceptability curve – Atezo+Bev (with PAS) vs sorafenib and lenvatinib (list price)

B.3.8.2 Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was performed to investigate key drivers of the cost-effectiveness model. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. The upper and lower bounds around the mean value for each input parameter were based upon the 10% and 90% percentile values obtained from the PSA input distribution. Where percentile estimates were not available, the input parameter was varied by ±20%.

The tornado diagram for Atezo+Bev versus sorafenib is presented in Figure 29. The tornado diagram for Atezo+Bev versus lenvatinib is presented in Figure 30.

The OWSA highlighted that the discount rate on costs and outcomes and the weekly progressed health state cost had the greatest impact on the cost-effectiveness results vs sorafenib and lenvatinib, respectively.

Figure 29: Tornado diagram (versus sorafenib)

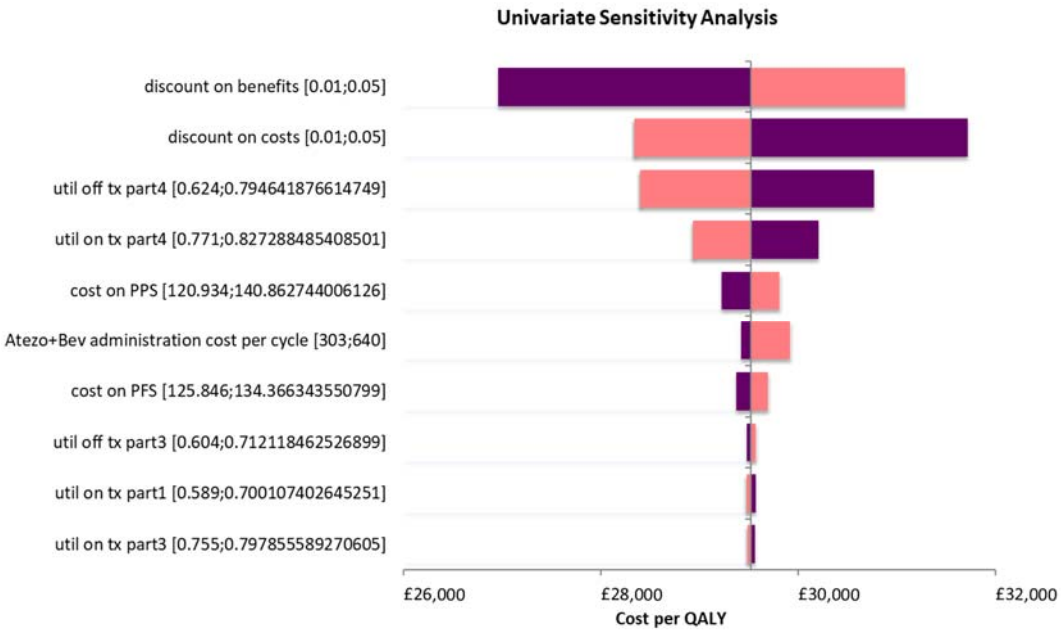
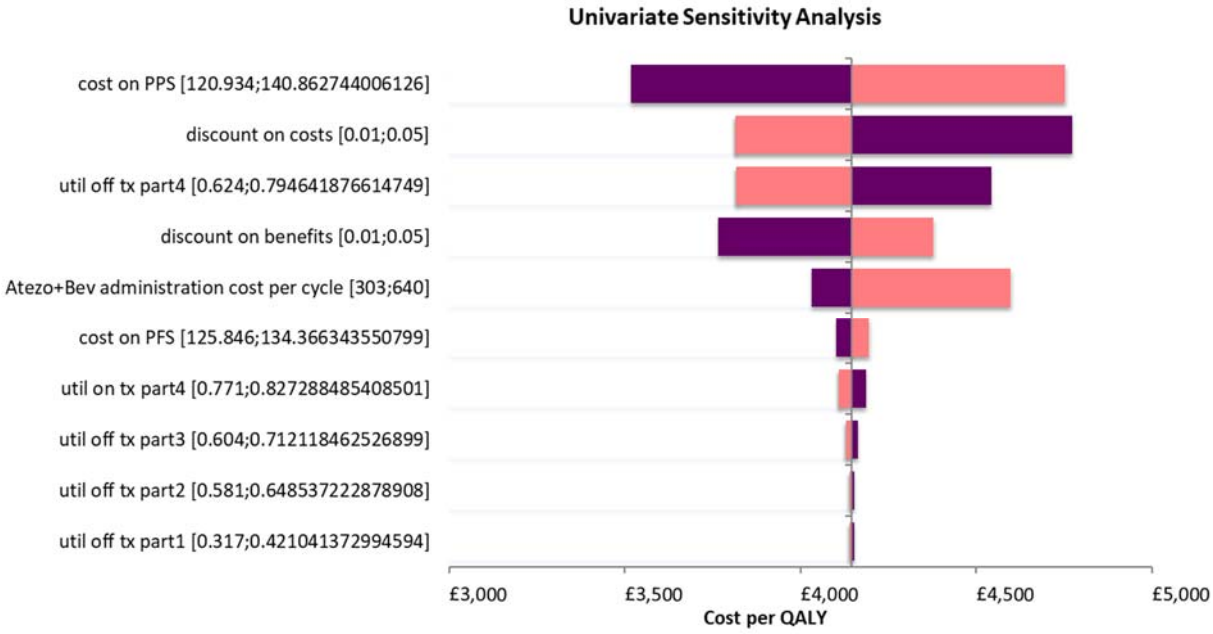


Figure 30: Tornado diagram (versus lenvatinib)



B.3.8.3 Scenario analysis

The list of scenarios explored in the model are listed in Table 57. Results including the Atezo+Bev PAS are presented in Table 58. Results excluding the PAS are reported in Appendix L.

All scenarios presented for Atezo+Bev compared to sorafenib and lenvatinib resulted in ICERs that fell below the £50,000 willingness to pay threshold.

Table 57: Scenario analyses explored in the model

No.	Parameters	Scenario	Base case
1	Time Horizon	5-year time horizon	20 years
2		10-year time horizon	
3		15 - year time horizon	
4	Atezo+Bev OS curve	Generalised Gamma	Exponential
5		Log-logistic	
6	Sorafenib OS curve	Generalised Gamma	Exponential
7		Log-logistic	
8	Atezo+Bev PFS curve	Exponential	Log-normal
9		Log-logistic	
10	Sorafenib PFS curve	Exponential	Log-normal
11		Log-logistic	
12	Atezo+Bev TTD curve	Weibull	KM + Exponential
13		Exponential	
14	Discount rate – costs and QALYS	0%	3.5%
15		5%	

16	Stopping rule in place	Yes (after 2 years)	No
17	Treatment duration assumption	Until progression	Actual treatment duration
18	Dosing	Planned ind. dose without vial sharing	Planned ind. dose with vial sharing
19	Utilities	IMbrave150 (On/Off treatment)	Proximity to death
20		IMbrave150 (Off/On progression)	
21		IMbrave150 (Off/On progression)+ AE3+	
22	Scenario for Sorafenib	ITC	IMbrave150
23	Resource use	TA551	Expert questionnaire 2020
24	Subsequent therapy	IMbrave150 trial data	Sorafenib arm only receive regorafenib (proportion from trial)
25		Sorafenib arm only receive regorafenib (clinical expert opinion)	

OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

Table 58: Scenario analysis results: Atezo+Bev (with PAS) versus sorafenib and lenvatinib (list price)

No.	Scenario	ICER versus sorafenib	ICER versus lenvatinib
Base case		29,524	4,146
1	5-year time horizon	33,921	4,049
2	10-year time horizon	30,034	3,943
3	15 - year time horizon	29,580	4,109
4	Atezo+Bev OS - Generalised Gamma	23,836	5,029
5	Atezo+Bev OS - Log-logistic	28,156	4,471
6	Sorafenib OS - Generalised Gamma	32,317	4,146
7	Sorafenib OS - Log-logistic	38,644	4,146
8	Atezo+Bev PFS - Exponential	29,540	14,030
9	Atezo+Bev PFS - Log-logistic	29,518	2,155
10	Sorafenib PFS - Exponential	29,523	4,146
11	Sorafenib PFS - Log-logistic	29,528	4,146
12	Atezo TTD - Exponential	27,910	2,138
13	Atezo TTD - Weibull	37,537	14,198
14	Discount rate – costs - 0%	32,682	5,055
15	Discount rate – costs - 5%	28,340	3,814
16	Discount rate – effects - 0%	25,944	3,617
17	Discount rate – effects - 5%	31,079	4,377

18	Stopping rule - Yes	21,210	Atezo Dominant
19	Treatment duration: Until progression	29,547	4,365
20	Dose: Planned ind. dose without vial sharing	29,559	4,185
21	Utilities: IMbrave150 (On/Off treatment)	29,571	4,246
22	Utilities: IMbrave150 (Off/On progression)	29,916	3,997
23	Utilities: IMbrave150 (Off/On progression)+ AE3+	30,641	4,118
24	Modelling sorafenib: ITC	28,132	4,146
25	Resource use estimates: TA551	34,766	14,633
26	Subsequent therapy: IMbrave150 trial data	33,076	Atezo Dominant
27	Subsequent therapy: Sorafenib arm only receive regorafenib (clinical expert opinion)	35,354	4,146

B.3.8.4 Summary of sensitivity analyses results

- The ICERs for Atezo+Bev versus sorafenib and lenvatinib are below the WTP threshold of £50,000
- Atezo+Bev was cost-effective in 100% of the PSA iterations vs sorafenib at the WTP threshold of £50,000.
- Key drivers of the model include the discount rates for costs and effects, utility values and health state resource use costs.
- The ICER for Atezo+Bev versus sorafenib and lenvatinib remained below the WTP threshold of £50,000 for all scenarios, with the most significant increase in the ICER being related to the Atezolizumab TTD distribution. The change in sorafenib OS distribution also significantly increased the ICER vs sorafenib.

B.3.9 Subgroup analysis

No subgroup analyses are presented as part of this submission.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Selection of the appropriate distributions for time-to-event endpoints was driven by statistical fit to the data, visual fit to the KM and, importantly, clinical plausibility of the outcomes. All outcomes of the economic model have been extensively compared to and validated against all available evidence, as well as clinical expert opinion, to assess the accuracy of the modelled survival (See Section B.3.3).

The economic model was developed specifically from the UK NHS and PSS perspective. The structure is consistent with other cancer immunotherapy models and previous HCC submissions to NICE and all costs are sourced from UK published sources. In addition, the model approach and inputs were validated by a number of UK clinical experts to ensure the model is reflective of clinical practice. This includes, but is not limited to: health state inclusion, relevant comparators, resource use, OS and PFS projections and extrapolation techniques.

Internal quality control and validation of the model was conducted by an external consultancy. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of pressure tests were also conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

B.3.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of Atezo+Bev as a first-line treatment of adult patients with metastatic unresectable HCC.

No study assessing the cost-effectiveness of Atezo+Bev for the target population outlined above was identified from the SLR. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation is consistent with the population in our pivotal study IMbrave150 and our anticipated licence. As mentioned previously (see section B.3.3), efficacy and safety data from IMbrave150 were used for Atezo+Bev and sorafenib, and results of the indirect treatment comparison outlined in Section B.2.9 were used to inform relative efficacy and safety for lenvatinib.

Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in IMbrave150 and the de novo economic evaluation are reflective of first-line patients with locally advanced or metastatic and/or unresectable HCC in the UK. Advice from UK clinical experts suggested that the patient population in IMbrave150 is broadly consistent with UK patients treated in clinical practice. Despite the post-progression therapies in IMbrave150 being inconsistent with UK clinical practice, the outcomes seen from the study are expected in UK patients.

- The economic model structure is consistent with other oncology models and previous NICE submissions in HCC.
- The resource utilisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs, PSSRU and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of Atezo+Bev.
- Given lenvatinib was not included as a comparator in IMbrave150, an ITC was conducted to enable Atezo+Bev to be compared to lenvatinib, making use of all available evidence and the appropriate methodologies.
- Extensive scenario and sensitivity analyses were conducted in the economic model, considering alternative approaches to the extrapolation of time-to-event endpoints, alternative parameter inputs and data sources.
- The 5-year landmark OS projections from the model were validated against all available UK sources and UK clinical expert opinion to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

Strengths and weaknesses of the evaluation

The key strengths associated with the cost-effectiveness analysis are related to the use of the best available evidence and methods to inform the model:

- Efficacy and safety data from IMbrave150 were used to model OS, PFS and TTD for Atezo+Bev and sorafenib.
- Utility values were obtained directly from EQ-5D IMbrave150 data. The proximity to death approach was used in our model base-case (four intervals before death were considered). The proximity to death approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease.
- Resource utilisation used in the analysis is derived from a questionnaire of 6 UK clinicians currently treating patients with HCC. Unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from UK published sources and previous NICE appraisals, accounting for the feedback provided by NICE and ERGs in the most recent submissions.
- The ITC implemented enabled a comparison between Atezo+Bev and lenvatinib, by applying appropriate methodology and making use of all available evidence.
- Extensive sensitivity and scenario analyses were conducted in the economic model to inform the uncertainty around the parameters used and help understand what key variables and assumptions potentially have a major impact on cost-effectiveness results.

Nevertheless, the economic analysis is also associated with limitations:

- Lenvatinib was not included as a comparator in IMbrave150 and as such, we had to implement an ITC to enable a comparison between Atezo+Bev and lenvatinib. The base case network for the ITC is associated with limitations, primarily resulting from the different levels of detail available for the studies included and the censoring of OS outcomes.

  We have however implemented extensive sensitivity and scenario analyses to inform the long-term plausibility and appropriateness of alternative ITC networks, approaches and methodology. In addition, lenvatinib OS outcomes are expected to be similar to sorafenib.
- Extrapolation of time-to-event endpoints is also subject to uncertainty. Nevertheless, by following a robust and comprehensive approach for the survival extrapolation, the best efforts have been taken to ensure the methods were statistically sound, clinically plausible, and reflective of real-world clinical practice. Extensive sensitivity and scenario analyses were conducted to inform the impact of alternative extrapolation models and assess the long-term plausibility and appropriateness of each scenario
- Post-progression survival was not adjusted for in the sorafenib arm. Therefore the overall survival of sorafenib could be over-estimated compared to UK clinical practice as patients received immunotherapy such as nivolumab after progression, which is not an option in the UK.

Conclusions

There is an unmet need for cancer immunotherapies in patients with locally advanced, metastatic and/or unresectable HCC who have not received prior systemic therapy. IMbrave150 is the first randomised phase III study in over ten years to show a significant improvement in overall survival over sorafenib, with a 42% reduction in the risk of death and is the first positive phase III study of a cancer immunotherapy in patients with locally advanced or metastatic and/or unresectable HCC. The significantly longer overall survival versus sorafenib achieved with Atezo+Bev is underpinned by a 2.5-month increase in PFS, a response rate of 27.3%, and a median duration of response that still has not been reached. These clinically meaningful outcomes, combined with the safety and patient-reported outcome findings, demonstrate that the combination of Atezo+Bev has a favourable benefit/risk profile and addresses the unmet need for this population.

Since the majority of the key approaches and assumptions in the base-case analysis of our economic evaluation are conservative, we believe that the cost-effectiveness results are appropriate for decision-making. The model results support the conclusion that, within the context of innovative end-of-life therapies, and at PAS price for atezolizumab and

bevacizumab and list price for all comparators, Atezo+Bev is a cost-effective treatment option versus sorafenib and lenvatinib in first line patients with locally advanced or metastatic and/or unresectable HCC.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **4 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement 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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Eisai Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Distribution chosen for overall survival	
What percentage of people would you expect to still be alive, having received sorafenib, at 2 years, 5 years and 10 years?	
Issue 2: Indirect treatment comparison	
Would the relative effectiveness of lenvatinib compared with atezolizumab plus bevacizumab be expected to remain constant over time?	We agree with the technical teams' preliminary judgement that it may have been inappropriate to use the hazard ratio from the NMA to model lenvatinib overall survival. Conclusions from TA551 and the REFLECT study suggest that the proportional hazards assumption does not hold for the comparison between lenvatinib and sorafenib, this would imply that it is also unlikely to hold for the comparison between lenvatinib and atezolizumab plus bevacizumab. Furthermore, in the REFLECT study, there were key imbalances across the study arms in terms of prognostic factors (AFP ≥200 ng/mL and Hepatitis C aetiology) and subsequent therapies received. The manufacturers' NMA uses unadjusted estimates of overall survival from REFLECT. We believe it would be more appropriate to take the estimated treatment effect for lenvatinib vs sorafenib from published re-analysis which adjusts for important imbalances in prognostic baseline characteristics [1]. As documented during TA551 and reported by Briggs et al [1], the imbalance in the baseline prognostic factors in REFLECT appeared to bias the outcomes against lenvatinib. There was

	furthermore a greater number of post-treatment therapies used after sorafenib compared with lenvatinib, leading the authors of the original study to speculate that: "If post-progression survival is prolonged by…post-study treatments, this could lead to a dilution of the observed overall survival treatment benefit". Briggs et al [1] use multivariable analysis to adjust for these imbalances. The chosen multivariable Cox model analysis resulted in an estimated adjusted hazard ratio for lenvatinib of 0.814 (95% CI: 0.699–0.948) when only baseline variables were included. Adjusting for post-randomisation treatment variables further increased the estimated superiority of lenvatinib. As such, we believe the manufacturers' NMA, which uses the unadjusted estimated reported in the original study publication, will underestimate the efficacy of lenvatinib. [1] Briggs, A., et al., Covariate-adjusted analysis of the Phase 3 REFLECT study of lenvatinib versus sorafenib in the treatment of unresectable hepatocellular carcinoma. British Journal of Cancer, 2020. 122(12): p. 1754-1759.
A. Why is it not feasible to fit time-varying random effects models as described by Ouwens et al (2010), given that it would require the same likelihood function for the fractional polynomial analysis provided by the company in response to clarification question A7? B. Can these now be provided?	
Issue 3: The effect of subsequent treatments on overall survival	
Please can full details be provided of the company's analysis conducted to adjust overall survival for the	

subsequent treatments not currently recommended in England?	
Issue 4: Capping of utilities	
Is it plausible that the health-related quality of life of a person with unresectable or advanced hepatocellular carcinoma would be better than the general population average for the same age and sex?	We concur with the technical team that it is not plausible that the health-related quality of life of patients with advanced hepatocellular carcinoma would be better than the general population average for the same age and sex.
Issue 5: Dosing assumptions	
To what extent can unused tablets for oral chemotherapy be reused?	Section B3.5.1 of the manufacturer submission reports dosing assumptions for lenvatinib: "Lenvatinib: in line with its marketing authorisation and use in UK clinical practice, i.e. 12 mg for patients ≥60 kg and 8 mg for patients <60 kg, once-daily" However, Table 42 reports a total dose of 12mg, which would not be reflective of a lower dose for patients <60kg. All analyses should include dosing of lenvatinib 8mg dose for patients <60kg. Furthermore, as mentioned in the ERG report section 4.3.4.3, the manufacturer also applies a relative dose intensity (RDI) for atezolizumab plus bevacizumab and sorafenib but assumes the RDI for lenvatinib was equal 1. Assuming an RDI of 1 is inconsistent with the conclusions of TA551 and the REFLECT clinical study. We believe the value of 0.88, which is available in TA551 should be reflected in the base case analysis.

	In addition, the manufacturer assumes that patients remain on lenvatinib until disease progression or death, on the basis that TTD was not explicitly reported in REFLECT. In fact, the primary publication for REFLECT reports: *"The median duration of study treatment for patients in the lenvatinib group was 5.7 months (IQR 2.9–11.1), compared with 3.7 months (1.8–7.4) in the sorafenib group." [1]* Given the manufacturer has assumed that time to discontinuation follows an exponential distribution, it would have been straightforward to estimate the rate of discontinuation, as the hazard h can be calculated from the median survival time (MST) as: $$h = \ln(2) / MST$$ Full Kaplan-Meier curves of TTD from RELFECT are also presented, unredacted, in the ERG report for TA551. Median time to progression of lenvatinib in the REFLECT study was 8·9 months (95% CI 7·4–9·2) compared to 3·7 months (3·6–5·4) for patients in the sorafenib group [1], therefore, assuming that patients remain on lenvatinib until disease progression or death will result in an overestimation of time on treatment. As a consequence of these omissions, the manufacturer has overestimated the costs of lenvatinib and will therefore overestimate the cost-effectiveness of atezolizumab plus bevacizumab vs lenvatinib.

	[1] Kudo, M., et al., Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet, 2018. 391(10126): p. 1163-1173.
Issue 6: Wastage assumptions for oral chemotherapy	
Is it appropriate to consider up to 7 days wastage for oral chemotherapy treatments?	
Issue 7: Costing subsequent treatments	
Which of the 4 approaches to the costing of subsequent treatments outlined in issue 7 is the most appropriate?	

Atezolizumab with bevacizumab for untreated hepatocellular carcinoma. A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	Date completed (14/09/2020)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 13/14/17.

1 Background

In April 2020, the company submitted to the National Institute for Health and Care Excellence (NICE) the evidence for use of atezolizumab with bevacizumab (A+B) in the treatment of adults with locally advanced or metastatic and/or unresectable hepatocellular carcinoma (HCC) who have had no previous systemic treatment. The Evidence Review Group (ERG) submitted a report in June 2020. The ERG identified two base cases, base case A where the relative dose intensities (RDI) for sorafenib and lenvatinib were applied from the IMbrave150 and REFLECT trials respectively, and base case B where the RDI was assumed equal to 1 for both drugs. The ERG explored both base cases using survival data for all patients in the IMbrave150 and alternatively the non-Asian subgroup plus Japanese patients of the same trial. This was also further stratified by weight using a weight cut of 60kg (i.e. patients weighing under 60kg and others weighing 60kg and over). Table 1 presents the ERG-preferred ICER ranges for the four scenarios (reproduced from Table 26 in the ERG report). It's to be noted that the confidential patient access scheme (PAS) prices for sorafenib, lenvatinib and regorafenib are not included.

Table 1: Summary of ERG-preferred ICER (cost per QALY gained) ranges for the four scenarios

	All patients in IMbrave150		**Non-Asian plus Japanese patients in IMbrave150**	
	Sorafenib	**Lenvatinib**	**Sorafenib**	**Lenvatinib**
Costs associated with patients weighing under 60kg	£16,567 to £21,843	£83 to £3,962	£15,387 to £21,488	Dominant to £3,381
Costs associated with patients weighing 60kg or more	£21,427 to £26,653	Dominant to Dominant	£20,837 to £27,017	Dominant to Dominant

The NICE technical team prepared a technical report where eight related issues were identified for discussion at the appraisal committee meeting. The company replied to seven issues providing new analyses and economic model. The ERG discusses herein the impact of this on the ERG base case with the least favourable ICER for A+B which was 'ERG base case B assuming costs for patients weighing more than or equal to 60kg excluding Asia (except Japan)', in which A+B has a deterministic ICER of £26,525 compared with sorafenib (Table 2).

2 ERG's exploratory analysis incorporating new data and model provided by the company in response to NICE technical document

The company did not provide new data in their response to Technical Engagement Issues 1, 4, 5 and 6. For Issue 1 the company stated that both exponential and log-normal curve fits for OS data are clinically plausible, for Issues 4, 5 and 6 the company agreed with the position taken by the ERG. However, for Issue 6, the ERG believes that the approach implemented by the company is slightly incorrect and would result in 3.5 days' wastage of oral chemotherapy rather than 7 days as intended. If this was corrected the cost-effectiveness of A+B would become more favourable.

In response to issue 2, the company submitted a random effects fractional polynomial analyses for overall survival (OS) hazard ratios of A+B versus sorafenib and lenvatinib. The new analyses impact only on lenvatinib OS estimates as sorafenib OS is modelled using data directly from the IMbrave150 trial, and is noted to be of trivial impact. The effect of using the fractional polynomial on the incremental costs and QALYs were relatively small. (See Table 2). Given these differences and the potential uncertainty associated with the results from the fractional polynomial analyses the ERG prefer to maintain the analyses undertaken in the ERG report.

The company provided the detailed analyses adjusting survival estimates using an accelerated failure time model by removing the effects of subsequent treatments not recommended in England in response to Issue 3, and therefore deemed it reasonable to account for costs of regorafenib (a recommended treatment after sorafenib) as administered as per the IMbrave150 trial (Issue 7). The ERG did not have detailed explanations of the method and analyses performed at the time of writing the original report (see Section 4.3.4.8 of the ERG report). The ERG included the costs of subsequent immunotherapy and tyrosine kinase inhibitors in its base cases. For complacency, the ERG explored the impact of using the adjusted OS estimates and account only for regorafenib cost. As shown in Table 2, the use of the company's analysis for subsequent treatments results in the costs of the lenvatinib arm decreasing, although this would not reflect the treatments used post-progression in the REFLECT study, which compared lenvatinib and sorafenib. Given this limitation, which is unfavourable to A+B the ERG prefers to maintain its original assumptions.

Table 2: Assessing the impact of the company's new analyses post technical engagement to ERG base case B for patients weighing more than 60kg and excluding Asian patients (except Japanese: deterministic results)

Analysis	Discounted costs			Discounted QALYS			ICER (A + B versus sorafenib)	ICER (A + B versus lenvatinib)
	A+B	Sorafenib	Lenvatinib	A+B	Sorafenib	Lenvatinib		
ERG base case B assuming costs for patients more than or equal to 60kg excluding Asia (except Japan)	[redacted]	£46,897	£67,927	[redacted]	1.25	1.09	£26,525	A+B dominant
Issue 2: Using random effects fractional polynomial model to estimate lenvatinib OS	[redacted]	£46,897	£68,266	[redacted]	1.25	1.13	£26,525	A+B dominant
Issues 3 and 7: Adjusting OS and costs to reflect subsequent treatments recommended in England	[redacted]	£42,219	£59,668	[redacted]	1.02	1.17	£19,224	£359

3 Conclusions

No data were seen by the ERG to suggest that the exploratory analyses undertaken by the ERG in its original report were not plausible estimates of the cost-effectiveness of A+B for untreated hepatocellular carcinoma. As such, no changes have been made to the results contained within the ERG report

Atezolizumab with bevacizumab for untreated hepatocellular carcinoma. A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	Date completed (01/10/2020)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 13/14/17.

Atezolizumab with bevacizumab

Issue 2

There are several issues that are pertinent to the assertion that an adjusted hazard ratio for the effect of lenvatinib versus sorafenib should be used in the economic model:

- Stratification
- Observed prognostic factors
- Baseline balance
- Generating a multivariable model
- Cox proportional hazards versus parametric modelling
- Marginal versus conditional expectation in the target population
- Post-treatment therapies

Stratification

A principle of clinical trials is that the analysis of study data should be done using a statistical model that reflects the way in which the randomisation was conducted. Hence, if randomisation is conducted according to any stratification factors then these should be included in a statistical model irrespective of whether their effect is statistically significant at some arbitrary level of significance at the analysis stage.

Patients in REFLECT were stratified by geographical region; presence of macroscopic portal vein invasion (MPVI), extrahepatic spread (EHS) or both; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; and bodyweight (< 60 kg or ≥ 60 kg). Hence, these variables should be included in any multivariable model. Furthermore, the effect of bodyweight should not be included as a dichotomous variable in which the suggestion is that effect of bodyweight changes abruptly at 60 kg; rather it should be included as a continuous variable with its relevance evaluated using splines.

Observed prognostic factors

It is not clear from the REFLECT manuscript whether the clinical study protocol pre-defined any covariates of interest. Nevertheless, if any known prognostic were observed then it is not permitted to exclude these from the model irrespective of whether they were statistically significant at some arbitrary level of significance.

Baseline balance

The issue of baseline balance is related to that of having to adjust for observed prognostic factors but is different for non-linear models. The authors of the REFLCT manuscript recognise the benefit of including prognostic factors in linear model in order to increase the precision of the estimate of treatment effect. However, the issue is different in the case of non-linear models such as Cox regression. A hazard ratio is a non-collapsible measure of relative treatment effect. An unadjusted estimate of a hazard ratio (i.e. marginal effect) will be different to an adjusted estimate of a hazard ratio (i.e. a conditional effect) even if there is no confounding. This is because in non-linear models there are no residual terms, and unaccounted outcome heterogeneity is absorbed into the regression coefficients in the model, attenuating them towards zero (on the log scale). Hence it is irrelevant whether a stratification factor or observed prognostic factor is balanced or imbalanced; prognostic

variables should automatically be included in a model. An adjusted hazard ratio will be greater than an unadjusted hazard ratio.

Generating a multivariable model

Again, it is not clear from the REFLECT manuscript whether the clinical study protocol pre-defined any covariates of interest, although it appears that potential prognostic factors were specific by clinical authors of the manuscript.

Potential covariates to include in the multivariable model were identified following univariate adjustment of treatment effect, including the stratification factors (with bodyweight dichotomised) as potential covariates. The procedure allows for stratification factors to be dropped from the model, thereby violating the principle that the data should be analysed using a statistical model that reflects the way in which the randomisation was conducted. Furthermore, the use of univariate analyses is generally misleading and should be avoided.

A multivariable model was evaluated using forward selection with the stratification factors included as covariates (with bodyweight dichotomised). It is well known that stepwise methods are misleading for the following reasons:

- R^2 values used to quantify the proportion of variance explained by the model are biased high.
- The F statistics that are produced do not have the claimed distribution.
- Standard errors of parameter estimates are too small.
- Confidence intervals for parameter estimates are too narrow.
- p-values are too low because of multiple comparisons, and are difficult to correct.
- Parameter estimates are biased away from 0.
- Collinearity problems are exacerbated.

The authors of the manuscript generate a multivariable model with nine covariates in addition to the effect of lenvatinib. Of the stratification factors, only the effect of MPVI was retained as a covariate in the final model. Hence, it is not clear what the true estimate is of the effect of lenvatinib versus sorafenib.

Cox proportional hazards versus parametric modelling

A hazard ratio is a convenient estimate of the relative effect of treatment for drug regulatory purposes and for describing the average effect of treatment over the duration of a study ignoring any treatment by time interaction. However, in the case of an economic evaluation where interest is in estimating population mean survival, assuming proportional hazards will not necessarily reflect the true relationship.

Ultimately, in order to generate treatment-specific survival functions, it is necessary to assume a parametric baseline survival function. Hence, not only is the perceived benefit of using Cox regression lost but some of the parametric distributions, such as a log-logistic distribution, cannot be parameterised as a proportional hazards model.

The ideal scenario, as recommended by the ERG is to use a coherent meta-analysis model that allows for time-varying treatment effects for each treatment and not a single hazard ratio. Hence, the issue of whether to use an adjusted or unadjusted hazard ratio should be academic. Furthermore, the gold standard would be a patient-level parametric meta-regression in which both prognostic factors and

treatment effect modifiers could be evaluated. At the moment, it would appear that only the effect of prognostic factors have been evaluated.

Marginal versus conditional expectation in the target population

The issue of marginal versus conditional expectation in the target population is more complex. In general, most meta-analyses are marginal analyses in the sense that they ignore covariates that affect outcome (e.g. a marginal survival function). Strictly, because an economic evaluation is essentially interested in generating marginal survival functions and/or estimating marginal mean survival, it is necessary to integrate the conditional model over the joint distribution of the covariates in the target population. It is no obvious whether the joint distribution of the covariates in the target population is the same as the joint distribution of the covariates in the study(s).

Post-treatment therapies

The effect of post-treatment therapies should not be evaluated as if they were baseline characteristics that could be used to predict outcome. If interest is in an estimand that reflect the effect of treatment without the use of additional treatments post-randomisation then these should be accounted for using treatment switching methodology.

Conclusions

The ERG reiterates its recommendation that relative treatment effects between A+B, sorafenib and lenvatinib should be estimated using a coherent model that allows for time-varying treatment effects.

While adjusting for relevant prognostic factors (and treatment effect modifiers) is ideal it is not clear that the multivariable model generated in the REFLECT manuscript produces an unbiased estimate of the conditional hazard ratio. Furthermore, the relevance of a hazard ratio in the context of an economic evaluation is questionable. The impact of stratification factors and known and potential prognostic factors (and treatment effect modifiers) should be evaluated with respect to plausible parametric models.

No attempt has been made to adjust for prognostic factors when comparing A+B and sorafenib, although because adjusted hazard ratios are greater than unadjusted hazard ratios, the conditional estimate of the effect of A+B versus sorafenib is likely to be greater than the marginal estimate.

Estimation of marginal survival functions and population mean survival from a conditional model requires knowledge of the joint distribution of covariates in the target population.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab with Bevacizumab for Untreated, Unresectable or Advanced Hepatocellular Carcinoma (ID1655)

Clarification questions

May 2020

File name	Version	Contains confidential information	Date
ID1655_Atezo+Bev HCC_ERG Clarification Questions	1	Yes	21 May 2020

Section A: Clarification on effectiveness data

Systematic Literature Review

A1. Please provide the full search strategy of the International Clinical Trials Registry Platform as this is absent on page 12 in Appendix D: Identification, selection and synthesis of clinical evidence. Also please provide the full reference list of trials retrieved from ICTRP search.

Table 1 provides a summary of relevant ongoing trials that were identified as part of the SR. The search terms that were used include HCC and Hepatocellular cancer.

Table 1: Summary of relevant ongoing trials identified as part of the SR in the first-line treatment setting (n=10)

NCT (trial name)	Title	Details of study design	Dates
NCT03755791	Study of Cabozantinib in Combination With Atezolizumab Versus Sorafenib in Subjects With Advanced HCC Who Have Not Received Previous Systemic Anticancer Therapy (COSMIC-312)	**Design:** Phase II, open label RCT **Sponsor:** Exelixis **Estimated enrolment:** 740 **Population** • HCC that is not amenable to a curative treatment approach • BCLC B or C • Child-Pugh class A • ECOG ≤1 **Interventions**: • Cabozantinib + atezolizumab • Sorafenib • Cabozantinib **Primary outcome:** PFS	**Current status**: Recruiting **Estimated primary completion date**: August 2020
NCT04000737	YIV-906 (Formerly PHY906/KD018) With Sorafenib in HBV(+) Hepatocellular Carcinoma (HCC)	**Design:** Phase II, open label RCT **Sponsor:** Yiviva Inc. **Estimated enrolment:** 125 **Population** • Advanced HCC with HBV • Never received anti-tumour therapy • Child-Pugh class A • ECOG ≤1 **Interventions**: • YIV-906 + sorafenib	**Current status**: Recruiting **Estimated primary completion date**: June 2021

NCT (trial name)	Title	Details of study design	Dates
		• Placebo + sorafenib **Primary outcome:** PFS	
NCT04050462	A Phase II, Randomized, Controlled Trial of Nivolumab in Combination With BMS-986253 or Cabiralizumab in Advanced Hepatocellular Carcinoma (HCC) Patients	**Design:** Phase II, open label RCT **Sponsor:** NYU Langone Health **Estimated enrolment:** 74 **Population** • HCC localised to the liver and not amenable to curative treatment • Child-Pugh Score ≤7 • ECOG ≤1 **Interventions**: • Nivolumab + cabiralizumab • Nivolumab + BMS-986253 • Nivolumab **Primary outcome:** ORR	**Current status**: Recruiting **Estimated primary completion date**: August 2020
NCT04246177 (LEAP-012)	Safety and Efficacy of Lenvatinib (E7080/MK-7902) With Pembrolizumab (MK-3475) in Combination With Transarterial Chemoembolization (TACE) in Participants With Incurable/Non-metastatic Hepatocellular Carcinoma (MK-7902-012/E7080-G000-318/LEAP-012)	**Design:** Phase III, double-blind RCT **Sponsor:** Merck Sharp & Dohme Corp **Estimated enrolment:** 950 **Population** • HCC • Not to be a candidate for resection or other local-regional therapy • Not received any other systemic therapy **Interventions**: • Lenvatinib + pembrolizumab + TACE • Placebo + placebo + TACE **Primary outcome:** PFS	**Current status**: Recruiting **Estimated primary completion date**: April 2025
NCT03713593 (LEAP-002)	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-	**Design:** Phase III, double-blind RCT **Sponsor:** Merck Sharp & Dohme Corp **Estimated enrolment:** 750 **Population** • HCC • BCLC B or C t amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach • Child-Pugh Score class A • ECOG ≤1	**Current status**: Recruiting **Estimated primary completion date**: May 2022

NCT (trial name)	Title	Details of study design	Dates
	G000-311/LEAP-002)	**Interventions**: • Lenvatinib + pembrolizumab + TACE • Lenvatinib + placebo + TACE **Primary outcome:** PFS & OS	
NCT03412773 (RATIONALE 301)	Phase 3 Study of BGB-A317 Versus Sorafenib in Patients With Unresectable HCC	**Design:** Phase III, open-label RCT **Sponsor:** BeiGene **Estimated enrolment:** 660 **Population** • HCC based on histopathological confirmation • BCLC B or C and not amenable to or progressing after loco-regional therapy and not amenable to a curative treatment approach • No prior systemic therapy for HCC • Child-Pugh Score class A • ECOG ≤1 **Interventions**: • Tislelizumab • Sorafenib **Primary outcome:** OS	**Current status**: Recruiting **Estimated primary completion date**: May 2022
NCT03905967	Transarterial Chemoembolization With Lenvatinib Versus Lenvatinib Alone in First-line Treatment of Advanced Hepatocellular Carcinoma: a Phase III, Multicentre, Randomized Controlled Trial	**Design:** Phase III, open-label RCT **Sponsor:** Sun Yat-sen University **Estimated enrolment:** 336 **Population** • Age 18-75 years • HCC based on histopathological confirmation • No prior therapy for HCC • Child-Pugh Score class A • ECOG PS 0 or 1 at enrolment • ≥1 lesion with measurable disease at baseline by RECIST • Adequate organ and bone marrow function • Expected survival time ≥6 months **Interventions**: • Lenvatinib + TACE • Lenvatinib **Primary outcome:** OS	**Current status**: Not yet recruiting **Estimated primary completion date**: April 2023

NCT (trial name)	Title	Details of study design	Dates
NCT03895359	A Phase III Randomized Trial of Transarterial Chemoembolization (TACE) Versus TACE Plus Stereotactic Body Radiation Therapy (SBRT) in Primary or Secondary Liver Carcinoma	**Design:** Phase III, open-label RCT **Sponsor:** Lawson Health Research Institute **Estimated enrolment:** 128 **Population** • Age >18 years • HCC • Patient must be judged medically or surgically unresectable • Previous liver resection or ablative therapy is permitted. **Interventions**: • TACE + SBRT • TACE **Primary outcome:** OS/Time to intrahepatic progression	**Current status**: Not yet recruiting **Estimated primary completion date**: June 2027
NCT03794440 (ORIENT-22)	A Randomized, Open-label, Multi-centre Study to Evaluate the Efficacy and Safety of the Combination of Sintilimab and IBI305 Compared to Sorafenib in the First-Line Treatment of Patients With Advanced Hepatocellular Carcinoma	Design: Phase II/III, open-label RCT Sponsor: Innovent Biologics (Suzhou) Co. Ltd. Estimated enrolment: 566 Population • HCC based on histopathological confirmation • No prior systemic therapy for HCC • BCLC stage B or stage C • Child-Pugh Score ≤7 • ECOG PS 0 or 1 at enrolment • ≥1 lesion with measurable disease at baseline by RECIST V1.1. • Adequate organ and bone marrow function Interventions: • Sintilimab • IBI305 • Sorafenib **Primary outcome**: OS/ORR	**Current status**: Recruiting **Estimated primary completion date**: December 2022
NCT03298451 (HIMALAYA)	A Randomized, Open-label, Multi-centre Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced	**Design:** Phase III, open-label RCT **Sponsor:** AstraZeneca **Estimated enrolment:** 1,310 **Population** • HCC based on histopathological confirmation	**Current status**: Recruiting **Estimated primary completion date:** June 2020

NCT (trial name)	Title	Details of study design	Dates
	Hepatocellular Carcinoma	• No prior systemic therapy for HCC • BCLC stage B or stage C • Child-Pugh Score class A • ECOG PS 0 or 1 at enrolment **Interventions**: • Durvalumab + tremelimumab (2 regimens) • Durvalumab • Sorafenib **Primary outcome:** OS	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; PS, performance scale; RCT, randomised controlled trial; SBRT, Stereotactic ablative body radiotherapy; TACE, transarterial chemoembolisation.

A2. Please clarify whether quality assessment was undertaken by one analyst and checked by a second, as for data extraction?

Quality assessment was undertaken by one analyst and quality checked for 100% of data elements by a second analyst or project lead. The two reviewers independently assessed the likelihood of bias and any disagreements or disputes were referred to a third party (strategic advisor).

Adverse Events

A3. Please define serious adverse events as used within the company submission.

In the IMbrave150 study, a serious adverse event was defined as being one that met any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalisation
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardise the patient or may require medical/surgical intervention)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness were independently assessed for each adverse event recorded on the eCRF. Serious adverse events were reported by the investigator within 24 hours after learning of the event.

A4. Please clarify whether the data in Table 9 in the Appendix are from a safety population (rather than ITT). Please provide a column for A+B group combined.

We can confirm that the data in Table 9 of the appendix are from the safety-evaluable population. This has been updated below to include a column for Atezo+Bev combined.

Table 2: Reasons for discontinuation from study treatment

n, (%)	Atezo+Bev n=329			Sorafenib n=156
	Atezo	Bev	Atezo+Bev	
Received at least one study treatment				
Yes	329 (100)	329 (100)	329 (100)	156 (100)
Treatment status				
Ongoing	146 (44.4)	137 (41.6)	146 (44.4)	24 (15.4)
Withdrawn from treatment	183 (55.6)	192 (58.4)	183 (55.6)	132 (84.6)
Withdrawn from treatment reason				
Death	15 (4.6)	16 (4.9)	15 (4.6)	7 (4.5)
Adverse event	29 (8.8)	49 (14.9)	26 (7.9)	16 (10.3)
Symptomatic deterioration	10 (3.0)	9 (2.7)	9 (2.7)	4 (2.6)
Progressive disease	111 (33.7)	100 (30.4)	98 (29.8)	93 (59.6)
Physician decision	3 (0.9)	4 (1.2)	3 (0.9)	4 (2.6)
Withdrawal by subject	15 (4.6)	14 (4.3)	14 (4.3)	7 (4.5)
Other	0	0	0	1 (0.6)

A5. The rate of adverse events for lenvatinib is a naive indirect comparison. Please clarify the impact of applying the relative frequency between sorafenib and lenvatinib in REFLECT to the IMbrave 150 sorafenib data.

If the relative frequency between sorafenib and lenvatinib in REFLECT were applied to the IMbrave 150 sorafenib data, the rate of lenvatinib adverse events would be lower as the length of follow-up in the REFLECT trial is much longer than in the IMbrave150 trial. This would result in a more accurate rate of lenvatinib adverse events, as the current naive indirect comparison relies on the assumption that time doesn't determine the relative frequency of adverse events, as well as comparability of populations.

A6. Please clarify the average duration of each adverse event. Please also comment on the likelihood that the negative impacts of the adverse events would be captured in the EQ-5D questionnaires, which were completed on treatment administration, and 3 monthly thereafter, given that the recall period of the EQ-5D is instantaneous.

Table 3 highlights the average duration of each adverse event. If an adverse event coincided with when the EQ-5D questionnaire was measured, the negative impact of the adverse event was captured. A regression analysis was carried out to determine if the EQ-5D questionnaire was measured whilst an adverse event was active. The results show that adverse events did have a statistically significant impact on the EQ-5D measurement (-0.04 - this is for any AE), but this impact is not considered clinically significant. This is why we decided to implement the scenario with serious AE/AE3+ utilities, to compensate for those effects.

Table 3: Average duration of adverse events in days

Adverse Event	Mean	Median
Abdominal discomfort	90	32
Abdominal distension	69	45
Abdominal pain	77	25
Abdominal pain lower	25	25
Abdominal pain upper	81	36
Acetabulum fracture	12	12
Activated partial thromboplastin time prolonged	52	45
Acute coronary syndrome	5	5
Acute kidney injury	17	12
Acute myocardial infarction	6	6
Adrenal insufficiency	170	170
Aerophagia	8	8
Ageusia	35	35
Alanine aminotransferase increased	67	29
Albumin globulin ratio decreased	41	41
Albuminuria	91	91
Alopecia	200	205
Ammonia increased	289	289
Amnesia	190	187
Amylase increased	93	19
Amyotrophy	185	185
Anaemia	73	36
Anal fissure	36	20
Anal fungal infection	15	15
Anal haemorrhage	1	1
Anal incontinence	2	2
Anaphylactic reaction	1	1
Angina pectoris	12	12
Angular cheilitis	10	10
Anxiety	145	145
Aortic valve disease	134	134

Aortic valve stenosis	42	42
Aphthous ulcer	63	63
Arrhythmia	224	224
Arthralgia	166	137
Arthritis	107	107
Ascites	79	42
Aspartate aminotransferase increased	89	57
Asthenia	92	58
Asthma	57	57
Asymptomatic bacteriuria	25	25
Atrial fibrillation	82	29
Autoimmune arthritis	61	61
Autoimmune haemolytic anaemia	111	111
Autoimmune hepatitis	13	13
Back pain	79	22
Balance disorder	85	85
Balanoposthitis	15	15
Basal cell carcinoma	27	27
Benign prostatic hyperplasia	96	96
Bile duct stone	242	242
Bilirubin conjugated increased	76	23
Bleeding varicose vein	4	4
Blepharitis	155	155
Blindness	171	171
Blister	48	24
Blood albumin decreased	132	41
Blood alkaline phosphatase increased	122	86
Blood bilirubin increased	75	31
Blood bilirubin unconjugated increased	55	22
Blood calcium decreased	11	11
Blood calcium increased	13	13
Blood chloride decreased	82	82
Blood cholesterol increased	155	155
Blood cholinesterase decreased	15	15
Blood creatine phosphokinase increased	2	2
Blood creatinine decreased	184	184
Blood creatinine increased	53	25
Blood glucose increased	21	21
Blood lactate dehydrogenase increased	96	37
Blood magnesium decreased	73	43
Blood phosphorus decreased	22	22
Blood potassium decreased	14	19
Blood potassium increased	11	11
Blood pressure diastolic increased	2	2
Blood pressure increased	99	43
Blood sodium decreased	48	29
Blood thyroid stimulating hormone increased	111	96
Blood urea increased	45	45
Blood urine present	20	20
Body temperature increased	6	6

Bone pain	40	40
Bradycardia	197	197
Bradypnoea	5	5
Bronchitis	13	13
Bronchitis viral	NA	NA
Bundle branch block left	28	28
Burkholderia pseudomallei infection	313	313
C-reactive protein increased	27	27
Carbon dioxide decreased	3	3
Cardiac arrest	1	1
Cardiac failure	124	153
Cardiac ventricular disorder	23	23
Cataract	178	178
Catheter site pain	25	25
Cells in urine	150	150
Cellulitis	30	39
Cerebral infarction	79	79
Cerebrovascular accident	2	2
Cheilitis	206	296
Chest discomfort	27	23
Chest pain	35	22
Chills	66	8
Cholangitis	13	8
Cholelithiasis	193	193
Cholestasis	3	3
Chronic myeloid leukaemia	38	38
Chronic obstructive pulmonary disease	50	50
Coagulopathy	75	58
Coccydynia	26	26
Colitis	46	16
Colon adenoma	179	179
Compression fracture	19	19
Conduction disorder	21	21
Confusional state	11	2
Conjunctival deposit	4	4
Conjunctival haemorrhage	32	32
Conjunctivitis	49	49
Constipation	100	62
Contrast media allergy	2	2
Contusion	249	249
Cough	80	42
Cystitis	64	57
Cytokine release syndrome	73	73
Death	1	1
Decreased appetite	125	103
Deep vein thrombosis	81	42
Dehydration	10	8
Delirium	136	136
Dementia	77	77
Dental caries	51	51

Dental gangrene	3	3
Depression	61	61
Dermal cyst	79	79
Dermatitis	123	104
Dermatitis acneiform	157	97
Dermatitis allergic	77	77
Dermatochalasis	84	84
Diabetes mellitus	59	60
Diarrhoea	67	18
Diarrhoea haemorrhagic	130	130
Dizziness	109	64
Drug eruption	37	37
Drug-induced liver injury	40	40
Dry eye	91	91
Dry mouth	146	144
Dry skin	210	191
Dry throat	182	182
Duodenal ulcer	68	67
Dysaesthesia	384	384
Dysgeusia	211	242
Dyspepsia	105	43
Dysphagia	208	231
Dysphonia	208	229
Dyspnoea	60	39
Dyspnoea exertional	133	128
Dysuria	54	24
Ear infection	9	9
Ear pain	81	81
Early satiety	70	70
Eczema	61	61
Electrolyte imbalance	239	239
Embolism	142	131
Embolism venous	156	156
Emphysema	212	212
Empyema	10	10
Encephalopathy	93	93
Eosinophilia	4	4
Epistaxis	61	8
Erectile dysfunction	140	140
Eructation	119	119
Erysipelas	8	8
Erythema	108	25
Erythropenia	82	82
Escherichia sepsis	10	10
Eye pain	63	63
Eyelid boil	16	16
Face oedema	7	7
Fall	82	47
Fatigue	156	129
Feeling cold	129	129

Femur fracture	8	8
Flank pain	184	187
Flatulence	136	132
Folliculitis	77	77
Gait disturbance	130	130
Gamma-glutamyltransferase increased	131	105
Gastric cancer	160	160
Gastric infection	10	10
Gastric mucosal lesion	175	175
Gastric ulcer	44	44
Gastric ulcer haemorrhage	8	8
Gastric ulcer perforation	127	127
Gastric varices	62	62
Gastric varices haemorrhage	4	4
Gastritis	121	88
Gastritis erosive	94	94
Gastroenteritis	5	3
Gastroenteritis viral	10	10
Gastrointestinal haemorrhage	10	7
Gastrointestinal infection	5	5
Gastrointestinal motility disorder	64	64
Gastrointestinal necrosis	13	13
Gastroesophageal reflux disease	97	72
General physical condition abnormal	13	13
General physical health deterioration	35	18
Generalised oedema	34	34
Genital erythema	27	27
Gingival bleeding	58	37
Gingival pain	96	96
Gingival recession	154	154
Gingival swelling	96	96
Gingivitis	99	9
Glossitis	296	296
Glossodynia	433	433
Glucose urine present	21	21
Granulocyte count decreased	8	8
Groin infection	6	6
Groin pain	69	65
Gynaecomastia	60	60
Haematemesis	10	10
Haematochezia	9	3
Haematoma	20	20
Haematuria	93	78
Haemoglobin decreased	82	82
Haemophilus infection	7	7
Haemoptysis	45	31
Haemorrhage	131	131
Haemorrhoidal haemorrhage	223	241
Haemorrhoids	111	77
Hair colour changes	114	114

Hallucination	1	1
Head injury	1	1
Headache	69	10
Heart rate increased	31	31
Hepatic cirrhosis	121	92
Hepatic encephalopathy	33	6
Hepatic failure	14	14
Hepatic function abnormal	76	62
Hepatic pain	73	7
Hepatitis	56	33
Hepatitis B DNA increased	55	55
Hepatitis E	23	23
Hepatobiliary disease	20	20
Hepatorenal failure	2	2
Hernia pain	1	1
Herpes simplex encephalitis	47	47
Hiatus hernia	113	113
Hiccups	40	23
Hip fracture	16	16
Hordeolum	10	8
Hot flush	245	245
Humerus fracture	203	203
Hydrocele	18	18
Hyperammonaemia	26	26
Hyperbilirubinaemia	39	29
Hypercalcaemia	41	35
Hypercholesterolaemia	99	109
Hypercreatinaemia	22	22
Hyperglycaemia	72	32
Hyperhidrosis	30	22
Hyperkalaemia	14	9
Hyperkeratosis	138	82
Hyperlipidaemia	197	197
Hypermagnesaemia	136	136
Hyperphosphataemia	22	22
Hypersensitivity	1	1
Hypertension	119	47
Hyperthyroidism	64	57
Hypertransaminasaemia	95	95
Hypertriglyceridaemia	22	22
Hyperuricaemia	34	22
Hypoacusis	305	305
Hypoaesthesia	119	95
Hypoalbuminaemia	79	34
Hypocalcaemia	82	33
Hypochloraemia	21	22
Hypoglycaemia	34	30
Hypogonadism	97	97
Hypokalaemia	56	22
Hypomagnesaemia	57	31

Hyponatraemia	48	27
Hypophosphataemia	67	51
Hypopituitarism	84	84
Hypoproteinaemia	53	24
Hypotension	22	7
Hypothyroidism	139	149
Hypovolaemia	1	1
Ileus	24	24
Immune-mediated hepatitis	58	58
Incisional hernia	114	114
Infected dermal cyst	115	115
Infective exacerbation of bronchiectasis	81	81
Inflammation	NA	NA
Influenza	24	11
Influenza like illness	7	6
Infusion related reaction	3	1
Infusion site extravasation	5	5
Inguinal hernia	73	73
Insomnia	143	115
International normalised ratio increased	24	19
Interstitial lung disease	84	84
Intestinal obstruction	6	6
Iron deficiency	227	227
Iron deficiency anaemia	10	10
Irritability	31	31
Jaundice	32	8
Joint swelling	138	172
Keratoacanthoma	25	25
Ketonuria	20	20
Lacrimation increased	225	225
Lactic acidosis	3	3
Large intestinal haemorrhage	5	5
Laryngeal haemorrhage	42	42
Laryngeal pain	127	127
Lethargy	NA	NA
Leukocytosis	79	26
Leukopenia	77	43
Libido disorder	226	226
Limb discomfort	184	184
Limb injury	202	235
Lip dry	15	15
Lip swelling	150	150
Lipase increased	81	38
Liver disorder	191	191
Liver function test abnormal	8	8
Liver function test increased	164	164
Liver injury	24	24
Lower gastrointestinal haemorrhage	9	9
Lower respiratory tract infection	7	7
Lung infection	11	10

Lymph node pain	4	4
Lymphadenopathy	4	4
Lymphocyte count decreased	103	43
Lymphopenia	113	113
Macular degeneration	225	225
Malaise	100	67
Malnutrition	33	33
Melaena	10	10
Menstrual cycle management	266	266
Menstruation irregular	NA	NA
Mental status changes	5	5
Mesangioproliferative glomerulonephritis	62	62
Mesenteric vein thrombosis	336	336
Metabolic acidosis	1	1
Metabolic encephalopathy	3	3
Micturition urgency	292	292
Mitral valve disease	134	134
Mouth haemorrhage	85	85
Mouth ulceration	27	24
Mucosal dryness	86	86
Mucosal inflammation	126	74
Multiple organ dysfunction syndrome	5	5
Muscle spasms	128	77
Muscle spasticity	11	11
Muscle tightness	226	226
Muscle twitching	25	25
Muscular weakness	61	57
Musculoskeletal chest pain	106	10
Musculoskeletal pain	144	118
Myalgia	128	66
Myocardial infarction	16	12
Nasal congestion	117	117
Nasal dryness	139	139
Nasal inflammation	21	21
Nasopharyngitis	26	13
Nausea	84	42
Neck pain	109	24
Nephritis	192	192
Nephrolithiasis	59	59
Nephrotic syndrome	157	157
Nervousness	277	277
Neuropathy peripheral	107	107
Neutropenia	49	24
Neutropenic sepsis	20	20
Neutrophil count decreased	51	22
Neutrophil count increased	48	34
Night sweats	16	10
Nipple pain	22	22
Non-cardiac chest pain	16	22
Occult blood positive	22	22

Odynophagia	27	27
Oedema	116	107
Oedema peripheral	92	74
Oesophageal haemorrhage	7	8
Oesophageal squamous cell carcinoma	67	67
Oesophageal stenosis	239	239
Oesophageal varices haemorrhage	11	6
Oral candidiasis	53	26
Oral discharge	106	106
Oral fungal infection	1	1
Oral herpes	14	14
Oral pain	118	118
Orbital oedema	3	3
Oropharyngeal neoplasm	214	214
Oropharyngeal pain	109	58
Osteoarthritis	269	269
Otitis media	8	8
Pain	90	22
Pain in extremity	145	116
Pain of skin	11	11
Palmar-plantar erythrodysaesthesia syndrome	154	138
Pancreatic enzymes increased	12	12
Pancreatitis	23	9
Papilloma	259	259
Papule	218	218
Paraesthesia	100	100
Parkinson's disease	297	297
Paronychia	65	65
Parosmia	304	304
Parotitis	19	19
Pathological fracture	27	27
Pelvic fluid collection	68	68
Pelvic pain	4	4
Penile ulceration	142	142
Periarthritis	190	190
Pericardial effusion	8	8
Perineal erythema	22	22
Periodontal disease	332	332
Periodontitis	67	34
Peripheral arterial occlusive disease	63	63
Peripheral sensory neuropathy	143	148
Peripheral swelling	61	54
Peritoneal haemorrhage	19	19
Peritonitis	104	104
Peritonsillar abscess	27	27
Petechiae	27	27
Pharyngeal haemorrhage	5	5
Pharyngeal inflammation	119	119
Pharyngitis	10	10
Phimosis	144	144

Phlebitis	35	11
Platelet count decreased	101	43
Pleural effusion	75	55
Pleuritic pain	19	19
Pneumonia	25	22
Pneumonia aspiration	13	13
Pneumonitis	21	19
Pneumothorax	231	231
Pollakiuria	185	138
Polycythaemia	246	246
Poor quality sleep	2	2
Portal hypertension	27	27
Portal vein thrombosis	200	191
Post procedural infection	30	30
Presyncope	1	1
Proctalgia	179	150
Productive cough	121	22
Protein total decreased	34	34
Protein urine present	150	134
Proteinuria	100	58
Prothrombin time prolonged	33	25
Pruritus	106	73
Pruritus generalised	319	319
Psoriasis	311	295
Pulmonary embolism	46	36
Pulmonary haemorrhage	56	56
Pulmonary hypertension	8	8
Pulmonary sepsis	7	7
Pulpitis dental	9	6
Pyrexia	19	4
Pyuria	306	306
QRS axis abnormal	19	19
Rash	109	53
Rash erythematous	22	22
Rash maculo-papular	70	40
Rash papular	195	195
Rash pruritic	65	65
Rectal haemorrhage	15	3
Red blood cell count decreased	82	82
Red blood cells urine positive	128	128
Regurgitation	164	164
Renal failure	37	30
Renal impairment	149	149
Respiratory distress	2	2
Respiratory rate increased	33	33
Respiratory tract infection	3	3
Retching	1	1
Rhinitis	7	7
Rhinitis allergic	233	197
Rhinitis atrophic	22	22

Rhinorrhoea	44	17
Rib fracture	32	32
Salivary gland calculus	99	99
Scab	22	22
Sciatica	154	154
Scleral disorder	43	43
Scrotal angiokeratoma	NA	NA
Scrotal erythema	5	5
Scrotal infection	43	43
Scrotal oedema	22	22
Senile dementia	141	141
Sepsis	19	14
Septic shock	13	13
Sinus bradycardia	21	21
Sinus tachycardia	6	6
Sinusitis	130	58
Skin abrasion	41	41
Skin disorder	164	164
Skin exfoliation	3	3
Skin fissures	130	130
Skin hyperpigmentation	81	81
Skin infection	132	132
Skin laceration	81	81
Skin lesion	21	21
Skin mass	22	22
Skin toxicity	32	32
Skin ulcer	57	34
Sleep disorder	62	62
Soft tissue inflammation	13	13
Somnolence	28	28
Spinal compression fracture	213	213
Spinal osteoarthritis	59	59
Spinal pain	24	24
Splenic infarction	211	211
Splenomegaly	192	192
Steatorrhoea	168	168
Stomatitis	111	84
Subarachnoid haemorrhage	6	6
Subcutaneous abscess	35	35
Subdural hygroma	3	3
Supraventricular extrasystoles	19	19
Swelling	92	92
Swollen tongue	10	10
Syncope	2	2
Synovitis	10	10
Tachycardia	7	7
Taste disorder	135	178
Tendonitis	58	58
Testicular pain	3	3
Thermal burn	76	76

Thirst	173	173
Throat irritation	12	12
Thrombocytopenia	88	49
Thrombocytosis	66	66
Thrombophlebitis superficial	130	130
Thyroid disorder	8	8
Thyroxine free increased	50	50
Tinea pedis	3	3
Tinnitus	32	31
Tongue fungal infection	163	163
Tongue ulceration	53	26
Tooth abscess	32	32
Tooth extraction	5	5
Tooth infection	26	4
Toothache	43	13
Total bile acids increased	19	21
Toxic skin eruption	20	20
Transaminases increased	161	182
Tremor	78	38
Tri-iodothyronine free increased	44	44
Tricuspid valve disease	134	134
Troponin I increased	8	8
Tumour associated fever	99	99
Tumour haemorrhage	14	14
Tumour lysis syndrome	134	134
Tumour pain	287	287
Type 2 diabetes mellitus	264	227
Ulcerative keratitis	10	10
Umbilical hernia	106	106
Upper gastrointestinal haemorrhage	21	8
Upper respiratory tract infection	35	16
Urinary incontinence	12	12
Urinary retention	15	15
Urinary tract infection	17	14
Urinary tract pain	33	33
Urine ketone body present	82	82
Urobilinogen urine increased	33	44
Urticaria	118	113
Vaginal haemorrhage	1	1
Varices oesophageal	39	37
Varicose ulceration	60	60
Vasculitis	16	16
Vertigo	26	26
Viral hepatitis carrier	212	212
Viral infection	12	12
Viral upper respiratory tract infection	8	8
Vision blurred	198	198
Visual impairment	272	272
Vitamin D deficiency	23	23
VIth nerve disorder	153	153

VIth nerve paralysis	277	277
Vitiligo	83	83
Vomiting	39	4
Vulvovaginal dryness	22	22
Vulvovaginal inflammation	7	7
Weight decreased	127	110
Weight increased	1	1
Wheezing	227	227
White blood cell count decreased	48	23
White blood cell count increased	25	25
White coat hypertension	3	2
Wound infection	392	392
Xerosis	162	162

Network of evidence

A7. Priority: Please perform network meta-analyses allowing for time varying treatment effects (i.e. not necessarily hazard ratios) for different survival models including all treatments of interest. (See Res. Syn. Meth. 2010, 1 258--271 and BMC Medical Research Methodology 2011, 11:61 for details of how to do this for standard parametric models and fractional polynomials, respectively).

A first degree Bayesian fixed effect fractional polynomial (FP) NMA has been added to the cost-effectiveness model as an option to model sorafenib and lenvatinib OS. See 'Model Inputs' tab cell G59-G60. The FP NMA was unattainable for PFS due to the different methodologies in data collection in the REFLECT and Imbrave150 trials, mRECIST and RECIST 1.1, respectively. Likewise, the Ouwens approach was unfeasible, as that also required individual patient level data.

Table 4 highlights the model results using the fractional polynomial NMA for sorafenib and lenvatinib OS.

Table 4: Fractional Polynomial NMA applied to sorafenib and lenvatinib OS: Atezo+Bev (with PAS) versus sorafenib and lenvatinib (list price)

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	44,736	1.46	1.02	[redacted]	[redacted]	[redacted]	16,817	21,813
Lenvatinib	63,513	1.66	1.22	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A8. Priority: Please provide predictive intervals for the effects of treatments from the revised network meta-analysis and use the joint predictive distributions to represent uncertainty in the economic model.

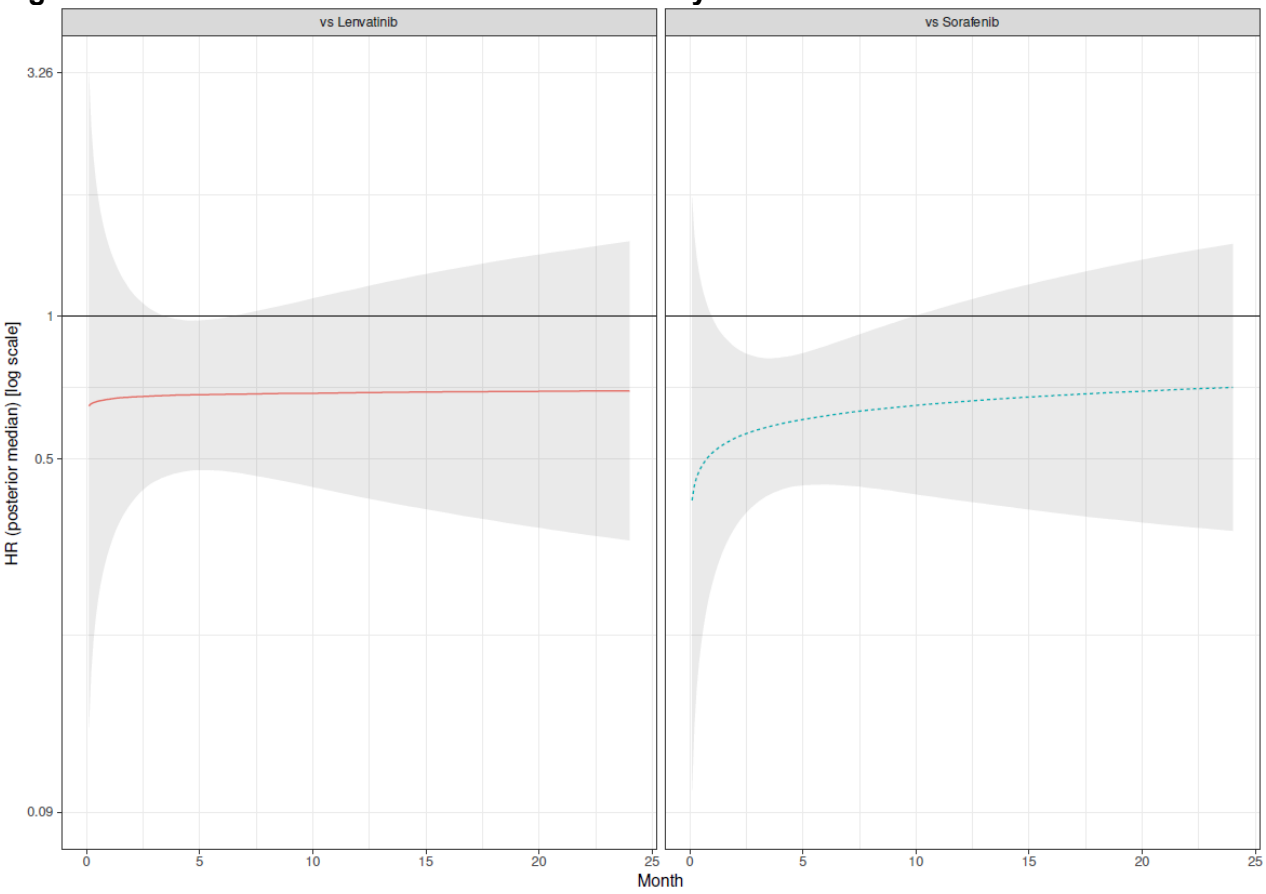
Table 5 highlights a range of median hazard ratios over 75 months, demonstrating to what extent the 95% credibility intervals can vary. The full range over 25 months is illustrated in Figure 1.

Table 5: Median Hazard Ratio with 95% Credibility Intervals

Time	Median	uCI	lCI	Comparison
0.1	0.409088	1.778229	0.10016	AB vs Sorafenib
1	0.515283	0.988941	0.274467	AB vs Sorafenib
1.5	0.536648	0.905448	0.323245	AB vs Sorafenib
2.5	0.565576	0.832751	0.385688	AB vs Sorafenib
5	0.605532	0.835417	0.440176	AB vs Sorafenib
7.5	0.630519	0.914978	0.437646	AB vs Sorafenib
10	0.648496	1.002345	0.421338	AB vs Sorafenib
12.5	0.662999	1.085648	0.405598	AB vs Sorafenib
15	0.675307	1.165769	0.391331	AB vs Sorafenib
20	0.694843	1.314734	0.367349	AB vs Sorafenib
25	0.710532	1.445249	0.348879	AB vs Sorafenib
35	0.734659	1.672717	0.320947	AB vs Sorafenib
50	0.761667	1.948768	0.293326	AB vs Sorafenib
75	0.79297	2.337265	0.264904	AB vs Sorafenib
Time	**Median**	**uCI**	**lCI**	**Comparison**
0.1	0.646975	3.246971	0.136055	AB vs Lenvatinib
1	0.668239	1.394121	0.324008	AB vs Lenvatinib
1.5	0.673147	1.222486	0.371927	AB vs Lenvatinib
2.5	0.677098	1.062539	0.431133	AB vs Lenvatinib
5	0.682633	0.979432	0.473804	AB vs Lenvatinib
7.5	0.68581	1.024567	0.460643	AB vs Lenvatinib
10	0.687868	1.090117	0.436508	AB vs Lenvatinib
12.5	0.690119	1.158212	0.412496	AB vs Lenvatinib
15	0.691947	1.225959	0.39217	AB vs Lenvatinib
20	0.694301	1.347789	0.358292	AB vs Lenvatinib
25	0.696011	1.458502	0.332107	AB vs Lenvatinib

35	0.69819	1.647422	0.296042	AB vs Lenvatinib
50	0.701266	1.88424	0.260185	AB vs Lenvatinib
75	0.704614	2.200217	0.224821	AB vs Lenvatinib

Figure 1: Median Hazard Ratio with 95% Credibility Intervals



A9. Please clarify why nivolumab is included in the NMA given that it is not a comparator.

When the NMA was being developed, it was unclear whether Nivolumab would be approved or not. In addition, the NMA covers all systemic therapies with information published in 1L in HCC since the sorafenib approval in 2007. The NMA has been re-run without nivolumab and produced the hazard ratios reported below in Table 6. Evidently, the inclusion of Nivolumab does not significantly influence the hazard ratios.

Table 6: ITC results from the RE mode, base-case and without Nivolumab: Matrix of HRs (95% CrI)

Hazard ratios vs Atezo+Bev	Lenvatinib		Sorafenib	
	OS	PFS	OS	PFS
Original NMA	0.63 (0.32, 1.25)	0.91 (0.23, 3.65)	0.58 (0.35, 0.99)	0.59 (0.23, 1.58)
Updated NMA (without Nivolumab)	0.63 (0.33,1.24)	0.91 (0.25, 3.18)	0.58 (0.35, 0.97)	0.59 (0.23, 1.45)

Extrapolation of time to event data

A10. Priority: Please provide a justification for suggesting that "*only the exponential model and the Generalised Gamma model represented clinically plausible estimates, as the remaining four models projected a higher OS for sorafenib than lenvatinib, which is not aligned with the REFLECT trial clinical data which showed lenvatinib OS to be non-inferior to sorafenib*". The ERG notes that follow-up in REFLECT was up to approximately 40 months compared to approximately 100 months predicted in Figure 19 of the submission; that the treatment effect was a hazard ratio, although hazards may not be proportional; and that the 95% CI for the hazard ratio showed that the hazard ratio for lenvatinib compared to sorafenib could be greater than one.

Despite the OS HR of lenvatinib vs sorafenib in the REFLECT trial crossing 1, numerical improvements in median OS were seen in the lenvatinib arm (3.6 month OS benefit of lenvatinib vs sorafenib).

All curves were presented to clinical experts at an advisory board. The log-normal and log-logistic curves were deemed clinically implausible due to the over-estimated survival benefit of sorafenib, reporting an incremental gain in mean time alive of 3.7 and 5 months, respectively, compared with lenvatinib. Given the malalignment in OS estimates, the clinicians felt that these OS curves were clinically implausible.

The Weibull and Gompertz reported a very slight sorafenib OS gain vs lenvatinib, 0.15 and 0.14 respectively, however were a terrible visual fit to the REFLECT KM data, and were therefore excluded as potential options.

The Exponential and Generalised-Gamma reported a marginally higher mean OS for lenvatinib, 0.6 months and 0.7 months respectively. Furthermore, the extrapolated curves fitted the REFLECT KM data, with the exponential being chosen by the group of clinical

experts as the best fit. The extrapolated exponential curves fits well to the 40 months of KM data from the REFLECT trial (see Figure 2).

Figure 2: REFLECT KM fit to exponential overall survival curves

A11. Please clarify why a gamma distribution or other more flexible survival models were not considered when modelling OS, PFS or time to discontinuation (TTD) data

The generalised gamma distribution was considered as a viable option to model OS, PFS and TTD; however on the basis of visual fit and clinical plausibility, other models were selected to be used in the base case analysis. More flexible survival models such as spline models were not deemed necessary due to the good fit of the data to standard distributions. More flexible survival models are more commonly used when the survival curves do not follow a specific distribution and the data is slightly more complex to extrapolate. That was not the case when fitting the IMbrave150 data or the ITC data to parametric distributions.

A12. Please clarify whether there is a consistent relationship between mean TTD estimates and mean PFS estimates. If so, please clarify whether this results in a bias for the estimated lenvatinib drug costs through using PFS instead of TTD, which is not known.

There is a consistent relationship between the mean TTD estimates and the mean PFS estimates. As we use TTD to estimate drug acquisition costs for Atezo+Bev and sorafenib and PFS to estimate the drug acquisition costs for lenvatinib, there is inevitably bias in some form. However, as evident in Figure 3, the Atezo+Bev PFS curve sits below the TTD curve

until approximately month 25. It is only at this time point that the PFS curve is above the TTD curve. This is expected given the continuing treatment effect with an immunotherapy, once treatment has been discontinued.

Therefore, it is likely that using PFS in the absence of lenvatinib TTD data does introduce some sort of bias, albeit small given the similarity of these curves. This logic holds if the relationship between TTD and PFS curves is similar in the REFLECT trial as compared to IMbrave150.

Figure 3: Atezo+Bev and sorafenib TTOT vs Atezo+Bev, sorafenib and lenvatinib PFS

A13. Please provide a plot of the survival functions (separately for OS, PFS and TTD) extrapolated out to 20 years.

Figure 4, Figure 5 and Figure 6 plot all distributions extrapolated out to 20 years for Atezo+Bev and sorafenib for OS, PFS and TTD, respectively.

Figure 4: Atezo+Bev and Sorafenib overall survival extrapolated over 20 years

Figure 5: Atezo+Bev and Sorafenib progression-free survival extrapolated over 20 years

Figure 6: Atezo+Bev and Sorafenib time to off treatment extrapolated over 20 years

A14. Please provide smoothed hazard rates and log-cumulative hazard plots against time for OS and PFS.

Figure 7 and Figure 8 illustrate the Atezo+Bev and sorafenib OS smoothed hazard function plots. Figure 9 and Figure 10 illustrate the Atezo+Bev and sorafenib OS log-cumulative hazard plots. Figure 11 and Figure 12 illustrate the Atezo+Bev and sorafenib PFS smoothed hazard function plots. Figure 13 and Figure 14 illustrate the Atezo+Bev and sorafenib PFS log-cumulative hazard plots.

Please note the kernel graphs (Figure 7, Figure 8, Figure 11 and Figure 12) are a smoothed approximation so they should be interpreted with caution. They are different visually due to the difference in number of events between Atezo+Bev and sorafenib, and due to the different bandwidths for the estimation, which have been chosen independently and optimally based on a minimization of the mean integrated squared error.

Figure 7: Atezo+Bev OS Kaplan Meier Smoothed Hazard Function

Figure 8: Sorafenib OS Kaplan Meier Smoothed Hazard Function

Figure 9: Atezo+Bev OS Kaplan Meier Log-Cumulative hazard plot

Figure 10: Sorafenib OS Kaplan Meier Log-Cumulative hazard plot

Figure 11: Atezo+Bev PFS Kaplan Meier Smoothed Hazard Function

Figure 12: Sorafenib PFS Kaplan Meier Smoothed Hazard Function

Figure 13: Atezo+Bev PFS Kaplan Meier Log-Cumulative hazard plot

Figure 14: Sorafenib PFS Kaplan Meier Log-Cumulative hazard plot

A15. Please justify the clinical plausibility of assuming the same underlying hazard functions for different treatments for each of OS, PFS and TTD.

Clinical experts were consulted to confirm the clinical plausibility of assuming the same underlying hazard function for the different treatments. There was a consensus that the

beginning of the curves for different treatments for OS, PFS and TTD would be very similar. Likewise, the tail of the PFS and TTD curve may also follow a similar shape. However, the tail of the curve OS would naturally differ due to the different mechanism of action between an immunotherapy and a TKI, as one may expect a prolonged tail of patients who have not relapsed on Atezo+Bev therapy. Nevertheless, it was agreed that as extrapolated survival curves are based on assumptions, it is justified to assume the same hazard function for all treatments, and it was deemed a conservative approach by the clinical community.

A16. Please provide results using the following TTD survival functions: atezolizumab (Weibull), bevacizumab (Weibull) and sorafenib (Log-normal).

Please see Table 7 for results using the Weibull survival function for atezolizumab and bevacizumab TTD, and the Log-normal survival function to model sorafenib TTD.

Table 7: Results using the following TTD survival functions: atezolizumab (Weibull), bevacizumab (Weibull) and sorafenib (Log-normal).

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	46,950	1.50	1.05	[redacted]	[redacted]	[redacted]	23,303	29,284
Lenvatinib	62,580	1.54	1.13	[redacted]	[redacted]	[redacted]	5,761	7,750

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A17. Please clarify why in the two-year stopping rule scenario analysis it is assumed that the reduction in treatment duration would not impact on OS / PFS outcomes.

Apologies this is an error in the scenario analysis. It isn't assumed that the reduction in treatment duration would not impact on OS / PFS outcomes; this is an error in the scenario analysis as the treatment effect option doesn't automatically update to no ‘more effect after cut-off point' for PFS and OS. When the stopping rule is selected and the treatment effect is updated to ‘no more effect after cut-off point’, the model assumes the treatment effect is capped at 5 years. The 5-year cap is in line with previous atezolizumab appraisals (1).

Please see below updated results for when this scenario is applied correctly.

Table 8: Two-year stopping rule scenario analysis

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	44,983	1.50	1.05	[redacted]	[redacted]	[redacted]	12,411	15,827
Lenvatinib	61,723	1.52	1.11	[redacted]	[redacted]	[redacted]	Dominant	Dominant

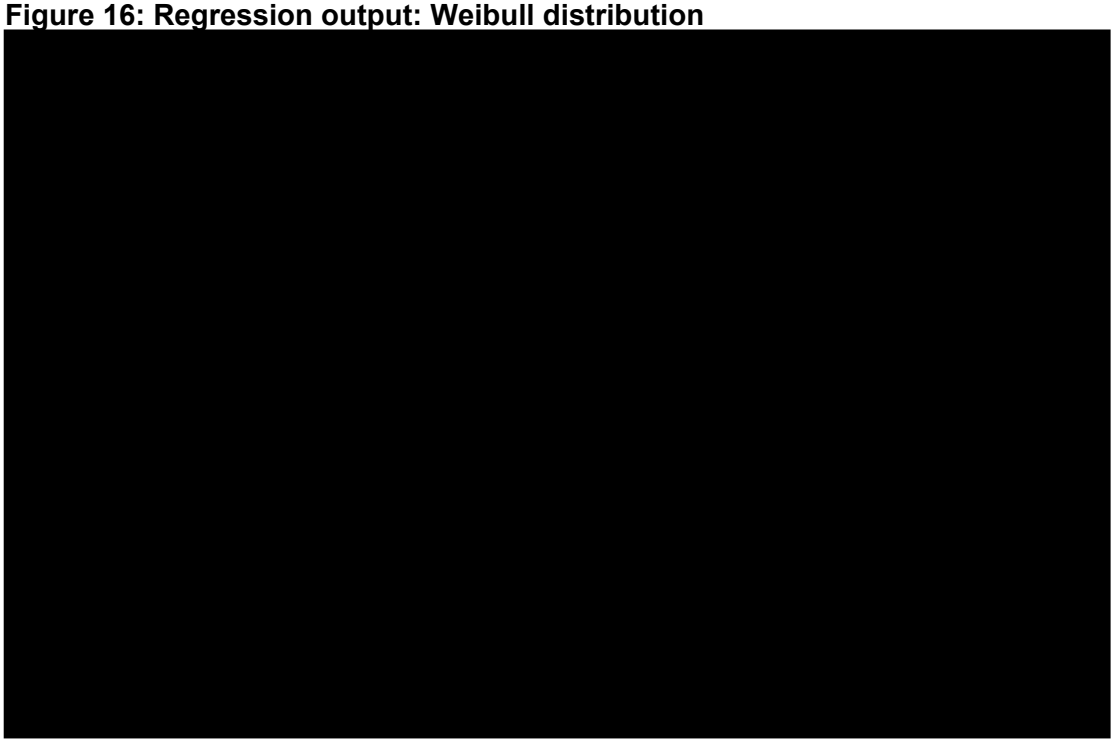
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A18. Please clarify the schedule of assessments for PFS. Please provide results of an interval censored analysis of PFS.

Patients will undergo tumour assessments at baseline, then every 6 weeks (+-1 week) for the first 54 weeks following treatment initiation, and every 9 weeks (+-1 week) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator. Figure 15 shows the non-parametric maximum likelihood estimation of interval-censored PFS, and using the regression output from the Weibull distribution (Figure 16) one can show that the resulting hazard ratio for interval censored PFS would be 0.6 (0.47, 0.77).

Figure 15: Non-parametric maximum likelihood estimation of interval-censored PFS

Figure 16: Regression output: Weibull distribution



Section B: Clarification on cost-effectiveness data

Please provide an updated ICER incorporating all changes simultaneously, including any changes that are made in light of clinical effectiveness comments.

Table 9: Updated base case results with all corrections applied

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	44,983	1.50	1.05	[redacted]	[redacted]	[redacted]	17,257	22,267
Lenvatinib	62,580	1.54	1.13	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

*Please note, since the time of submission in April 2020, a higher discount of [redacted] for Atezolizumab has been approved. The above results and all scenarios include the updated discount.

Decision Problem

B1. Priority. Please clarify whether, based on Figure 1 of the CS, the company is positioning Atezo + Bev where sorafenib and lenvatinib are not recommended (in Stage B). [Clinical advice to the ERG and statements in the advice provided to the ERG in the STA of regorafenib suggests that sofarenib and lenvatinib would also be used in this population.]

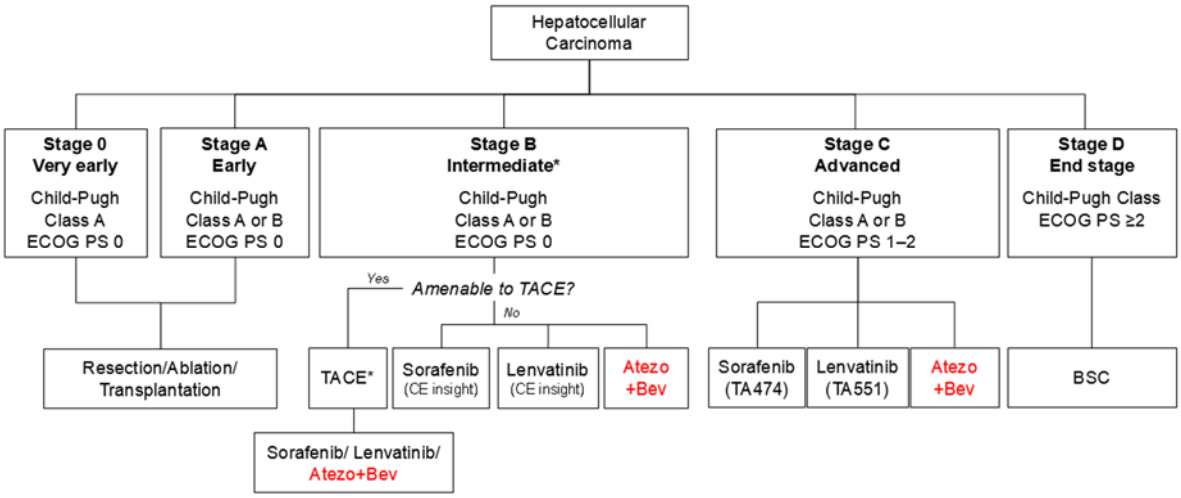
- **If the company believes that sorafenib and lenvatinib can be used in this population, please update Figure 1.**
- **If the company believes sorafenib and lenvatinib are not used in this population please provide a separate ICER for this population compared with BSC.**
- **If the stage B and Stage C populations are distinct with characteristics known in advance, provide ICERs separately for Stage C and Stage B.**

Roche agrees with the clinical advice given to the ERG and the statements of advice provided to the ERG in the regorafenib STA that sorafenib and lenvatinib are used in BCLC Stage B patients. We have updated the positioning pathway figure below to clarify this (Figure 17).

During consultations with Roche, clinical experts stated that the BCLC staging system is not a true reflection of UK clinical practice. While the NICE guidance for sorafenib and lenvatinib stipulate use in advanced HCC, clinical experts confirm that these regimens are also used in Stage B intermediate disease for those patients who are not amenable to TACE or progress following TACE or locoregional therapies. Atezo+Bev is therefore positioned in those populations to align with the use of sorafenib and lenvatinib in UK clinical practice.

Due to the highly heterogeneous nature of patients with BCLC Stage B intermediate disease, clinical experts have advised Roche that it is clinically difficult to distinguish those Stage B patients who are not amenable to or who progress on TACE/locoregional therapies from Stage C patients. Therefore, it is not currently possible to separate these populations into distinct groups or to provide separate ICERs for each.

Figure 17: Updated Figure 1 in the CS: Proposed positioning of Atezo+Bev in treatment pathway for adult patients with unresectable HCC



* TACE or locoregional therapies

B2. Priority. Please provide a scenario analysis where patients from Asia (excluding Japan) are excluded from the analysis. [The ERG notes that the relative impact of sorafenib may differ by geographical region based on the results of the SHARP study and the ASIA-PACIFIC study.]

An option to exclude patients from Asia (excluding Japan) has been added to the model. Please see the 'Model Inputs' tab, cell F32.

Table 10 highlights the results from this scenario. As you can see, the results are similar to the base-case analysis.

Table 10: Scenario analysis excluding patients from Asia (excluding Japan)

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	44,802	1.50	1.05	[redacted]	[redacted]	[redacted]	17,557	22,368
Lenvatinib	59,103	1.43	1.04	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B3. Priority. Please provide incremental analyses for patients below 60kg and separate analyses for patients greater than or equal to 60kg, to account for the different acquisition cost of lenvatinib between these groups.

An option to change the lenvatinib drug acquisition cost based on the weight of the patients has been added into the model. Please see the 'Cost Inputs' tab cell F46. The user can select to model the drug cost based on the average weight from the IMbrave 150 trial, only patients ≥60kg or only patients <60kg.

Using a dose based on the average weight of all patients in IMbrave150, (11.1mg) results in an acquisition cost of £930 per week. This is what is used in the base-case analysis.

Eighty percent of these patients were ≥60kg, and therefore require a dose of 12mg per day. For these patients, the drug acquisition cost of lenvatinib is £1005.90 per week. Please see Table 11 for a scenario analysis whereby the lenvatinib drug acquisition cost is based on the higher dose of lenvatinib.

The remaining 20% of patients were <60kg and require of dose of 8mg. For these patients, the drug acquisition cost is £670.60 per week. Table 12 provides the scenario analysis results using a lenvatinib drug acquisition cost based on the 8mg dose of lenvatinib.

Table 11: Scenario analysis: Lenvatinib dose ≥60kg

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	44,983	1.50	1.05	[redacted]	[redacted]	[redacted]	17,257	22,267
Lenvatinib	66,144	1.54	1.13	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 12: Scenario analysis: Lenvatinib dose <60kg

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	44,983	1.50	1.05	[redacted]	[redacted]	[redacted]	17,257	22,267
Lenvatinib	50,345	1.54	1.13	[redacted]	[redacted]	[redacted]	11,733	16,391

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B4. Please clarify why the company believes lenvatinib is reserved for those intolerant of sorafenib. This does not appear to be stated within the lenvatinib FAD.

Apologies, the statement in the company submission is not clear. As stated in the lenvatinib FAD, sorafenib is not tolerated by all patients, therefore NICE recommended lenvatinib as an additional option for patients with untreated, advanced, unresectable HCC, although its use is not restricted to patients intolerant of sorafenib, which is suggested by the original wording in the company submission. The statement on page 17 of the company submission should read as follows:

Lenvatinib was approved in 2018 by the FDA and EMA for use in the same population as sorafenib and was approved by NICE (TA551) as an additional option for untreated, advanced, unresectable HCC patients, particularly those who cannot tolerate sorafenib.

Conceptual Modelling questions

B5. Priority: Please clarify the rationale for assuming that patients who require less than 5% of a vial of atezolizumab or bevacizumab, do not receive that vial and have a reduced dose from that recommended. Please provide results assuming that the full recommended dose is provided.

Atezolizumab is a flat dose so this only applies to bevacizumab, and the impact on the cost is minimal. See Table 13 for results assuming that the full-recommended dose is provided. The use of 5% is in line with NHSE bevacizumab dose banding table, which are typically based on a +/- 5% variation of the dose to avoid small wastage and optimise drug use.

Table 13: Scenario analysis: Full recommended dose

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	44,983	1.50	1.05	[redacted]	[redacted]	[redacted]	17,289	22,308
Lenvatinib	62,580	1.54	1.13	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B6. Please clarify whether the time to death approach for utility is assuming that the probability of death is independent of whether a patient is on treatment. If so, please comment on the impact of the ICER if people not on treatment were more likely to die.

The time to death approach for utility does not assume the probability of death is independent to whether a patient is on treatment. The utility regression included an interaction term between the proximity to death and a dummy variable that determines whether the patient is on treatment or not.

This means that in addition to having a term for on treatment and a term for proximity to death, we also have an interaction term which determines how the proximity to death is different depending on being on treatment or not.

B7. Within the scenario analyses it is assumed that patients on A/B in PFS are in a better health state than those in PFS on sorafenib. Please clarify whether any tests were undertaken to explore whether there is a statistically-significant difference between systemic treatments (excluding the impact of AEs). Did clinical advice indicate that there would be a difference in utility based on which treatment was provided (excluding the impact of AEs)?

The coefficient in the regression that compared the PFS utility values of Atezo+Bev with Sorafenib was not statistically significant. No further specific tests were undertaken to explore the difference in utility values for patients on Atezo+Bev or sorafenib during PFS, as the differences are not big enough to be considered clinically significant. Clinical advice indicated that they would expect to see a higher utility value for patients on Atezo+Bev rather than sorafenib.

B8. Please clarify why in column BY there is no half-cycle correction for atezolizumab, but in column CP bevacizumab is half-cycle corrected given that these are given simultaneously.

This an error, the formula has been amended.

Model Implementation questions

B9. Priority In 'Settings' E82 it appears that the sample size for sorafenib safety population was used to calculate total patients time for lenvatinib. If there is a mistake, please amend the formula.

The formula has been amended.

B10. Priority: The ERG believes the equations in 'Model Inputs' H91:H93 do not correctly estimate the starting points for applying parametric distributions based on the percentage at risk. The equations unnecessarily divide the indexed value by number of weeks in a month. Please amend the formulae for this potential mistake.

The formula has been amended.

B11. Priority: In 'Model Inputs' F107:F110 the values mistakenly represent the proportion of patients still on Atezolizumab instead of bevacizumab. Please amend the formula for the potential mistake.

The formula has been amended.

B12. Priority: The value in 'Model Inputs' F173 does not link to 'Life tables' AP4 as the ERG thinks it should. If there is an error, please amend the formula.

The formula has been amended.

B13. Priority: In 'Post disc. therapy cost' K14 & K22 the equations assume that regorafenib costs will incur every 21 days. However, this does not take into account the 1 week off treatment per each 28-day cycle of regorafenib. Please amend the formula for this potential mistake.

The formula has been amended.

B14. Priority: In 'Post disc. therapy cost' M14, E25, E26, I25, I26 clarify why the mean duration was not weighted based on the number of patients in each group. Please amend the formulae to account for the potential mistake.

The formula has been amended.

B15. Priority: 'Cost Inputs' F50:F53. The ERG thinks that the cells should reference E11-14, H11-14, and K11-14, rather than F11-14, I11-14 and L11-14. Please amend if this is a mistake.

This formula is correct. If vial sharing is selected, the proportion of vial sharing needs to take into account, in this case the 5%. If the formula was updated to select vial sharing from columns E, H and K, the proportion is not taken into account.

B16. Priority: Applying the logic in B8 for bevacizumab would require two 400mg and two 200mg vials to account for a recommended 1004mg. However, the patient is getting three 100mg vials(see S30 of the 'Dosing' sheet). Please amend the formulae to account for these apparent inconsistencies.

Bevacizumab only comes in two vial sizes, 100mg and 400mg. Therefore, for a dose of 1004mg, the patient requires 2 x 400mg vials and 3 x 100mg vials.

B17. Explain why for bevacizumab there are 4 100mg vials used rather than 1 400mg vial; this unnecessarily increases the cost of the intervention. Please amend the formulae to correct this potential mistake.

The formula in column R on the 'Dosing tab' has been amended.

B18. Priority: Please clarify the method for calculating the actual dose for atezolizumab and bevacizumab. If modifications were not allowed for atezolizumab / bevacizumab then it is likely be more accurate to multiply the number of vials by the RDI, rather than the planned dose which would not give a reduction in acquisition costs. Please amend if incorrect. Similarly, please clarify the method for calculating the actual dose for sorafenib and lenvatinib. If the RDI was less than 1 then please also clarify whether the sorafenib tablets and lenvatinib tablets were wasted or assumed to be re-used with potentially fewer packs prescribed.

The actual dose for atezolizumab was calculated by multiplying the planned dose by the relative dose intensity (1200mg*95.1%). The actual dose for bevacizumab was calculated by multiplying the planned dose by the average weight, by the relative dose intensity (15*71.74*93.3%).

Modifications for atezolizumab and bevacizumab were not allowed in IMbrave150. Therefore, the calculation to estimate the actual dose has been updated to multiply the number of vials by the RDI. Please see the 'Dosing' tab cells L30 and Q-S30.

The same method was used to calculate the actual dose for sorafenib (planned dose multiplied by an RDI of 83.8% as per the CSR). As dose modification for sorafenib was

allowed, the calculation has not been amended. It is assumed that excess tablets were wasted.

As the RDI for lenvatinib was assumed to equal 1, the actual dose for lenvatinib is based on the average weight of the individual patients in the IMbrave150 clinical trial.

B19. Priority: For the duration of the trial please provide a comparison between the estimated number of vials used for atezolizumab and bevacizumab compared with that actually used. Please provide a similar calculation for sorafenib.

Please see Table 14 for the number of vials used over the duration of the IMbrave150 clinical trial, compared with the estimated number of vials used over the duration of the cost-effectiveness model.

Table 14: Estimated number of vials used for atezolizumab and bevacizumab compared with that actually used

	Imbrave150 (duration of trial)	Cost-effectiveness model
Atezolizumab	10.4 1200mg vials	[redacted]
Bevacizumab	23.81 400mg vials 14.60 100mg vials	[redacted]
Sorafenib	3.8 packs of 112x200mg tablets	5.7 packs of 112x200mg tablets

B20. Priority: In 'Dosing' AC30 please clarify why this cell is linked to the average weight rather than the calculating the percentage of patients with a weight equal, or above, 60kg and those with a weight below 60kg. Similarly, in 'Post disc. therapy cost' K21 please clarify why the calculations assume 3x 4mg lenvatinib tablets per day (i.e. a patient's weight is above 60kg). Note that this problem will disappear if the separate analyses by weight detailed in B3 are performed.

Cell AC30 in the 'Dosing' tab has been amended. It was previously incorrect as the average dose should not have been linked to the average weight but instead based on the individual dose according to the patient characteristics.

Cell K21 in the 'Post disc. therapy cost' has also been updated to equal 'Cost_Inputs' cell F53. The subsequent therapy cost of lenvatinib will therefore update in correlation with when the lenvatinib dose is changed.

B21. Priority: In the generalised gamma analyses the parameters in the 'Sorafenib' sheet columns K, and AB may be using distributions fitted to the atezolizumab data.

This may also be occurring in column CC of the 'Atezo + Bev' sheet. Please check and amend if appropriate.

The formulae in tab 'Atezo+Bev' column CC, tab 'Sorafenib' columns K and AB have been amended

B22. Priority: In the 'Atezo + Bev' sheet column CA the formula used for the Weibull distribution fitted to the bevacizumab TTOT data seems to be mistakenly using the lambda parameter of the Weibull distribution fitted for Atezolizumab TTOT data. Please amend the formula for this potential mistake.

The formula has been amended

B23. Please clarify the sources of parameters that were used for both of OS_scenarios 2 & 3 (RWD time, KM max time, KM data used, and type and parameters of the distributions used in 'Life Tables' columns AT:BK).

All parameters for the regorafenib data (OS_scenario2) were sourced from the following paper: "Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: Multicentre, open-label, phase II safety study", Bruix et al, 2013 (2).

The parameters for the real word data (OS_scenario3) were sourced from the Flatiron database (3).

The 'Rego tail time' and 'RWD time' of 16 months is based on the time point in which the IMbrave150 data ends.

The 'Regora max time' of 23 months was taken from the Regorafenib paper, while the RWD KM Max time of 91 months is the maximum time available from Flatiron.

Parameters in both cases were chosen by fitting a log normal distribution in R for the tail. However, the parametric choice of the tail does not really affect the main results, as it affects a minor share of the cohort (in the case of RWD, the parametric extrapolation is applied to only 5% of the remaining patients).

B24. In 'Life tables' Column BF please clarify why the formula used to decide on final OS extrapolation for regorafenib (Column AW) was not used for sorafenib.

The formulae in column BF and AW differ because the regorafenib data (column AW) is for second line therapy and is therefore applied as a tail, at the time of data cut-off (16 months). The regorafenib data starts right after the 16 months as it is a survival conditional on being in second line.

The sorafenib real-world data starts from "time 0", i.e. at the same time as our survival, so we assume that the RWD starts at the same time of our survival model, and we use the Flatiron mortality rate after the pre-selected cut-off point of 16 months.

B25. Please clarify why vial sharing calculations are applied to sorafenib and lenvatinib. Amend the sheet omitting vial sharing calculations for oral drugs, if appropriate.

The model is built to include options for vial sharing for IV and oral therapies. However, the calculations for vial sharing for lenvatinib and sorafenib have been amended.

B26. Please clarify why the RDI for lenvatinib is assumed to be 1.00, as shown by no adjustment in 'Dosing' AC30.

The RDI for lenvatinib was assumed to be 1.00 in the absence of trial information. The RDI for lenvatinib can easily be updated to equal the sorafenib RDI (83.8%), or alternatively a value of 88% can be applied, sourced from Kudo et al (4).

B27. Please clarify why in 'BIM' Row 51 the calculated number of patients eligible for atezolizumab include stages 0, A, and D.

In the original submission, the number of patients was over estimated by including all unresectable HCC patients, regardless of BCLC stage. The company acknowledges Stage 0, A and D patients would not receive Atezo+Bev in clinical practice, as evident in Figure 17. The BIM has been updated to include BCLC Stage B and BCLC Stage C patients only, thereby reducing the number of eligible patients which consequently lowers the overall budget impact of Atezo+Bev. An updated budget impact report has been submitted.

Subsequent Treatments

B28. Priority: Please provide more details on the cox regression analysis performed to test the impact of subsequent treatments.

In order to test the impact of subsequent treatments, the coxph function (i.e. a cox proportional hazards model) from the survival package in R was used on OS, setting the parameter ties equal to "exact". The model was fitted with treatment indicator variable (atezo+bev vs. sorafenib) interacted with a dummy that takes value 1 if the patient had a "FOLLOW-UP CANCER SYSTEMIC THERAPY" and 0 otherwise. The regression was stratified by the main stratification factors of baseline AFP levels, region and MVI/EHS, in a similar fashion to the main results shown.

B29. Priority: Please provide a scenario analysis where the full costs of all treatments used post-progression are included in the model.

A scenario costing all subsequent therapies used in the IMbrave150 clinical trial has been added to the model. See 'Cost_Input' tab cell F94. Table 15 demonstrates that this scenario results in Atezo+Bev dominance, due to the higher proportion of patients who received subsequent therapy after sorafenib in IMbrave150 and therefore an increased cumulative cost is applied to the sorafenib arm.

Table 15: Scenario analysis: Full costs of all treatments used post-progression are included

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	78,863	1.50	1.05	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Lenvatinib	102,433	1.54	1.13	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B30. Priority: Please provide a scenario analysis which attempts to use statistical methods such as the IPCW to exclude treatments not recommended in England.

An option to adjust overall survival by removing subsequent therapies not recommended in England has been added to the model. Please see the 'Model inputs' tab cell F168 'OS_scenario4'. Table 16 highlights the impact that subsequent therapy had on overall survival for patients who received sorafenib. Excluding treatments not recommended in England has reduced the sorafenib QALYs and therefore reduced the ICER.

Table 16: Scenario analysis: Adjusted OS excluding subsequent treatments not recommended in England

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	43,325	1.25	0.87	[redacted]	[redacted]	[redacted]	15,474	Dominant
Lenvatinib	62,163	1.49	1.10	[redacted]	[redacted]	[redacted]	20,307	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B31. For information, please provide a scenario where no costs are incurred for subsequent treatments. This isn't a plausible scenario for generating a central estimate but may provide useful information for the committee.

A scenario removing all subsequent therapy costs has been added to the model. See 'Cost_Input' tab cell F94. Table 17 provides the model results when this scenario is applied.

Table 17: Scenario analysis: No subsequent therapy costs applied

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	38,335	1.50	1.05	[redacted]	[redacted]	[redacted]	24,842	32,054
Lenvatinib	62,580	1.54	1.13	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Utility

B32. Priority: Please provide a justification for using a statistical model that assumes that health-related quality-of-life data are normally distributed rather than according to a more appropriate data generation process.

It is standard procedure to use a statistical model that assumes that health-related quality of life data are normally distributed. Furthermore, estimates are unbiased even under non-normality assumption; standard errors and confidence intervals are still consistent under non-normality as long as the correlation structure of the data is correct (5).

B33. Priority: Please comment on why the number of EQ-5D questionnaires completed varies considerably across time and whether there could be informative censoring in the data. For instance, because patients who are sick choose not to complete the questionnaire. Would this also affect the time to death utility values?

Questionnaires in the study are not all completed with the same frequency in the survival follow-up period (every 3 months for 1 year vs. every cycle), so as patients progress through the disease there are less questionnaires completed. If patients that are sick choose to complete less questionnaires, the utilities measured closer to death would be higher than they should be. In this case, sorafenib would have higher utilities than it should have with respect to Atezo+Bev, as the Sorafenib arm shows lower survival and therefore has more patients closer to death at an early point in time (which are time discounted). Correcting for that bias would be favourable to the Atezo+Bev values.

B34. Priority: The mean age in the IMbrave 150 study age is associated with a utility of [redacted] for the general population using the Ara and Brazier equation detailed in the model. Please comment on the plausibility that patients more than 15 weeks from death and on treatment would have a higher utility than an age and sex-matched population without advanced hepatocellular carcinoma.

Assuming a higher utility for patients on treatment more than 15 weeks from death than for the IMbrave 150 age-matched general population is a plausible assumption. This is because the age-matched general population are also composed of observations that are closer to

the death of the patient, which have a negative impact on the general utility level (the brazier regression does not include any time coefficients that may control for this effect). This means that a patient who is more than 15 weeks from death can have a higher utility than the general population average.

Results

B35. Priority: The values for lenvatinib on the cost effectiveness plane (Figure 27) appear to have points missing on its upper left side as though some data have been excluded. Please clarify if any manipulation has occurred, and if not, provide an explanation for our observation.

There has been no manipulation or exclusion of observations. This effect is most likely due to a parameter that depends on the life years and that affect the costs taking the maximum value. This is probably be related to the fact that we are using PFS as TTD, so there is a very high correlation between PFS/TTD and costs, which influence the overall picture.

Section C: Textual clarification and additional points

C1. Please confirm that the following statement is correct in the CS: *"as the remaining four models projected a higher OS for sorafenib than lenvatinib"*. [The ERG thinks that the Gompertz and Weibull distributions generated central survival functions that were worse.]

Apologies, the statement in the company submission is not clear. The statement was referring to the graphical representation of the curves, which were presented to clinical experts as part of an advisory board. Graphically, only the exponential and Generalised Gamma models produced a lenvatinib curve slightly above the sorafenib curve. The Gompertz and Weibull distributions do generate survival functions that are marginally worse for sorafenib than lenvatinib; however, when viewed graphically, both models produce a lenvatinib OS curve behind the sorafenib OS curve, although very slightly.

C2. Please explain the discrepancy in the OS HR found between Table 8 (0.58) and Figure 4 in the appendices (0.6).

The hazard ratio presented in Table 8 of the company submission is from the stratified analysis where the forest plots in Appendix E present hazard ratios estimated using unstratified Cox regression.

C3. Please confirm whether the eight beta distributions for utilities on and off treatment specified in Appendix M are not parameter values but 2.5%-iles and 97.5%-iles of distributions.

The eight beta distributions for utilities on and off treatment specified in Appendix M are not parameter values.

C4. Please clarify whether the maximum dose intensity in Table 23 for bevacizumab is meant to read 404.

Apologies, there is a typo in Table 23 of the submission document; the maximum dose intensity for bevacizumab should read 104.

C5. Please clarify why the value in 'Post disc. therapy cost' E26 (14.4) does not match with the value reported in Table 46 of the CS (13.4)

Apologies, there is a typo in Table 46 of the submission document; the duration of subsequent therapy after Atezo+Bev is 14.4 weeks.

C6. Please confirm whether the following statement in the CS is worded as intended: "*as the treatment effects from the ITC are HRs, it was deemed appropriate to apply them to an accelerated failure time (AFT) model".*

Apologies, this sentence can be removed. It is not meant to be a justification as the hazard ratios can be applied to any type of model.

C7. Please confirm whether it is correct as stated in Appendix M that OS and PFS hazard ratios for atezolizumab versus lenvatinib are inputted as fixed values.

Apologies this is a typo. The values should be as follows:

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Hazard ratio ITC			
OS hazard ratio: Atezo+Bev vs Lenva	0.63	Log normal (0.31, 1.23)	B.2.9
PFS hazard ratio: Atezo+Bev vs Lenva	0.91	Log normal (0.22, 3.50)	B.2.9

C8. On p109: Please clarify what is meant by "*The Exponential curve was also used to extrapolate PFS and therefore demonstrates consistent long-term behaviour*". This may be a typo as log-normal distributions were selected to model PFS in the base case.

Apologies, that sentence is incorrect and needs to be removed.

C9. Please clarify the apparent discrepancies between Table 9 of the Appendix and Table 5 of document B, which report that the number of patients randomised were 329 and 156, and 336 and 165, respectively.

The baseline characteristics presented in Table 5 of document B include all patients randomised to Atezo+Bev (n=336) and sorafenib (n=165).

Seven patients and nine patients did not receive treatment with Atezo+Bev or sorafenib respectively, therefore these patients are excluded in the data presented regarding reasons for discontinuation of study treatment (Atezo+Bev n=329 and sorafenib n=156).

C10. Please clarify how the number of deaths in Table 9 of the appendix is defined. These values are much less than the number of deaths reported in Table 8 of the main document.

The number of deaths in Table 9 of the appendix reflect the deaths that occurred in both arms while on treatment only. This is much lower than the number of deaths reported in Table 8 of Document B as these reflect all deaths during the study, with the majority of these taking place during the follow-up period after treatment has stopped. The number of deaths in Table 8 of Document B align with the number of deaths in Table 10 of the appendix (reasons for study discontinuation).

References

1. National Institute for Health and Care Excellence. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer [TA584]. 2019.
2. Bruix J, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. European journal of cancer (Oxford, England : 1990). 2013;49(16):3412-9.
3. Hoffmann La-Roche Ltd. Flatiron CSR: clinical outcomes in HCC patients treated with first line sorafenib. 2020.
4. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-73.
5. Verbeke G, Molenberghs G. Linear Mixed Models For Longitudinal Data2005.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

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].

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	British Liver Trust
3. Job title or position	[redacted]

4a. Brief description of the organisation (including who funds it). How many members does it have?	The British Liver Trust is the leading UK patient charity for adults living with liver disease and liver cancer. It is funded entirely by voluntary donations apart from restricted funding from Public Health Wales to help implement the Welsh Liver Plan, and deliver patient services in Wales until 2020. We receive no other statutory funding. Our services reach over two million people every year. The website receives over 120,000 visits from new unique users each month. We have a monthly newsletter which goes to people living with liver disease and liver cancer, an online support forum with over 20,000 involved users, an active social media following of over 15,000. We support people with liver disease and liver cancer by providing evidence based information (both online and in print) and run a nurse-led Helpline where people are able to ask questions and receive advice. We use the qualitative and quantitative data from our services to provide feedback to clinicians and policy makers.
4b. 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	The British Liver trust has not received any funding from Roche or Eisai. In September 2019, we received £10,000 from Bayer for support with a project raising awareness of liver disease and liver cancer in primary care. The money supported a joint tool kit with RCGP and a mailing to GP surgeries.
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?	To support the information in this submission, we have put a call out through our various channels for people living with liver cancer to come forward and provide information. We also keep a confidential quote log of Helpline callers and monitor our online social media communities (which include almost 25,000 members (online forum and open and closed Facebook groups). As part of this process, we also conducted in depth interviews with people who have liver cancer and their carers and asked participants of our support groups (held virtually).

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Primary liver cancer (HCC) is complex, varied and fluctuates, meaning that no one person's experience is the same as another. Many patients (approx. 80%) also have underlying liver cirrhosis, which not only makes treatment difficult but also means that they may have other complications. Many patients live with the risk of HCC, knowing they have cirrhosis. They live with uncertainty, hopelessness and often stigma and isolation due to the image of liver disease. Primary liver cancer in adults has a poor outlook because it tends to be diagnosed late (only 10% of people are diagnosed in the early stages, when surgery can help). The five-year survival rate is only 12-15%. 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. 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 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". Patients live with uncertainty, hopelessness and often stigma and isolation due to the image of liver disease. 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.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients are really shocked when they realise the lack of treatment options. When there is no option for surgical treatments or liver transplant, the current only life extending treatment options for patients with advanced liver cancer are sorafenib (Nexevar) or lenvatinib (Lenvima). Patients report side effects and for some people these are severe. Once sorafenib stops working, they can then use Regorafenib (Stirvaga). Once these options are exhausted the only option is palliative care. HCC patients are disadvantaged purely because they have a disease which does not have an extensive number of treatments available. For example in many other cancers, there are several life-extending chemotherapy treatments available, and it may be appropriate to consider whether new medicines are effective. This is not the case in liver cancer.
8. Is there an unmet need for patients with this condition?	Yes.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The British Liver Trust has not managed to speak to any of the patients who have been on clinical trials for Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma or who have been treated by these therapies in other countries or outside of the NHS. However there is a desperate need for new treatment options and we understand that new data has been published indicating atezolizumab/bevacizumab offers significant overall survival (OS) benefit compared to the current UK standard of care therapy.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	See above – we have not had any specific reports from patients.
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.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Patients with liver cancer are often stigmatised due to perceived links with alcohol and drug use.
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 (average 5 year survival of 12 years)
- There are very few treatment options currently available
- Any new treatment that may prolonged their life and provided them with a real chance of survival is desperately needed for these patient
- 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
- We understand that new data has been published indicating atezolizumab/bevacizumab offers significant overall survival (OS) benefit compared to the current UK standard of care therapy.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

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.

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- 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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Association for the Study of the Liver (BASL) / HCC-UK

3. Job title or position	**Consultant Medical Oncologist**
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BASL is a multi-disciplinary society with over 1,000 members composed of interested individuals from clinical medicine, clinical and basic research and allied professions. BASL is funded through membership and running an Annual Meeting. HCC-UK is a cross specialty organisation composed of individuals from different specialties of clinical medicine involved in managing patients with HCC at all stages. The organisation promotes best clinical practice and research into HCC with the aim of improving the outcomes and experience of patients with HCC at all stages.
4b. 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.]	Yes BAYER (manufacturer) – received £2,000 of sponsorship funding towards an annual meeting of HCC-UK that is taking place in March 2020. HCC-UK are a special interest group of BASL. EISAI (comparator) – received £4,000 of sponsorship funding towards an annual meeting of HCC-UK that is taking place in March 2020. HCC-UK are a special interest group of BASL. Roche (comparator) – received £4,000 of sponsorship funding towards an annual meeting of HCC-UK that is taking place in March 2020. HCC-UK are a special interest group of BASL.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
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.)	The main aims of treatment for patients with unresectable or advanced hepatocellular carcinoma (HCC) are to prolong life by delaying cancer progression, and to maintain quality-of-life (QoL). There are no options for cure, since by definition the patient will not be suitable for curative treatments such as ablation, surgery, or liver transplantation. Therapies that achieve improvements in overall survival (OS), progression free survival (PFS) or increased objective response rate (ORR) will very likely also lead to improved quality of life since uncontrolled tumour progression will give rise to symptoms that will adversely impact on QoL.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A clinically significant treatment response or effect is any statistically significant improvement in either OS, PFS, or ORR. An improvement in ORR is also important particularly if the duration of response is long (over 3 months).

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The median survival with currently available therapies is less than 1 year, hence advanced HCC is a definite area of unmet clinical need.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In the NHS, unresectable/advanced HCC is currently managed with either sorafenib or lenvatinib. Both of these drugs are oral multi-targeted tyrosine kinase inhibitors which are taken continuously until either disease progression or intolerable toxicity. To be suitable for treatment with these therapies patients need to be of good Eastern Cooperative Oncology Group Performance Status (PS); PS 0-2 for sorafenib, and PS 0-1 for lenvatinib. Patients also need to be Child-Pugh class A; hence if they have liver dysfunction due to cirrhosis this needs to be well compensated. In the NHS, patients who tolerate sorafenib well but experience disease progression can be considered for second-line systemic therapy with regorafenib. Regorafenib is another multi-targeted tyrosine kinase inhibitor, and to be eligible for this therapy patients must have PS 0-1 and be Child Pugh class A. Regorafenib is taken continuously (days 1-21 of 28-day cycles) until either disease progression or intolerable toxicity.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, clinical guidelines have been published by the European Association for the Study of the Liver (EASL; Galle PR., *et al*. 2018 *Journal of Hepatology* 69 (1), p182-236) and the European Society of Medical Oncology (ESMO; Vogel A., *et al*. 2018 *Annals of Oncology* 29 (supplement 4), p238-255). UK guidelines are currently in the process of being updated, and this process is being overseen by HCC-UK on behalf of and at the request of BASL.

• 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 pathway of care for patients with Barcelona Clinic Liver Cancer (BCLC) stage C disease is well-defined and these patients are treated with systemic therapies only. For patients with BCLC stage B disease the pathway is less well defined and these patients may be treated with either loco-regional therapies, such as trans-arterial chemoembolization (TACE) or stereotactic ablative radiotherapy (SABR), or systemic therapy depending on the extent of intrahepatic disease. Suitability for loco-regional therapies is decided on by case-review at a hepatobiliary MDT.
• What impact would the technology have on the current pathway of care?	The current technology would replace sorafenib (or lenvantinib) as the first-line systemic therapy of choice for eligible patients with PS 0-1 and Child-Pugh class A.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The current technology would be used in the same way as sorafenib (or lenvatinib) is currently used in NHS clinical practice, except that patients with PS 2 can also currently be considered for sorafenib.
• How does healthcare resource use differ between the technology and current care?	Sorafenib or lenvatinib (current care) are oral therapies. Once patients are stable on current care they are usually reviewed in the outpatient clinic on a 4-weekly basis. Atezolizumab/bevacizumab (atezo/bev) are both administered intravenously, once every 3 weeks. Patients will probably be reviewed prior to therapy administration on a 3-weekly basis. Prior to commencing either current care or atezo/bev patients should undergo upper gastrointestinal UGI) endoscopy to look for and appropriately manage gastric varicies. This is to prevent variceal bleeding on commencement of therapy. Patients with known cirrhosis who are receiving atezo/bev should also have regular endoscopies whilst on therapy (every 4-6 months) to exclude development of varicies due to the risk of variceal bleeding.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Atezo/bev will need to be administered in a hospital setting, and patients will need to be reviewed in specialist medical oncology clinics to ensure suitability for ongoing therapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Medical oncologists, clinical nurse specialists (CNSs), and other healthcare professionals caring for patients with advanced HCC receiving atezo/bev will need to become familiar with recognising and managing immune-related adverse events. However, since immune checkpoint inhibitors are used in patients with a number of other tumour types it is likely that this knowledge and experience will already have been gained though treating other patient groups.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The IMbrave150 phase 3 randomised trial which compared atezo/bev with sorafenib in patients with advanced HCC has reported statistically significant and clinically meaningful improvements in OS, PFS, and ORR (Cheng A-L., *et al*. abstract presentation at ESMO Asia meeting, Nov 2019). In addition the trial reported reduced grade 3 or 4 adverse events with atzeo/bev, and a clinically meaningful delay in time-to-deterioration in symptoms with atezo/bev. I therefore definitely expect the technology will provide clinically meaningful benefits compared to current care.
• Do you expect the technology to increase length of life more than current care?	Yes, the trial data indicates that atezo/bev will result in significantly longer OS than sorafenib. The median survival with sorafenib was 13.2 months, whereas that with atezo/bev was not estimable (but will likely be 16-18months). A formal estimate of median survival will require longer follow up and further data to be published. The hazard ratio (HR) for OS indicated that at any given time point patients receiving atezo/bev were 42% more likely to be alive than those receiving sorafenib.
• Do you expect the technology to increase health-related quality of	Yes, the published patient reported outcome (PRO) data from the IMbrave150 trial (Galle P.R., *et al*., abstract publication (abstract #GI20) at ASCO GI symposium, Jan 2020) reported clinically meaningful

life more than current care?	improvements in key aspects of patient experience (including QoL, functioning, and key symptoms) for patients receiving atezo/bev.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are no subgroups of patients expected to experience significantly more or less benefit from atezo/bev based on baseline patient or tumour factors, and similarly there are no currently available biomarkers for identifying patients likely to experience enhanced benefit with atze/bev.
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	The differences in mode of administration between atezo/bev (IV infusion) and current care (oral tablets) will need to be considered by patient and healthcare professionals. However, it is very likely that patients will accept IV administration as atezo/bev is associated with increased clinical benefit and reduced toxicity compared to current care. The differences in side effect profile will also need to be considered but (as described above) atezo/bev is expected to be better tolerated than current care.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will continue to receive atezo/bev until either disease progression on imaging, clinical progression (as judged by the treating healthcare professional), or intolerable toxicity. Patients will have 3-monthly imaging whilst on therapy to monitor for radiological progression.
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?	Around 30% of patients receiving atezo/bev are expected to experience an objective response to therapy, and responses can be durable – extending to many months. The patient group who experience prolonged tumour responses will not be captured well by simply comparing the median OS of atezo/bev with that of sorafenib.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	This technology is highly innovative. The improvements to OS, PFS, and ORR compared to current care are highly significant, as demonstrated by the impressive HRs from the trial data (and associated P values), and extremely clinically relevant. The use of atezo/bev will mean that patients with advanced HCC can be expected to live longer and enjoy a better quality of life whilst on treatment compared with current care.

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?	Yes, this is a 'step-change' in the management of advanced HCC, as demonstrated by the HRs for OS and PFS, and the improvements in ORR compared to current care.
• Does the use of the technology address any particular unmet need of the patient population?	This technology addresses the current poor life expectancy in patients with advanced HCC, and will also improve their QoL whilst receiving systemic therapy.
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?	Patients will need to be monitored for development of immune-related adverse events due to atezolizumab, and hypertension, gastro-intestinal bleeding and thrombosis related to bevacizumab. However, these events were uncommon, and overall there are significant gains in QoL for patients receiving atezo/bev compared to current care.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, many patients with advanced HCC in the UK would fit the eligibility criteria for entry into the IMbrave 150 trial. Indeed a number of UK patients were actually recruited to the trial.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are OS, ORR, and QoL. All of these outcomes were measured in the IMbrave150 trial and have reported significant benefits compared with current care.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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	No

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	There are no published real world experience data regarding use of atezo/bev for patients with advanced HCC.
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.	N/A

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Atezo/bev results in a statistically highly significant and clinically relevant improvement in overall survival compared to current care. • Atezo/bev results in a statistically highly significant and clinically relevant improvement in tumour response rate compared to current care. • Atezo/bev is better tolerated with fewer grade 3 or 4 adverse events compared to current care. • Atezo/bev results in improved patient reported outcome measures, including quality-of-life and key symptoms, compared to current care. • For patients who experience a tumour response with atezo/bev the duration of response may be prolonged with a possibility of ongoing response beyond 12 months.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

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

- 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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	For the British Society of Gastroenterology (BSG)

3. Job title or position	**Consultant Medical Oncologist**
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BSG is a multi-disciplinary society with over 1,000 members composed of interested individuals from clinical medicine, clinical and basic research and allied professions. BSG is funded through membership and running an Annual Meeting.
4b. 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.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
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.)	The main aims of treatment for patients with unresectable or advanced hepatocellular carcinoma (HCC) are to prolong life by delaying cancer progression, and to maintain quality-of-life (QoL). There are no options for cure, since by definition the patient will not be suitable for curative treatments such as ablation, surgery, or liver transplantation. Therapies that achieve improvements in overall survival (OS), progression free survival (PFS) or increased objective response rate (ORR) will very likely also lead to improved quality of life since uncontrolled tumour progression will give rise to symptoms that will adversely impact on QoL.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A clinically significant treatment response or effect is any statistically significant improvement in either OS, PFS, or ORR. An improvement in ORR is also important particularly if the duration of response is long (over 3 months).

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The median survival with currently available therapies is less than 1 year, hence advanced HCC is a definite area of unmet clinical need.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In the NHS, unresectable/advanced HCC is currently managed with either sorafenib or lenvatinib. Both of these drugs are oral multi-targeted tyrosine kinase inhibitors which are taken continuously until either disease progression or intolerable toxicity. To be suitable for treatment with these therapies patients need to be of good Eastern Cooperative Oncology Group Performance Status (PS); PS 0-2 for sorafenib, and PS 0-1 for lenvatinib. Patients also need to be Child-Pugh class A; hence if they have liver dysfunction due to cirrhosis this needs to be well compensated. In the NHS, patients who tolerate sorafenib well but experience disease progression can be considered for second-line systemic therapy with regorafenib. Regorafenib is another multi-targeted tyrosine kinase inhibitor, and to be eligible for this therapy patients must have PS 0-1 and be Child Pugh class A. Regorafenib is taken continuously (days 1-21 of 28-day cycles) until either disease progression or intolerable toxicity.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, clinical guidelines have been published by the European Association for the Study of the Liver (EASL; Galle PR., *et al*. 2018 *Journal of Hepatology* 69 (1), p182-236) and the European Society of Medical Oncology (ESMO; Vogel A., *et al*. 2018 *Annals of Oncology* 29 (supplement 4), p238-255). UK guidelines are currently in the process of being updated, and this process is being overseen by HCC-UK on behalf of and at the request of BASL.

• 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 pathway of care for patients with Barcelona Clinic Liver Cancer (BCLC) stage C disease is well-defined and these patients are treated with systemic therapies only. For patients with BCLC stage B disease the pathway is less well defined and these patients may be treated with either loco-regional therapies, such as trans-arterial chemoembolization (TACE) or stereotactic ablative radiotherapy (SABR), or systemic therapy depending on the extent of intrahepatic disease. Suitability for loco-regional therapies is decided on by case-review at a hepatobiliary MDT.
• What impact would the technology have on the current pathway of care?	The current technology would replace sorafenib (or lenvantinib) as the first-line systemic therapy of choice for eligible patients with PS 0-1 and Child-Pugh class A.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The current technology would be used in the same way as sorafenib (or lenvatinib) is currently used in NHS clinical practice, except that patients with PS 2 can also currently be considered for sorafenib.
• How does healthcare resource use differ between the technology and current care?	Sorafenib or lenvatinib (current care) are oral therapies. Once patients are stable on current care they are usually reviewed in the outpatient clinic on a 4-weekly basis. Atezolizumab/bevacizumab (atezo/bev) are both administered intravenously, once every 3 weeks. Patients will probably be reviewed prior to therapy administration on a 3-weekly basis. Prior to commencing either current care or atezo/bev patients should undergo upper gastrointestinal UGI) endoscopy to look for and appropriately manage gastric varicies. This is to prevent variceal bleeding on commencement of therapy. Patients with known cirrhosis who are receiving atezo/bev should also have regular endoscopies whilst on therapy (every 4-6 months) to exclude development of varicies due to the risk of variceal bleeding.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Atezo/bev will need to be administered in a hospital setting, and patients will need to be reviewed in specialist medical oncology clinics to ensure suitability for ongoing therapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Medical oncologists, clinical nurse specialists (CNSs), and other healthcare professionals caring for patients with advanced HCC receiving atezo/bev will need to become familiar with recognising and managing immune-related adverse events. However, since immune checkpoint inhibitors are used in patients with a number of other tumour types it is likely that this knowledge and experience will already have been gained though treating other patient groups.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The IMbrave150 phase 3 randomised trial which compared atezo/bev with sorafenib in patients with advanced HCC has reported statistically significant and clinically meaningful improvements in OS, PFS, and ORR (Cheng A-L., *et al*. abstract presentation at ESMO Asia meeting, Nov 2019). In addition the trial reported reduced grade 3 or 4 adverse events with atzeo/bev, and a clinically meaningful delay in time-to-deterioration in symptoms with atezo/bev. I therefore definitely expect the technology will provide clinically meaningful benefits compared to current care.
• Do you expect the technology to increase length of life more than current care?	Yes, the trial data indicates that atezo/bev will result in significantly longer OS than sorafenib. The median survival with sorafenib was 13.2 months, whereas that with atezo/bev was not estimable (but will likely be 16-18months). A formal estimate of median survival will require longer follow up and further data to be published. The hazard ratio (HR) for OS indicated that at any given time point patients receiving atezo/bev were 42% more likely to be alive than those receiving sorafenib.
• Do you expect the technology to increase health-related quality of	Yes, the published patient reported outcome (PRO) data from the IMbrave150 trial (Galle P.R., *et al*., abstract publication (abstract #GI20) at ASCO GI symposium, Jan 2020) reported clinically meaningful

life more than current care?	improvements in key aspects of patient experience (including QoL, functioning, and key symptoms) for patients receiving atezo/bev.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are no subgroups of patients expected to experience significantly more or less benefit from atezo/bev based on baseline patient or tumour factors, and similarly there are no currently available biomarkers for identifying patients likely to experience enhanced benefit with atze/bev.
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	The differences in mode of administration between atezo/bev (IV infusion) and current care (oral tablets) will need to be considered by patient and healthcare professionals. However, it is very likely that patients will accept IV administration as atezo/bev is associated with increased clinical benefit and reduced toxicity compared to current care. The differences in side effect profile will also need to be considered but (as described above) atezo/bev is expected to be better tolerated than current care.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will continue to receive atezo/bev until either disease progression on imaging, clinical progression (as judged by the treating healthcare professional), or intolerable toxicity. Patients will have 3-monthly imaging whilst on therapy to monitor for radiological progression.
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?	Around 30% of patients receiving atezo/bev are expected to experience an objective response to therapy, and responses can be durable – extending to many months. The patient group who experience prolonged tumour responses will not be captured well by simply comparing the median OS of atezo/bev with that of sorafenib.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	This technology is highly innovative. The improvements to OS, PFS, and ORR compared to current care are highly significant, as demonstrated by the impressive HRs from the trial data (and associated P values), and extremely clinically relevant. The use of atezo/bev will mean that patients with advanced HCC can be expected to live longer and enjoy a better quality of life whilst on treatment compared with current care.

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?	Yes, this is a 'step-change' in the management of advanced HCC, as demonstrated by the HRs for OS and PFS, and the improvements in ORR compared to current care.
• Does the use of the technology address any particular unmet need of the patient population?	This technology addresses the current poor life expectancy in patients with advanced HCC, and will also improve their QoL whilst receiving systemic therapy.
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?	Patients will need to be monitored for development of immune-related adverse events due to atezolizumab, and hypertension, gastro-intestinal bleeding and thrombosis related to bevacizumab. However, these events were uncommon, and overall there are significant gains in QoL for patients receiving atezo/bev compared to current care.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, many patients with advanced HCC in the UK would fit the eligibility criteria for entry into the IMbrave 150 trial. Indeed a number of UK patients were actually recruited to the trial.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are OS, ORR, and QoL. All of these outcomes were measured in the IMbrave150 trial and have reported significant benefits compared with current care.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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	No

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	There are no published real world experience data regarding use of atezo/bev for patients with advanced HCC.
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.	N/A

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Atezo/bev results in a statistically highly significant and clinically relevant improvement in overall survival compared to current care. • Atezo/bev results in a statistically highly significant and clinically relevant improvement in tumour response rate compared to current care. • Atezo/bev is better tolerated with fewer grade 3 or 4 adverse events compared to current care. • Atezo/bev results in improved patient reported outcome measures, including quality-of-life and key symptoms, compared to current care. • For patients who experience a tumour response with atezo/bev the duration of response may be prolonged with a possibility of ongoing response beyond 12 months.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

Thank you for agreeing to give us your 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 expert statement

- 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 13 pages.

About you	
1. Your name	**Paul Ross**
2. Name of organisation	**Guy's &St Thomas' NHS Foundation Trust**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? **X**☐ other (please specify): Acting as Independent Medical Oncologist with expertise in HCC providing advice to Roche in respect of this process
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 **X**☐ other (they didn't submit one, I don't 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	☐ I have neither contributed to nor seen any submissions made to NICE by Roche

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to stop progression, improve quality of life and increase longevity for patients with hepatocellular cancer.
8. 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.)	A clinically significant response is a statistically significant improvement in overall survival with a quality of life advantage compared to standard of care
9. In your view, is there an unmet need for patients and	Yes

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Treatment of hepatocellular cancer depends on stage of tumour. 1. Early stage disease amenable to potentially curative treatment will principally be managed with ablation, resection or transplantation. 2. Intermediate stage disease treatment is initiated with intra-arterial therapy (chemo-embolisation or bland embolisation). 3. Advanced stage disease with good performance status and well preserved liver function (Child-Pugh score A) is managed with systemic therapy, commencing with sorafenib or lenvatinib in accordance with NICE guidance.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No current guidelines agreed for use within the NHS. Clinicians broadly follow algorithms based around the Barcelona Clinic Liver Cancer (BCLC) staging system.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway is substantially defined as above. However, there are variations of opinion in respect of: a. Timing of switching from intra-arterial therapy to systemic therapy in patients with sub-optimal response to the former. b. Role of locoregional therapy in preference to systemic therapy for some patients with branch or segmental portal vein involvement. Staging of this disease according to BCLC criteria is advanced. More active systemic therapy is starting to reduce this variation.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	As atezolizumab and bevacizumab demonstrates a clear incremental improvement on sorafenib it will result in patients ceasing intra-arterial therapy earlier where likely to be of marginal benefit
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No
• How does healthcare resource use differ between the technology and current care?	Current systemic therapy (sorafenib & lenavatinib) are administered orally. Patients are typically seen for review every 4 -6 weeks. Atezolizumab & bevacizumab is administered intravenously every 3 weeks.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This will need to administered in secondary care. Most of the administration will be within (or under the direction) of specialist clinics. There are between 15-20 centres in the UK treating hepatocellular cancer, the majority of which are in England.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	a. Patients receiving atezolizumab & bevacizumab whom have not had an upper GI endoscopy within 6 months of starting treatment will require same to exclude and treat untreated oesophageal varices.

	In the light of the COVID-19 pandemic and its effects on endoscopy capacity it will be important for centres to factor this workload into capacity plans. b. Hepatocellular cancer patients have required minimal support from chemotherapy day units. The introduction of atezolizumab + bevacizumab will change this. This will require capacity planning. In addition chemotherapy day unit teams may require educating into the overall management of patients with hepatocellular cancer.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or	No such groups have been identified

less effective (or appropriate) than the general population?	
The use of the technology	
14. 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.)	From a patient perspective it will be different – a requirement to attend a chemotherapy day unit 3-weekly but with a favourable toxicity profile and significantly longer time to deterioration in quality of life (median of 11.2 months with atezolizumab+bevacizumab v 3.6 months with bevacizumab) [Finn et al, NEJM 2020]. It is not difficult to administer from the perspective of healthcare professionals but does require the resources of a chemotherapy day unit. There are no concomitant treatments or additional clinical requirements.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The decision to start treatment will be based on the opinion of a hepatocellular carcinoma multi-disciplinary meeting that a patient should be treated with systemic therapy. Treatment will continue until loss of clinical benefit. No additional testing compared to current standards is required to implement these.
16. 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?	Yes in addition to improvements in global quality of life there are advantages specifically for: • Physical functioning (median time to deterioration 13.1 months v 4.9 months) • Role functioning (median time to deterioration 9.1 months v 3.6 months)
17. 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	Yes – this is the first immunotherapy and currently only immune checkpoint inhibitor based therapy to demonstrate a survival advantage (1-year survival improved from 54.6% to 67.2% and median survival not yet achieved compared to 13.2 months) with sorafenib. As demonstrated by the patient reported outcome measures it is expected to make a substantial impact on health related quality of life compared to current standards of care.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. The significant increment in efficacy extends to response and disease control rates with the potential to transform treatment for all those with incurable disease
• Does the use of the technology address any particular unmet need of the patient population?	. Yes current treatments result in modest improvements in survival often at the expense of chronic side effects including asthenia, diarrhoea, abdominal pain, plantar-palmar erythrodysaesthesia and rash. Atezolizumab + bevacizumab result in clear improvements in overall and progression free survival and improvements in patient reported outcomes (quality of life) and therefore fulfils the need for effective treatment.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of the technology are typical for the 2 agents involved. Despite same quality of life is improved significantly compared to current standard of care.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• 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?	Overall survival Quality of life Both were measured in the randomised controlled clinical trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate measures were not used.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA474 and TA551?	No
22. How do data on real-world experience compare with the trial data?	There is no real-world data at present as the trial first reported November 2019 at ESMO Asia meeting was published in April 2020 with an FDA license in May 2020.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Should best supportive care be considered as established clinical practice in the first line treatment of advanced unresectable HCC in the NHS?	The majority of patients with advanced HCC of good performance status with well-preserved liver function are offered first line treatment with sorafenib or lenvatinib. There continue to be a small group of patients whom decline these agents due to modest median survival advantage compared to best supportive care with considerable risk of toxicity.
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Atezolizumab + Bevacizumab results in a significant improvement in overall survival compared to standard first-line therapy • The improved survival is associated with significant delay in time to deteriotation in quality of life. • Toxicity is acceptable • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Atezolizumab with bevacizumab for untreated hepatocellular carcinoma. A Single Technology Appraisal

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens and Geoff Holmes critiqued the statistical aspects of the submission. Matt Stevenson and Andrew Metry critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

A+B	Atezolizumab in combination with bevacizumab
AEs	Adverse events
AFP	Alpha-fetoprotein
AIC	Akaike Information Criterion
BCLC	Barcelona Clinic Liver Cancer
BIC	Bayesian Information Criterion
BID	Twice-daily
CCOD	Clinical cut-off date
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CrI	Credible interval
CS	Company's submission
CSR	Clinical Study Report
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-3L	EuroQol 5 dimensions 3 level
EQ-5D-5L	EuroQol 5 dimensions 5 level
ERG	Evidence Review Group
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVRS/IWRS	Interactive voice/web response system
KM	Kaplan-Meier
mRECIST	Modified Response Evaluation Criteria In Solid Tumours
MRU	Medical resource use

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PRO	Patient-reported outcomes
PSM	Partitioned survival model
QA	Quality assessment
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SLR	Systematic literature review
STA	Single Technology Appraisal
TACE	Transarterial chemoembolisation
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TTP	Time to progression

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The NICE scope details the population to be adults with locally advanced or metastatic and/or unresectable hepatocellular carcinoma who have had no previous systemic treatment. The intervention is atezolizumab and bevacizumab (hereafter referred to as "A+B") with comparators being sorafenib, lenvatinib and best supportive care (BSC). The company provided an appropriate description of hepatocellular carcinoma (HCC). Following the clarification process, the company provided an appropriate overview of current practice guidelines regarding lines of treatment and the potential positioning of A+B in the treatment pathway, which is the current recommended position for both sorafenib and lenvatinib. The company did not include BSC in the decision problem as it argued that if A+B could be tolerated then so would either sorafenib or lenvatinib. Clinical advice provided to the ERG supported this view.

1.2 Summary of clinical effectiveness evidence submitted by the company

The key evidence of the clinical effectiveness of A+B was derived from one randomised controlled trial (RCT), IMbrave150. Safety data were available from IMbrave150 and the Phase 1b study GO30140.

IMbrave150 randomised adults with locally advanced or metastatic and/or unresectable HCC, who had no previous systemic treatment for HCC, to A+B (atezolizumab 1200 mg IV infusions every three weeks, and bevacizumab 15 mg/kg every three weeks, n=336) or sorafenib (400 mg orally twice per day n=165).

OS was statistically significantly higher for A+B, than for sorafenib HR (stratified) 0.58 (95% CI 0.42, 0.79) p=0.0006. Median OS for A+B was not estimable (NE), median OS for sorafenib was 13.2 months (95% confidence interval [CI] 10.4, NE). There was a statistically significant treatment group difference for PFS HR (stratified) 0.59 (95% CI 0.47, 0.76) p<0.0001. Median PFS was 6.8 months (95% CI 5.6, 8.3) in the A+B group, and 4.3 months (95% CI 4.0, 5.6) for the sorafenib group.

The most common National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or 4 AEs experienced in the A+B group were hypertension (10.3%), aspartate aminotransferase increased (4.3%) and proteinuria (2.7%). The most common Grade 3 or 4 AEs in the sorafenib group were hypertension (9.0%), palmar-plantar erythrodysaesthesia syndrome (8.3%), diarrhoea (3.8%), decreased appetite (3.8%), hypophosphataemia (3.2%), and fatigue (3.2%).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG believes that the only RCT with available data informing on the clinical effectiveness of A+B in adults with previously untreated locally advanced or metastatic and/or unresectable HCC was included in the company submission. The company's submission (CS) study selection criteria for the review were consistent with the decision problem defined in the final NICE scope. Although the CS study selection criteria for comparators were broader than the decision problem, this allowed inclusion of the relevant comparators, and best supportive care was excluded as deemed appropriate by the ERG's clinical advisor.

The quality of the IMbrave150 RCT was assessed using well-established and recognised criteria. IMbrave150 was an open label trial, but was of otherwise good methodological quality. A literature review of A+B and global comparators identified 59 studies of which 23 connected to provide an evidence network. One of the comparator studies was directly relevant to the decision problem, REFLECT, an open label RCT of otherwise good methodological quality, that compared sorafenib and lenvatinib.

1.4 Summary of cost effectiveness submitted evidence by the company

Following the clarification process, the ERG believes the company's model to be generally well programmed and free from major errors. The company submitted a partitioned survival model comprising three health states (progression-free, post progression, and death). Movements between health states were inferred via PFS and OS models fitted to data from IMbrave150 for A+B and sorafenib, with an indirect treatment comparison performed to inform an HR for lenvatinib versus A+B.

Health-related quality of life data (HRQoL) were collected using the EuroQol 5 dimensions 5 level (EQ-5D-5L) questionnaire within IMbrave150 and mapped to the 3L version using a published algorithm. The time horizon in the base case was 20 years, with discounting of both benefits and costs at 3.5% per annum. The company's base case results suggested that A+B compared with sorafenib had a probabilistic incremental cost-effectiveness ratio (ICER) £22,419 per QALY gained, whilst A+B dominated lenvatinib (i.e. provided more QALYs at a lower cost).

However, as recommended by NICE, confidential Patient Access Schemes (PAS) for sorafenib, lenvatinib and regorafenib were not included in the company's analyses; results incorporating these PASs are provided in a confidential appendix.

The company made the case that A+B met NICE's end of life criteria with patients receiving sorafenib estimated to live for 1.50 years, and those receiving lenvatinib estimated to live for 1.54 years. Those receiving A+B were expected to live for [redacted] years.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG identified seven limitations within the company's model and reporting of results. These were: i) identification of perceived modelling errors; ii) extrapolation of time-to-event data, in particular the use of an exponential model for overall survival; iii) the assumptions related to the dosage and acquisition costs of each treatment, in using planned dosages rather than actual dosages; iv) the use of utility values for patients with unresectable HCC which are on average higher than those for the general population; v) overestimation of the adverse events associated with lenvatinib; vi) underestimation of the relative efficacy of lenvatinib, and vii) uncertainty relating to subsequent treatments in IMbrave150 that are not recommended in England. The ERG explored the impact of amending some of these limitations; using the list prices of sorafenib, lenvatinib and regorafenib, these only had a moderate impact on the ICER for atezolizumab. In addition, the ERG conducted subgroup analyses as the acquisition price of lenvatinib is dependent on whether a patient weighs under 60kg or not, explored the impact on the ICER of excluding Asian patients (bar Japanese patients) from the analyses, and undertook analyses exploring the impact on the ICER of uncertainty in the acquisition costs of sorafenib and lenvatinib associated with reduced dose intensity (RDI).

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The search for A+B studies was comprehensive and the ERG believes that no relevant RCTs with relevant data for A+B were excluded from the company's review.

The one included RCT of A+B, IMbrave150, was of good methodological quality, apart from its use of an open-label design. IMbrave150 had an active comparator (not placebo).

According to clinical advice, prior treatments used in IMbrave150 were broadly reflective of UK practice, although prior radiotherapy is rare in the UK, whereas 10% of trial patients received prior radiotherapy.

According to the CS, subsequent treatments used in IMbrave150 were not reflective of UK practice but were unlikely to influence results to a great extent. Subsequent treatment in the UK would include regorafenib, or, where possible, interventions being assessed in ongoing trials.

According to clinical advice, the baseline characteristics of the IMbrave150 trial population were broadly representative of the UK population eligible for A+B treatment, although there are a smaller proportion of Asian patients, and patients with an aetiology of hepatitis B in the UK than is represented in the trial. In addition, more patients in the UK would have aetiology of alcohol or non-alcohol related fatty liver disease, than in the study. Baseline characteristics of REFLECT and IMbrave150 were similar although REFLECT had a higher proportion of patients from the Asia-Pacific region, and implied lower alpha-fetoprotein than IMbrave150.

The implementation of the submitted mathematical model was of good quality. The company responded well to the clarification questions raised and provided a revised model and undertook the analyses requested by the ERG.

1.6.2 Weaknesses and areas of uncertainty

Apart from one study providing additional safety data, there was only one trial of A+B. IMbrave150 was open-label, and also permitted the use of subsequent treatments not recommended in England. There were no head-to-head RCTs of A+B compared with lenvatinib.

There were limitations in the company's economic analyses as summarised in Section 1.5

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG modified the company's base case in the model submitted post-clarification to generate an ERG-preferred base case range. Five changes were made in both ERG base case A and ERG base case B. These were: adjusting for perceived modelling errors; use of log-normal distributions to model OS for all treatments; including seven days wastage for oral chemotherapy when discontinuing treatment; capping utilities for people with unresected HCC at the level of the age- and sex-matched general population, and costing subsequent TKIs and nivolumab treatments from IMbrave150, assuming that the resource use for lenvatinib was the same as for sorafenib. For ERG base case A, it was assumed that the RDI for A+B observed in IMbrave150 was used, whilst the RDI for lenvatinib and sorafenib was assumed to be 1.0. For ERG base case B, it was assumed that the RDI for A+B and sorafenib observed in IMbrave150 was used, whilst the RDI for lenvatinib was assumed based on the REFLECT study.

For the full IMbrave150 population assuming costs for patients weighing under 60kg, the probabilistic ICER range (ERG base case A to ERG base case B) for A+B was £16,567 to £21,843 per QALY gained when compared with sorafenib and £83 to £3,962 per QALY gained when compared with lenvatinib. Assuming costs for patients weighing 60kg or more these ranges were £21,427 to £26,653, and A+B dominant to A+B dominant, respectively.

When patients from Asia (bar Japanese patients) were excluded from the analysis, assuming costs for patients weighing under 60kg, the probabilistic ICER range for A+B was £15,387 to £21,488 per QALY gained when compared with sorafenib and A+B dominant to £3381 per QALY gained when compared with lenvatinib. Assuming costs for patients weighing 60kg or more these ranges were £20,837 to £27,017, and A+B dominant to A+B dominant, respectively.

These results do not incorporate the PAS discounts for sorafenib, lenvatinib and regorafenib. A confidential appendix provides results incorporating these PASs.

2 BACKGROUND

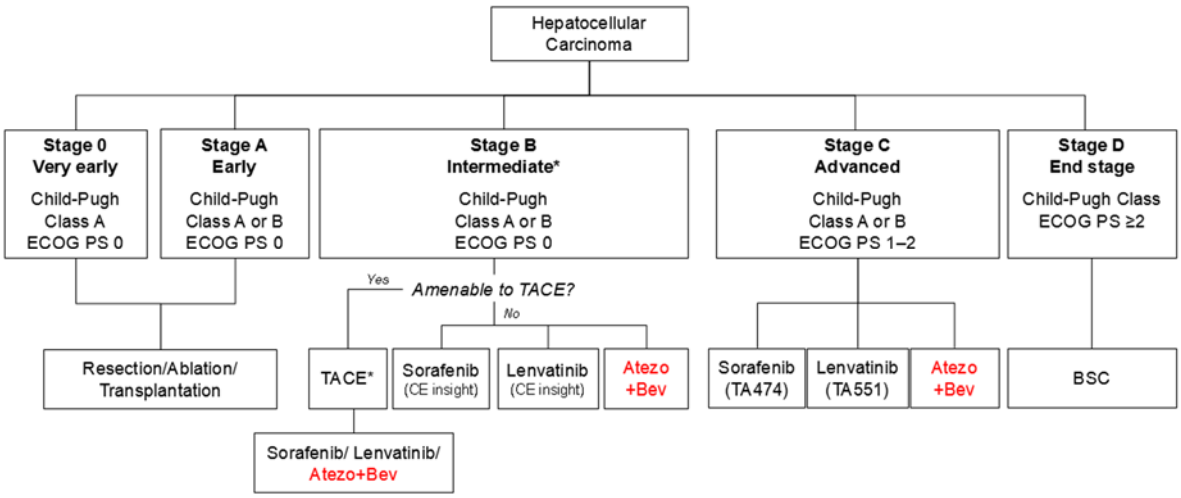
2.1 Critique of company's description of underlying health problem

The CS provide an acceptable description of hepatocellular carcinoma (HCC) in terms of prevalence, symptoms, staging and prognosis.

2.2 Critique of company's overview of current service provision

Following the clarification process, the company revised their diagram depicting the proposed positioning of atezolizumab and bevacizumab (hereafter referred to as "A+B") in the treatment pathway for adults with unresectable HCC (see Figure 1). The revised figure is more aligned to clinical advice provided to the ERG. The company states that "*Due to the highly heterogeneous nature of patients with [Barcelona Clinic Liver Cancer] BCLC Stage B intermediate disease, clinical experts have advised Roche that it is clinically difficult to distinguish those Stage B patients who are not amenable to or who progress on TACE/locoregional therapies from Stage C patients. Therefore, it is not currently possible to separate these populations into distinct groups.*" The positioning of A+B corresponds to the current positioning of sorafenib and of lenvatinib. However, Figure 1 does not show that regorafenib has a positive NICE recommendation for use after sorafenib, but cannot be used after lenvatinib, or A+B, were this to receive a positive recommendation.

Figure 1: Proposed positioning of A+B in treatment pathway for adult patients with unresectable HCC (reproduced from the company's clarification response to question B1)



2.3 Critique of company's definition of the decision problem

2.3.1 Population

The population chosen by the company appears appropriate and in line with NICE's final scope. This is "[redacted]" and covers the full marketing authorisation for A+B for this indication.

2.3.2 Intervention

The intervention is appropriate and matches that in the NICE scope and is A+B.

Atezolizumab (Tecentriq®) is a humanised IgG monoclonal antibody that is administered via an intravenous (IV) infusion of 1200mg every three weeks until the loss of clinical benefit or unmanageable toxicity.

Bevacizumab (Avastin®) is a vascular endothelial growth factor inhibitor which is administered via an IV infusion at a dose of 15mg/kg every three weeks until disease progression or unacceptable toxicity.

2.3.3 Comparators

The comparators included in the CS are sorafenib and lenvatinib. This deviates from the NICE scope which also included best supportive care. The CS states that "*Best supportive care is not a relevant comparator as patients considered eligible for Atezo+Bev would be eligible for alternative active treatment*." (Table 1) Clinical advice to the ERG concurred, stating that if a patient were considered for A+B then they would also be considered for sorafenib or lenvatinib.

2.3.4 Outcomes

The outcomes considered in the CS were consistent those listed in the NICE scope, namely overall survival (OS), progression-free survival (PFS), response rate, adverse effects of treatment and health-related quality of life (HRQoL).

2.3.5 Other relevant factors

Both atezolizumab and bevacizumab have existing Patient Access Schemes (PASs) which take the form of simple price discounts of [redacted]% for atezolizumab and [redacted]% for bevacizumab. Note that the discount for atezolizumab has increased since the CS. All results presented in this report use the new atezolizumab PAS unless explicitly stated.

Sorafenib, lenvatinib and regorafenib have simple PAS discounts. In accordance with NICE process, these price discounts were not considered in the CS, nor in this report. The results of the analyses including the cPAS discounts are provided in a confidential appendix to this ERG report.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical evidence submitted by the company to support the cost effectiveness of A+B for untreated locally advanced metastatic HCC patients.

3.1 Critique of the methods of review(s)

3.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical effectiveness and safety studies of A+B and comparators sorafenib or lenvatinib for the first-line treatment of locally advanced metastatic HCC. The company reportedly searched several electronic bibliographic databases in March 2020: MEDLINE [via Ovid], MEDLINE in Process [via Ovid], EMBASE [via Ovid], Cochrane Database of Systematic Reviews [via EBM Reviews], Cochrane Central Register of Controlled Trials [via EBM Reviews], The Health Technology Assessment [via EBM Reviews]), and Database of Abstracts of Reviews of Effects [via EBM Reviews].

The applied search strategy terms, headings, thesauri terms, syntax, recognised RCT filters, limits applied (update search) and concept combinations were correctly applied. A minor suggestion relating to the HCC concept would be to include free-text terms such as "oncolog*" or "adenocarcinoma*" or "sarcoma*" or "adenoma*" in statement 3 of all database strategies. The reasons for the company's inclusion of terms for "chemoembolization" and "radiation therapy" were unclear to the ERG, as they are not relevant comparators designated for this submission (Appendix D, page 12, Table 7: Inclusion and exclusion criteria). The inclusion of these terms would only increase the number of records required to screen and are unlikely to impact the sensitivity of the search for eligible studies. Nevertheless, the database search strategies are fully reported and comprehensive to retrieve all published and eligible studies that are relevant to the review.

The company also searched the International Clinical Trials Registry Platform. Upon ERG request in the clarification letter (page 2, question A1), the company provided search terms used (HCC and hepatocellular carcinoma) and a list of included studies from the trial's registry search. It is unclear to the ERG how many trials were retrieved, screened and excluded by the company. Whilst the search terms applied were broad and should retrieve all eligible trials, the ERG was unable to undertake searches in the ICTRP registry at the time of the company's clarification response.

Supplementary searches by the company include searching several conference abstract websites in the last three years: American Society of Clinical Oncology, European Society for Medical Oncology, American Association for Cancer Research, International Society for Pharmacoeconomics and

Outcomes Research: European Meeting, Health Technology Assessment International, Society for Medical Decision Making (Appendix D, Page 11 of the CS).

The company also searched several HTA websites for previous technology submissions: Scottish Medicines Consortium, All Wales Medicines Strategy Group, Pharmaceutical Benefits Advisory Committee, Canadian Agency for Drugs and Technologies in Health including the pan-Canadian Oncology Drug Review.

3.1.2 Inclusion criteria

The company conducted one systematic review to identify evidence relevant to the scope, and also to populate a network meta-analysis (Appendix D of the CS). The comparators within the inclusion criteria were broader than those in the scope.

Comparators in the inclusion criteria (Appendix D Table 7 of the CS) included not only the comparators in the scope, sorafenib and lenvatinib, but also nivolumab, transarterial chemoembolisation (TACE), radiotherapy, camrelizumab and tislelizumab. Nivolumab would not be used in the UK. Camrelizumab and tislelizumab were included by the CS as they had been tested in Chinese populations, but would not be used in the UK. TACE would be used at an earlier stage in the clinical pathway than is relevant to the decision problem and radiotherapy is rarely used in the UK for HCC. BSC was not included as a comparator in the CS, but was listed in the scope; as discussed in Section 2.3.3, this was deemed appropriate by the clinical advisor.

The population, intervention and outcomes reflected in the inclusion criteria (Appendix D Table 7 of the CS) were consistent with the decision problem set out in the final NICE scope. The population was adults (men or women aged 18+ years) with locally advanced or metastatic and/or unresectable hepatocellular carcinoma (HCC), who had no previous systemic treatment for HCC. The intervention was A+B.

Study selection was conducted by one reviewer and checked by another, as is good practice in systematic reviews (Appendix D.1 of the CS).

3.1.3 Critique of data extraction

Data in the CS were extracted by one reviewer and checked by another, as is good practice in systematic reviews (Appendix D.1 of the CS).

Data in the CS were checked by the ERG against trial publications (Cheng 2019)[1] (Galle 2020)[2] and the IMbrave150 Clinical Study Report (CSR).[3]

3.1.4 Quality assessment

Quality assessment (QA) in the CS was conducted by one reviewer and checked by another (CS Clarification response A2), as is good practice in systematic reviews.

Quality items assessed by the company (CS Section B.2.5) were taken from the Centre for Reviews and Dissemination guidelines for undertaking reviews in health care.[4] Quality assessment of IMbrave150 using Cochrane risk of bias[5] by the company was provided in CS Appendix D.3. Both of these tools are standard and appropriate criteria for assessing the risk of bias in RCTs, and applicable to the IMbrave150 trial. Quality assessment was checked by the ERG against information provided by the company, the CSR,[3] trial protocol[6] and publications (Table 1). [1, 2]

Table 1: IMbrave150 QA by the CS and by the ERG

CRD item	QA by CS (CS Table 7)	Cochrane Risk of bias item	Risk of bias by CS (Appendix D.3)	ERG assessment
Was randomisation carried out appropriately?	Yes	Was the allocation sequence adequately generated?	Low - Randomization was performed via an interactive voice/web response system (IVRS/IWRS) using permuted blocks	Low risk of bias IVRS/IWRS permuted-block randomisation method (protocol)[6]
Was the concealment of treatment allocation adequate?	Yes	Was the concealment of treatment allocation adequate?	Low - Randomization was performed via an interactive voice/web response system using permuted blocks	Low risk of bias Central allocation by IVRS/IWRS [6]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	NA	NA	Yes (CSR) [3]
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A (open label study)	Was knowledge of the allocated interventions adequately prevented from participants and personnel? Was knowledge of the allocated interventions adequately	Patients and participants High risk – open label. Outcome assessors Low – although open-label a blinded independent review of imaging for progression-free survival was selected	Patients and participants High risk – open label. Outcome assessors Mixed – high risk for PROs and investigator assessed outcomes Low risk for IRF assessed outcomes: Progression-Free

		prevented from outcome assessors?	for the co-primary endpoint	Survival; Objective Response; Time to Progression; Duration of response (protocol)[6]
Were there any unexpected imbalances in drop-outs between groups?	No	NA	NA	No (CSR)[3]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Are reports of the study free of suggestion of selective outcome reporting?	Low - The study reports outcomes of interest as specified	Not assessable until study is published. All outcomes relevant to the decision problem were provided in the CS
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Were incomplete outcome data adequately addressed?	Low - Primary and secondary endpoints reported	ITT analyses provided for primary endpoints AEs - safety evaluable population, as is appropriate
NA	NA	Was the study apparently free of other problems that could put it at a high risk of bias?	Low - The study appears to be free of other sources of bias	Risk of bias from funding source: F. Hoffmann-La Roche Ltd. (CSR) [3]

NA=not applicable

Randomised sequence generation and allocation concealment were conducted by interactive voice or web response technology (CS Appendix D.3 and study protocol[6]) giving a low risk of selection bias. IMbrave150 randomisation was stratified according to: geographic region (Asia excluding Japan vs. rest of world); macrovascular invasion and/or extrahepatic spread (presence vs. absence); Baseline AFP (<400 vs. ≥ 400 ng/mL); ECOG Performance Status (ECOG PS) (0 vs. 1) (study protocol).[6] Effectiveness analyses used the first three of these factors in stratified analyses (CS Section B.2.4), but not ECOG PS (CSR).[3] According to the CSR, *"ECOG PS was removed from the stratified analysis to avoid the potential risk of over-stratification"* (CSR).[3]

There was also a low risk of bias in respect of balance between groups as baseline characteristics appeared similar, and there were no unexpected imbalances in drop-outs between groups (CS Appendix D.3 and CSR[3]).

For effectiveness measures, an intention-to-treat analysis was presented for the primary outcomes of OS and PFS (CS Appendix D.3 and CSR[3]).

For secondary effectiveness outcomes, ITT or modified ITT analyses were employed. For overall response rates only patients with measurable disease were included. For PROs time-to-deterioration ITT analyses were provided. For the PRO measures of proportion of patients with clinically meaningful deterioration, patients required baseline and at least one follow-up measurement. However, patients were analysed within allocated groups in accordance with the principle of ITT (CS Section B.2.6.2) (CSR)[3]).

The IMbrave150 trial was open-label. Lack of blinding can lead to a high risk of performance and detection bias. Patient-reported outcome measures are more likely to be biased than objective measures such as overall survival.[4] Blinded outcome assessment by Independent Review Facility (IRF) was conducted for the measures of progression-free survival; objective response rate; time-to-progression; and duration of response (CS Section B.2.3.2 and study protocol[6]) which reduces the risk of detection bias. Given differences between the intervention and comparator in administration, blinding would require a double-dummy trial design. This would reduce bias for objective measures, but would disguise potential benefits to HRQoL resulting from mode of administration.

IMbrave150 is ongoing and therefore final results have not yet been published, so it cannot be assessed if the authors measured more outcomes than they published. However, data (from the clinical cut-off date 29 Aug 2019) for most outcomes of relevance to this review were provided by the company in the CS and accompanying documents. EuroQol 5 dimensions 5 level (EQ-5D-5L) questionnaire data were not provided; however, the company provided the ERG with mean utilities at each visit, in the model, using data derived from EQ-5D-5L data.

3.2 Critique of trial of the technology of interest

The search conducted in the CS, which sought more comparators than included in the scope (ERG report Section 4.1.2), identified 59 studies (CS Appendix D.1). Of these, one RCT of A+B, IMbrave150, met the inclusion criteria for the decision problem. The ERG does not believe that any relevant published RCTs of A+B that could have provided data have been omitted.

The clinical effectiveness evidence for A+B is based on one RCT, IMbrave150. IMbrave150 was ongoing at the time of writing, with the final OS analysis expected to occur June 2022 (CS Section

B.2.11). At time of writing, data were available from the final PFS analysis and the first interim OS analysis (clinical cut-off date 29 Aug 2019) (CS Section B.2.6).

Additional AE data were provided from the Phase Ib GO30140 study (CS Appendix F).

Other ongoing studies

The CS conducted a broad search for ongoing studies, and did not identify any studies of A+B in HCC. It did identify one RCT (NCT03755791) investigating combination therapy of atezolizumab and cabozantinib, compared with cabozantinib, and with sorafenib, with an estimated primary completion date of August 2020 (CS Clarification response A1). The CS search also identified four ongoing studies of sorafenib (NCT04000737, NCT03412773, NCT03794440, NCT03298451) (CS Clarification response A1). Of these, one RCT, with comparators durvalumab + tremelimumab and durvalumab monotherapy, had an estimated primary completion date of June 2020. Of the other three studies, the earliest estimated primary completion date was June 2021. Three ongoing studies of lenvatinib were identified (NCT04246177, NCT03713593, NCT03905967) with the earliest estimated primary completion date of May 2022 (CS Clarification response A1).

3.2.1 IMbrave150

IMbrave150 is a multicentre, international open-label RCT (CS Section B.2) with centres in Asia, Australia, Europe, and North America (

Table 2). It includes 13 patients at n=4 centres in the UK.

Table 2: IMbrave150 study references

Study name	Study design	Published References	Other references provided by CS
IMbrave150 150 NCT03434379 YO40245	Phase III, open-label, multicentre, international, RCT	Protocol on clinical trials registry NCT03434379: A Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150) https://clinicaltrials.gov/ct2/show/NCT03434379[7] Abstract of primary analysis results Cheng et al. (2019) European Society of Medical Oncology ASIA. Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150.[1] Abstract of patient-reported outcomes Galle et al. (2020) Patient-reported Outcomes from the Phase 3 IMbrave150 Trial of Atezolizumab + Bevacizumab Versus Sorafenib as First-line Treatment for Patients with Unresectable Hepatocellular Carcinoma. American Society of Clinical Oncology GastroIntestinal[2]	Study protocol Hoffmann La-Roche Ltd. (2019) IMbrave150 Study Protocol.[6] Clinical study report Hoffmann La-Roche Ltd. (2019) IMbrave150 Clinical Study Report (29 Aug 19 Clinical cut-off date (CCOD)). Report No.: 1092943.[3]

Patients were randomised to receive A+B or sorafenib until investigator-assessed unacceptable toxicity or loss of clinical benefit (CS Section B.2) (Table 3). Patients, in either trial arm, with disease progression were allowed to continue treatment if there was investigator-determined clinical benefit and absences of: symptoms and signs indicating unequivocal progression of disease; and decline in ECOG PS; and tumour progression at critical anatomical sites that cannot be managed by protocol-allowed medical interventions (CS Section B.2).

Dose modification or interruption was allowed for sorafenib (CS Section B.2) to allow management of toxicity. Dose modification was not allowed for A+B (CS Section B.2). However, dose interruption was allowed (CS Section B.2.10) to allow recovery from toxicity (CSR).[3]

The IMbrave150 trial allowed concomitant treatment with: oral contraceptives; hormone-replacement therapy; inactivated influenza vaccines; megestrol acetate administered as an appetite stimulant; mineralocorticoids; corticosteroids; low-dose aspirin; prophylactic use of low-dose anticoagulation, unfractionated heparin or low molecular weight heparin; palliative radiotherapy; radiotherapy to the brain; other local therapy (surgery, stereotactic radiosurgery, radiofrequency ablation) (CS Section B.2.3.2).

Table 3: IMbrave150 study characteristics (CS section B.2)

Study	Population	Intervention (n randomised)	Comparator (n randomised)	Primary outcomes
IMbrave150 150 NCT03434379 YO40245	Adults with locally advanced or metastatic and/or unresectable HCC who had not received prior systemic treatment	Combination atezolizumab 1200 mg IV infusions, Q3W plus bevacizumab 15 mg/kg IV Q3W (n=336)	sorafenib 400 mg oral, BID, continuously (n=165)	PFS: time from randomisation to the first documented disease progression as determined by an IRF according to response evaluation criteria in solid tumours (RECIST) Version 1.1 or death from any cause, whichever occurred first OS: time from randomisation to death due to any cause

IV=intravenous; Q3W= every three weeks; BID=twice a day

Eligibility criteria are provided in CS Section B.2.3.2. Included patients were adults with locally advanced or metastatic and/or unresectable HCC, with no previous systemic treatment (Table 4). Diagnosis was confirmed by histology/cytology or clinically by American Association for the Study of Liver Diseases criteria in cirrhotic patients.[8] Patients were also required to have at least one measurable (per RECIST v1.1) untreated lesion, and be scored as Child-Pugh class A and ECOG PS 0 or 1 within 7 days prior to randomisation.

Table 4: IMbrave150 eligibility criteria (reproduced from CS Section B.2.3.2 Summary of study methodology)

Inclusion criteria	**Exclusion criteria**
• Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/cytology or clinically by American Association for the Study of Liver Diseases criteria in cirrhotic patients • Disease that was not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies • No prior systemic therapy (including systemic investigational agents) for HCC • Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial	• History of malignancy other than HCC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer • Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC • Moderate or severe ascites • History of hepatic encephalopathy • Co-infection of HBV and HCV Patients with a history of HCV infection who were negative for HCV RNA by PCR were considered non-infected with HCV.

chemoembolisation, transarterial embolisation, etc.) were eligible provided the target lesion(s) had not been previously treated with local therapy or the target lesion(s) within the field of local therapy had subsequently progressed in accordance with RECIST v1.1.
• Child-Pugh class A within 7 days prior to randomisation
• Adequate haematologic and end organ function within 7 days prior to randomisation
  o Serum bilirubin ≤3x ULN
  o Serum albumin ≥28 g/L (2.8 g/dL) without transfusion
  o For patients not receiving therapeutic anticoagulation: INR or aPTT ≤2x ULN
• Documented virology status of hepatitis, as confirmed by screening hepatitis B virus (HBV) and hepatitis C virus (HCV) serology test
• At least one measurable (per RECIST v1.1) untreated lesion
• ECOG PS of 0 or 1 within 7 days prior to randomisation
• For patients with active HBV:
  o HBV DNA <500 IU/mL obtained within 28 days prior to initiation of study treatment, and
  o Anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study
	• Untreated or incompletely treated oesophageal and/or gastric varices with bleeding or high risk for bleeding
	
	Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrolment. Patients who have undergone an EGD within 6 months prior to initiation of study treatment do not need to repeat the procedure
	• A prior bleeding event due to oesophageal and/or gastric varices within 6 months prior to initiation of study treatment
	Exclusion criteria related to medications
	Patients who met any of the following criteria were excluded from study entry:
	• Prior allogeneic stem cell or solid organ transplantation
	• History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
	• Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulation
	• Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogues) or St. John's wort
	• Treatment with any agent that may interfere with the immunostimulatory nature of atezolizumab
	All patients had to meet several bevacizumab-specific criteria based on the known safety profile of this drug. These criteria excluded patients with evidence of or a possibility for bleeding issues, uncontrolled hypertension, and/or gastrointestinal perforations

The primary outcomes of IMbrave150 were OS and PFS (Table 5). Other outcomes were objective response rate (ORR), Duration of Response (DOR), Time to Progression (TTP), safety and HRQoL. Pharmacokinetic outcomes in A+B group were measured, but are not considered in this ERG report (CSR Table 10). Patients underwent tumour assessments at baseline, then every 6 weeks (+/-1 week) for the first 54 weeks following treatment initiation, and every 9 weeks (+/-1 week) thereafter until radiographic disease progression per RECIST v1.1 or (for patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (CS Clarification response A18).

Table 5: IMbrave150 outcome definitions (CS Section B.2.3 and CSR[3])

Outcome	Definition	Measured by
Overall survival (OS)	Time from randomisation to death due to any cause	
Progression-free survival (PFS)	Time from randomisation to the first documented disease progression, or death due to any cause, whichever occurred first	Independent Review Facility (IRF) Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1[9] IRF Modified Response evaluation criteria in solid tumours (mRECIST)[10] Investigator assessed RECIST v1.1
Objective response rate (ORR)	Complete or partial response	IRF RECIST v1.1 IRF mRECIST Investigator assessed RECIST v1.1
Duration of response (DOR)	Time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first)	IRF RECIST v1.1 IRF mRECIST Investigator assessed RECIST v1.1
Time to progression (TTP)	Time from randomisation to the first occurrence of disease progression	IRF RECIST v1.1 IRF mRECIST Investigator assessed RECIST v1.1
Safety	Safety and tolerability of atezolizumab administered in combination with bevacizumab compared with sorafenib monotherapy	severity determined according to NCI CTCAE v4.0 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0) [11]
HRQoL (Time to deterioration)	Time from randomisation to first deterioration (decrease from baseline of ≥10 points), maintained for two consecutive assessments or one assessment followed by death from any cause within 3 weeks: physical functioning; role functioning; and global health status/quality of life	Patient-reported outcomes (PROs) EORTC QLQ-C30 [12] and EORTC QLQ-HCC18 [13] questionnaires

IMbrave150 screened 725 patients, of whom 224 failed to meet eligibility criteria or withdrew consent prior to randomisation (CS Appendix D.2 and (CSR)[3]). Five hundred and one patients were randomised; 336 patients were randomised to A+B and 165 patients were randomised to sorafenib. These formed the ITT population for effectiveness analyses (CS Appendix D.2 and (CSR)[3]). Allocated treatment was not received by 7 patients in the A+B group, and 9 patients in the sorafenib group.

The safety population comprised any patients who received each treatment, regardless of allocated group: n=329 received A+B, and n=156 received sorafenib (CS Appendix D.2 and (CSR)[3]). The PRO-evaluable population comprised patients who had baseline PRO data and at least one other PRO assessment (A+B n=309, sorafenib n=145) (Galle 2020)[2] (CSR).[3]

Patient baseline characteristics were reported as being well balanced between treatment groups (CS Section B.2.3.3 and (CSR).[3]). CS B.2.3.3 Table 5 shows the key baseline demographics and disease characteristics. Median age was 64.0 years in the A+B group, and 66.0 in the sorafenib group (CS Section B.2.3.3). There was an ECOG PS score of 0 for 62.2% of the A+B group, and 62.4 % of the sorafenib group (CS Section B.2.3.3). Extrahepatic spread and/or macrovascular invasion was present in 76.8% of the A+B group, and 72.7% of the sorafenib group (CS Section B.2.3.3). The aetiology of HCC was HBV for 48.8% of the A+B group, and 46.1% of the sorafenib group (CS Section B.2.3.3). TACE had been received by 38.7% of the A+B group, and 42.4% of the sorafenib group (CS Section B.2.3.3).

[redacted]

Following discontinuation of study treatment, 20.5% of the A+B group, and 44.2% of the sorafenib group had subsequent HCC systemic therapy (CS Section B.2.3.3). Most of this was tyrosine kinase inhibitors, 18.8% of the A+B group, and 26.1% of the sorafenib group (CS Section B.2.3.3).

At the time of the clinical cut-off date (29 August 2019), 309 patients were still on study, of whom n=228 (67.9%) in the A+B group, and n=81 (49.1) in the sorafenib group (CS Appendix D.2). The most common reason for discontinuing the study was death (CS Appendix D.2). In the A+B group, n=108 discontinued the study, with death being the reason for n=95 (CS Appendix D.2). In the sorafenib group, n=84 discontinued the study, with death being the reason for n=65 (CS Appendix D.2).

At the time of the clinical cut-off date (29 August 2019), n=146 (43.5%) in the A+B group were still receiving study treatment, as were n=24 (15.4%) in the sorafenib group (

Table 6). In the safety evaluable population, median study-treatment duration was 7.4 months for atezolizumab, 6.9 months for bevacizumab, and 2.8 months for sorafenib (CS Section B.2.10) (Cheng 2019[1]).

Table 6: IMbrave150 Reasons for discontinuation from study treatment in safety evaluable population (reproduced from CS Appendix D.2 Table 9 and CS Clarification response A4)

n, (%)	A+B n=329			Sorafenib n=156
	Atezolizumab	Bevacizumab	A+B	
Received at least one study treatment Yes	329 (100)	329 (100)	329 (100)	156 (100)
Treatment status				
Ongoing	146 (44.4)	137 (41.6)	146 (44.4)	24 (15.4)
Withdrawn from treatment	183 (55.6)	192 (58.4)	183 (55.6)	132 (84.6)
Withdrawn from treatment reason				
Death	15 (4.6)	16 (4.9)	15 (4.6)	7 (4.5)
Adverse event	29 (8.8)	49 (14.9)	26 (7.9)	16 (10.3)
Symptomatic deterioration	10 (3.0)	9 (2.7)	9 (2.7)	4 (2.6)
Progressive disease	111 (33.7)	100 (30.4)	98 (29.8)	93 (59.6)
Physician decision	3 (0.9)	4 (1.2)	3 (0.9)	4 (2.6)
Withdrawal by subject	15 (4.6)	14 (4.3)	14 (4.3)	7 (4.5)
Other	0	0	0	1 (0.6)

3.2.2 IMbrave150 effectiveness

At time of writing, data were available for the clinical cut-off date (CCOD) 29th Aug 2019. Median follow-up at CCOD was 8.6 months (CS Section B.2.6) (Cheng 2019).[1]

3.2.2.1 IMbrave150 OS

At time of writing, data were available from the first interim OS analysis (clinical cut-off date 29th Aug 2019) (CS Section B.2.6). Deaths from any cause occurred in n=96 (28.6%) in the A+B group, and n=65 (39.4%) in the sorafenib group.

Median OS was not estimable in the A+B group (

Table 7). The Kaplan-Meier (KM) estimated median OS for the sorafenib group was 13.2 months (95% CI 10.4, NE) (CS Section B.2.6). There was a statistically significant advantage in OS for A+B over sorafenib, hazard ratio (HR) (stratified) 0.58 (95% CI 0.42, 0.79) log-rank *p*=0.0006 (CS Section B.2.6)(Cheng *et al.*2019[1])(Galle *et al.*[2]).

Table 7: IMbrave150 Overall Survival, first interim analysis, in the ITT population (adapted from CS Section B.2.6.1 Table 8 and B.2.10 and Cheng 2019[1] and Galle 2020[2])

	A+B n=336	**Sorafenib n=165**
Patients with event, n (%)	96 (28.6)	65 (39.4)
Median time to event, months (95% CI)	NE NE	13.2 (10.4, NE)
Stratified HR (95% CI) log-rank p value	0.58 (0.42, 0.79) *p*=0.0006	
Patients remaining event free at 6 months, % (95% CI)	84.8 (80.9, 88.7)	72.0 (65.1, 79.4)
Patients remaining event free at 12 months, % (95% CI)	67.2 (61.3, 73.1)	54.6 (45.2, 64.0)
Death due to progressive disease (safety evaluable population), n	71	51
Death due to AE (safety evaluable population), n	15	9
Other or unknown cause of death (safety evaluable population), n	7	4
Subgroups		
Geographic region (Asia excluding Japan), n/N	34/133	27/68
HR unstratified (95%CI)	0.53 (0.32,0.87)	
Geographic region (rest of world), n/N	62/230	38/97
HR unstratified (95%CI)	0.65 (0.44, 0.98)	
Macrovascular invasion and/or extrahepatic spread (presence), n/N	84/258	56/120
HR unstratified (95%CI)	0.55 (0.39, 0.77)	
Macrovascular invasion and/or extrahepatic spread (absence) n/N	12/78	9/45
HR unstratified (95%CI)	0.69 (0.29,1.65)	
Baseline AFP (<400) n/N	45/210	36/104
HR unstratified (95%CI)	0.52 (0.34, 0.81)	
Baseline AFP (≥ 400 ng/mL) n/N	51/126	29/61
HR unstratified (95%CI)	0.68 (0.43, 1.08)	
ECOG Performance Status 0, n/N	50/209	31/103
HR unstratified (95%CI)	0.67 (0.43, 1.06)	
ECOG Performance Status 1, n/N	46/127	34/62
HR unstratified (95%CI)	0.51 (0.33, 0.80)	

NE= not estimable

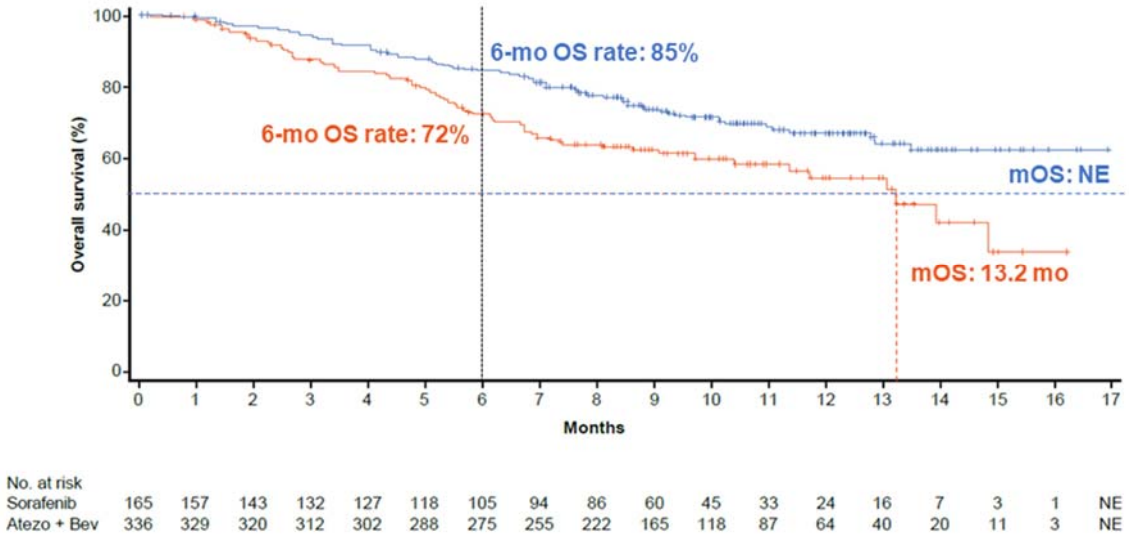
The OS event-free rate was higher for A+B than for sorafenib at 6 months (84.8% A+B, 72.0% sorafenib), and at 12 months (67.2% A+B, 54.6% sorafenib) (CS Section B.2.6).

Subgroups were investigated for OS; however, the study was not powered to detect differences in the individual subgroups, and so results should be interpreted with caution (CS Section B.2.7). Across subgroups (

Table 7) there was a trend for a survival advantage for A+B over sorafenib (CS Appendix E).

The OS KM survival function within IMbrave150 is shown in Figure 2.

Figure 2: KM survival function for OS (reproduced from Figure 4 of the CS)



3.2.2.2 IMbrave150 PFS

At time of writing, data were available from the final PFS analysis based on IRF-assessment per RECIST v1.1 (the co-primary endpoint) (clinical cut-off date 29th Aug 2019).

Events counted were the first documented disease progression (IRF-assessment per RECIST v1.1), or death due to any cause, whichever occurred first. Events occurred in 197 (58.6%) patients in the A+B group, and n=109 (66.1%) patients in the sorafenib group (

Table 8).

The KM estimated median PFS was 6.8 months (95% CI 5.6, 8.3) in the A+B group, and 4.3 months (95%CI 4.0, 5.6) for the sorafenib group (CS Section B.2.6.1).

There was a statistically significant advantage in PFS for A+B over sorafenib, HR (stratified) 0.59 (95% CI 0.47, 0.76) log-rank $p<0.0001$ (CS Section B.2.6.1).

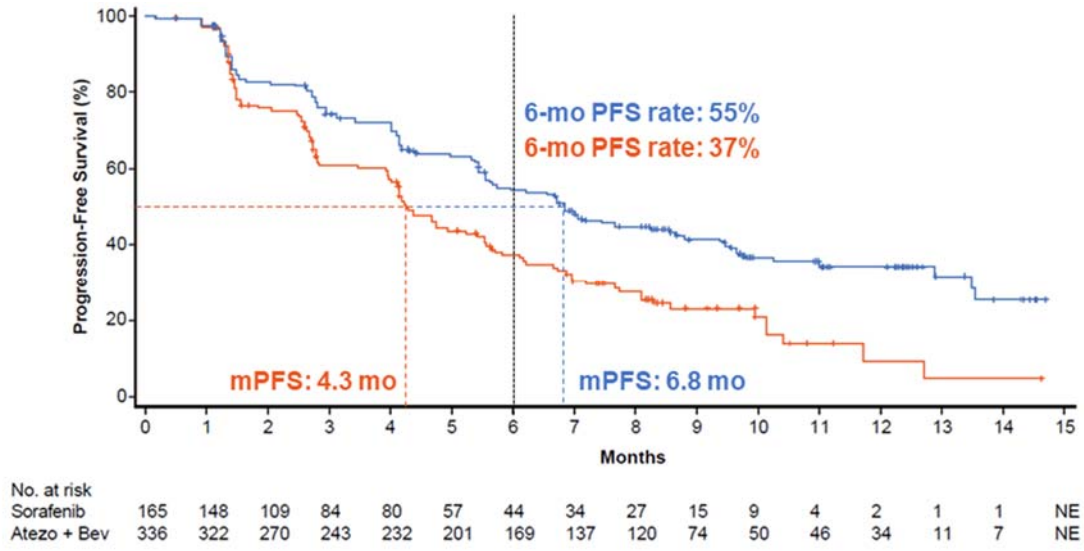
Table 8: IMbrave150 PFS IRF per RECIST v1.1 ITT population (from CS Section B.2.6.1 Table 9 and Cheng *et al.* 2019[1] and Galle *et al.* 2020[2])

	A+B n=336	**Sorafenib n=165**
Patients with event, n (%)	197 (58.6)	109 (66.1)
Earliest contributing event, (%) Death Disease progression	 34 163	 29 80
Median time to event, months (95% CI)	6.8 (5.7, 8.3)	4.3 (4.0, 5.6)
Stratified HR (95% CI) log-rank p value	0.59 (0.47, 0.76) p<0.0001	
Patients remaining event free at 6 months, % (95% CI)	54.5 (49.1, 60.0)	37.2 (29.0, 45.3)
Patients remaining event free at 12 months, % (95% CI)	34.0 (27.9, 40.1)	9.2 (0.0, 18.5)

The PFS event-free rate was higher for A+B than for sorafenib at 6 months (54.5% A+B, 37.2% sorafenib), and at 12 months (34.0% A+B, 9.2% sorafenib) (CS Section B.2.6).

The PFS KM) survival function within IMbrave150 is shown in Figure 3.

Figure 3: KM survival function for PFS (reproduced from Figure 5 of the CS)



For the secondary endpoint of PFS, measured by IRF-assessed HCC mRECIST, there were events in 199/336 (59.2%) patients in the A+B group, and 111/165 (67.3%) patients in the sorafenib group. Median PFS was 6.8 months (95% CI 5.7, 8.3) in the A+B group, and 4.3 months (95% CI 4.0, 5.6) in

the sorafenib group, stratified HR=0.59 (95%CI 0.47, 0.76) $p<0.0001$ (Cheng 2019)[1] (Galle 2020)[2] (CS Section B.2.6.2).

The secondary endpoint of TTP as measured by IRF-assessment RECIST v1.1, estimated median time to progression of 8.6 months (95% CI: 6.8, 9.9) in the A+B group, and 5.6 months (95% CI: 4.2, 7.7) in the sorafenib group. The stratified HR was 0.70 (95% CI 0.53, 0.92) (CS Section B.2.6.2) $p=0.0105$ (CSR).[3]

Subgroups were investigated for PFS measured by IRF-assessed RECIST v1.1; however, the study was not powered to detect differences in the individual subgroups, and so results should be interpreted with caution (CS Section B.2.7). Across subgroups there was a trend for a survival advantage for A+B over sorafenib (CS Appendix E).

3.2.2.3 IMbrave150 response rate

Objective response rate (IRF-assessment per RECIST v1.1) was measured from the ITT population with measurable disease at baseline, A+B n=326, sorafenib n=159 (CS Section B.2.6.2).

Non-measurable lesions were defined according to RECIST v1.1 as *"Non-measurable tumour lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥10 mm but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques"* (CSR).[3]

In the A+B group there were n=89 (27.3%) responders, of whom n=18 were assessed as having a complete response (Table 9). In the sorafenib group, there were n=19 (11.9%) responders. None of the sorafenib group were assessed as having a complete response (CS Section B.2.6.2). (Cheng 2019).[1] There was a statistically significant difference in confirmed ORR favouring A+B 15.4% (95% CI 7.9, 22.8) $p<0.0001$.

ORR measured by IRF-assessed mRECIST was measured from a population of n=325 A+B, and n=158 sorafenib. There was a statistically significant difference in this measure of ORR favouring A+B 19.9% (95% CI 12.1, 27.8) $p<0.0001$, based on a response rate of 33.2% in the A+B group, and 13.3% in the sorafenib group (CS Section B.2.6.2) (Cheng 2019[1]).

DoR was defined as time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first). DoR based on IRF-assessment per RECIST v1.1 was measured in the responders from ORR (IRF-assessment per RECIST v1.1), n=89 in the A+B group, and n=19 in the sorafenib group. There was a significant difference between groups favouring A+B in DoR, stratified HR=0.23 (95% CI 0.08, 0.70) *p*=0.0051 (Table 9).

Table 9: IMbrave150 Confirmed ORR (and DOR) based on IRF-assessment per RECIST v1.1 (Population with measurable disease at baseline) (adapted from CS Section B.2.6.2 Table 10 and Table 12 and Cheng 2019)[1]

	A+B n=326	**Sorafenib n=159**
ORR		
Responders, n (%) 95% CI	89 (27.3) (22.5, 32.5)	19 (11.9) (7.4, 18.0)
Stratified analysis Difference in ORR, % (95% CI) Odds ratio (95% CI) Cochran-Mantel-Haenszel p value	 15.4 (7.9, 22.8) 2.90 (1.68, 5.01) *p*<0.0001	
Complete response, n (%) 95% CI	18 (5.5) (3.3, 8.6)	0 (0.0, 2.3)
Partial response, n (%) 95% CI	71 (21.8) (17.4, 26.7)	19 (11.9) (7.4, 18.0)
Stable disease, n (%) 95% CI	151 (46.3) (40.8, 51.9)	69 (43.4) (35.6, 51.5)
Progressive disease, n (%) 95% CI	64 (19.6) (15.5, 24.4)	39 (24.5) (18.1, 32.0)
Not evaluable, n (%) Missing, n (%)	8 (2.5) 14 (4.3)	14 (8.8) 18 (11.3)
DoR		
Patients with event, n/N (%)	12/89 (13.5)	6/19 (31.6)
Median time to event, months (95% CI)	NE (NE)	6.3 (4.7, NE)
Stratified HR (95% CI) log-rank p value	0.23 (0.08, 0.70) *p*=0.0051	

3.2.2.4 IMbrave150 HRQoL

Baseline HRQoL data were taken from the PRO-evaluable population, that is, patients who had baseline data and at least one other PRO assessment (A+B n=309; sorafenib n=145) (Galle 2020).[2]

While on study treatment, patients completed the EORTC QLQ-C30 and EORTC QLQ HCC18 questionnaires every 3 weeks, and following treatment discontinuation, every 3 months (Galle 2020).[2]

Questionnaire completion rates were high (≥92%) (Galle 2020)[2] until Cycle 17, which was beyond the time the majority of participants remained on allocated study treatment (CS Section B.2.6.3).

The EORTC QLQ-C30 measures global health/quality of life; patient functioning (measured on aspects of physical, emotional, role, cognitive, and social); symptom scales (fatigue, nausea/vomiting, pain); and single items of (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties).[12,14] The EORTC QLQ-HCC18 is measured on six symptom scales (fatigue, body image, jaundice, nutrition, fevers, and pain), and two single items (abdominal swelling and sexual interest).[13, 15]

Time to deterioration was measured using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30) (CS Section B.2.3), measured on scales of 0-100. EORTC QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al.1993; Fitzsimmons et al. 1999).[12, 14] Clinically meaningful deterioration was defined as decrease from baseline of at least ten points (Osoba 1998).[16]

There was a longer time to deterioration for A+B over sorafenib in three of the domains measured. Median time to deterioration for patient-reported physical functioning was 13.1 months (95% CI 9.7, not estimable) in the A+B group, and 4.9 months (95% CI 3.5, 6.2) in the sorafenib group, HR (stratified) 0.53 (95% CI 0.39, 0.73) (Galle 2020)[2] (CSR)[3] (CS Section B.2.3).

The median time to deterioration for the role functioning domain was 9.1 months (95% CI 6.5, NE) in the A+B group, and 3.6 months (95% CI 2.2, 6.0) in the sorafenib group, HR (stratified) 0.62 (95% CI 0.46, 0.84) (Galle 2020)[2] (CS Section B.2.3).

Median time to deterioration in the Global Health Status/quality of life domain was 11.2 months (95% CI 6.0, NE) in the A+B group, and 3.6 months (95% CI 3.0, 7.0) in the sorafenib group, HR (stratified) 0.63 (95% CI 0.46, 0.85) (CS Section B.2.3). (Galle 2020)[2]

Exploratory endpoints were from EORTC-QLQ-C30 and EORTC QLQ-HCC18.[13, 15] Time to deterioration in symptoms was delayed for A+B over sorafenib, stratified HRs: Diarrhoea (QLQ-C30) HR=0.23 (95% CI 0.16, 0.34); Pain (QLQ-C30) HR=0.46 (95% CI 0.34, 0.62); Pain (QLQ-HCC18) HR=0.65 (95% CI 0.46, 0.92); Appetite Loss (QLQ-C30) HR=0.57 (95% CI 0.40, 0.81); Fatigue (QLQ-HCC18) HR=0.60 (95% CI 0.45, 0.80); Fatigue (QLQ-C30) HR=0.61 (95% CI 0.46, 0.81); Jaundice (QLQ-HCC18) HR=0.76 (95% CI 0.55, 1.07) (CS Section B.2.6.3) (Galle 2020).[2]

[redacted]

[redacted]

EQ-5D-5L were collected in IMbrave150 directly from the patients. These data were collected at "*each scheduled study visit prior to administration of study drug and prior to any other study assessment(s). During survival follow-up the EQ-5D-5L questionnaire was completed every 3 months (for 1 year) following disease progression or treatment discontinuation, unless the patient withdrew consent, whichever occurred first.*" Details on the use of EQ-5D-5L data are presented in Section 4.2.5.4 of this report.

3.2.3 Adverse events

The CS reference pack included the draft summary of product characteristics (SmPC) for atezolizumab. The following table showing frequency of adverse events with atezolizumab combination therapy is adapted from the draft SmPC (***[redacted]10).

[redacted]**10:**

[redacted]

Adverse events of special interest for atezolizumab (CS Appendix F) are immune-mediated reactions, including immune-mediated hepatitis, hypo/hyperthyroidism, pneumonitis and rash; and autoimmune haemolytic anaemia; and infusion-related reaction. Adverse events of special interest for bevacizumab (CS Appendix F) include bleeding, thromboembolism, congestive heart failure, gastrointestinal (GI)

perforation, fistula/Abscess (non-GI), Posterior Reversible Encephalopathy Syndrome, proteinuria and wound healing complications.

3.2.3.1 IMbrave150 AEs

Table 11: IMbrave150 AE overview (copied from CS Section B.2.10 Table 22)

n, (%)	**A+B n=329**	**Sorafenib n=156**
Total number of patients with at least one AE	323 (98.2)	154 (98.7)
Total number of AEs, n	3058	1299
Total number of patients with at least one		
AE related to any study treatment	276 (83.9)	147 (94.2)
AE related to atezolizumab	252 (76.6)	n/a
AE related to bevacizumab	241 (73.3)	n/a
Grade 3–4 AE	186 (56.5)	86 (55.1)
Treatment-related Grade 3–4 AE	117 (35.6)	71 (45.5)
Grade 5 AE	15 (4.6)	9 (5.8)
Treatment-related Grade 5 AE	6 (1.8)	1 (0.6)
Serious AE	125 (38.0)	48 (30.8)
Related serious AE	56 (17.0)	24 (15.4)
AE leading to withdrawal from any study treatment	51 (15.5)	16 (10.3)
AE leading to withdrawal from atezolizumab	28 (8.5)	0
AE leading to withdrawal from bevacizumab	48 (14.6)	0
AE leading to withdrawal from A+B	23 (7.0)	0
AE leading to dose modification/interruption of any study treatment	163 (49.5)	95 (60.9)
AE leading to dose interruption of any study treatment	163 (49.5)	64 941.0)
AE leading to dose reduction of sorafenib	n/a	58 (37.2)

The majority of patients experienced at least one AE of any severity (Table 11), 98.2% of the A+B group, and 98.7% of the sorafenib group (CS Section B.2.10). The most common AEs in the A+B group were hypertension (29.8%), fatigue (20.4%) and proteinuria (20.1%) (CS Section B.2.10). The most common AEs in the sorafenib group were diarrhoea (49.4%), palmar-plantar erythrodysaesthesia (hand-foot) syndrome (48.1%), decreased appetite (24.4%) and hypertension (24.4%) (CS Section B.2.10).

Grade 5 AEs were experienced by n=15 (4.6%) of the A+B group, of which n=6 (1.8%) were considered by the investigator to be related to treatment (CS Section B.2.10). Grade 5 AEs were experienced by n=9 (5.8%) of the sorafenib group, of which n=1 (0.6%) were considered by the investigator to be related to treatment (CS Section B.2.10).

[redacted]

Grade 3/4 AEs were experienced by n=186 (56.5) of the A+B group, of which n=117 (35.6%) were considered by the investigator to be related to treatment (CS Section B.2.10).(Cheng 2019).[1] The most

common Grade 3 or 4 AEs in the A+B group were hypertension (10.3%), aspartate aminotransferase increased (4.3%) and proteinuria (2.7%) (CS Section B.2.10).

Serious AEs (SAEs) were defined as events meeting one of the following criteria: fatal; life-threatening; requiring or prolonging hospitalisation; resulting in persistent or significant disability/incapacity; congenital anomaly/birth defect caused by mother's exposure to treatment; or is significant in the investigator's judgment (CS Clarification response A3). Treatment-related serious AEs (SAEs) were experienced by n=56 (17.0%) of the A+B group (CS Section B.2.10). The most common SAEs were gastrointestinal haemorrhage (2.4%), oesophageal varices haemorrhage (2.4%), and pyrexia (2.1%) (CS Section B.2.10).

Grade 3 or 4 AEs were experienced by n=86 (55.1%) of the sorafenib group, of which n=71 (45.5%) were considered by the investigator to be related to treatment (CS Section B.2.10).(Cheng 2019)[1]

The most common Grade 3 or 4 AEs in the sorafenib group were hypertension (9.0%), palmar-plantar erythrodysaesthesia syndrome (8.3%), diarrhoea (3.8%), decreased appetite (3.8%), hypophosphataemia (3.2%), fatigue (3.2%), aspartate aminotransferase increased (2.6%), blood bilirubin increased (2.6%) and rash (2.6%) (CS Section B.2.10).

Treatment-related SAEs were experienced by n=24 (15.4%) of the sorafenib group (CS Section B.2.10). The most common SAEs were gastrointestinal haemorrhage (1.9%), oesophageal varices haemorrhage (0.6%), and pyrexia (1.3%) (CS Section B.2.10).

There was a higher rate of discontinuations for AEs for A+B than for sorafenib; however, there was a shorter duration of study treatment in the sorafenib group due to progression or death. In the safety evaluable population, median study-treatment duration was 7.4 months for atezolizumab, 6.9 months for bevacizumab, and 2.8 months for sorafenib (CS Section B.2.10). AEs led to withdrawal from study treatment for n=51 (15.5%) in the A+B group, and n=16 (10.3%) in the sorafenib group (CS Section B.2.10).

The most common AE leading to discontinuation in the A+B group was oesophageal varices haemorrhage (1.2%) (CS Section B.2.10). All other AEs leading to discontinuation occurred in <1% of patients, in either treatment arm (CS Section B.2.10).

AEs led to dose interruption in n=163 (49.5%) of the A+B group, and to dose interruption or modification in n=95 (60.9%) of the sorafenib group (CS Section B.2.10).

The most common AEs leading to dose interruption in the A+B arm were proteinuria (6.7%), hypertension (6.1%), aspartate aminotransferase increased (5.2%), alanine aminotransferase increased (3.3%), hyperthyroidism (2.7%), platelet count decreased (2.4%), and pyrexia (2.4%) (CS Section B.2.10). The most common AEs leading to dose reduction/interruption in the sorafenib group were palmar-plantar erythrodysaesthesia syndrome (17.3%), diarrhoea (10.9%), blood bilirubin increased (5.1%), fatigue (4.5%), decreased appetite (4.5%), hypertension (3.8%), platelet count decreased (3.2%), pyrexia (3.2%), vomiting (3.2%), rash (3.2%), aspartate aminotransferase increased (3.2%), ascites (2.6%), nausea (2.6%), abdominal pain (2.6%), alanine aminotransferase increased (2.6%), and asthenia (2.6%) (CS Section B.2.10).

3.2.3.2 Study GO30140 (NCT02715531) AEs

AE data were available from the Phase Ib GO30140 study (NCT02715531) (CS Appendix F) (clinical trials gov).[17]

Participants in this study had advanced or metastatic and/or unresectable HCC who had received no prior systemic treatment (clinical trials gov).[17] The experimental group comparing A+B (n=60) to atezolizumab monotherapy (n=58) (CS Appendix F) administered atezolizumab at a dose of 1200 mg q3w, and for the combination group bevacizumab at 15 mg/kg q3w (clinical trials gov).[17]

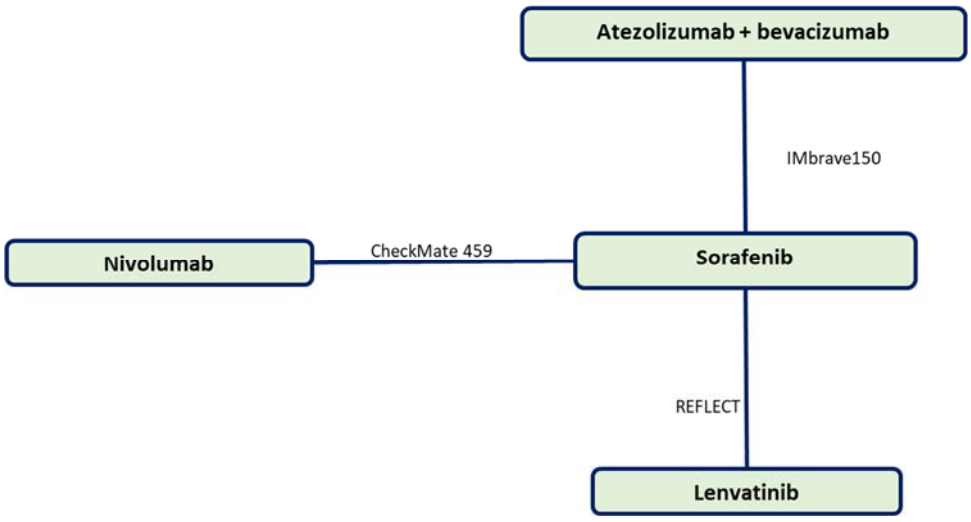
In the A+B arm (median study treatment duration 5.21 months), 95.0% experienced at least one AE of any grade (CS Appendix F). In the atezolizumab monotherapy arm (median study treatment duration 1.61 months), 89.7% experienced at least one AE of any grade (CS Appendix F). No fatal AEs were reported in either group. Grade 3/4 AEs were experienced by 36.7% of the A+B arm, and in 13.8% of the atezolizumab monotherapy arm (CS Appendix F). In the A+B arm the more common grade 3+ events were hypertension (5.0%) and proteinuria (3.3%) (CS Appendix F).

3.3 Critique of trial identified and relevant in the indirect comparison

The company presented the evidence network in

Figure 4.

Figure 4: Evidence network for level 1 comparators reporting OS and PFS (reproduced from Figure 7 of the CS)



REFLECT compared lenvatinib (n=478) with sorafenib (n=476) in first-line treatment of patients with unresectable HCC (Kudo 2018).[18] The primary endpoint was OS, which was assessed for non-inferiority of lenvatinib, and also for superiority over sorafenib. (Kudo 2018).[18] Sorafenib was administered orally at a dose of 400mg BID (as for IMbrave150). Lenvatinib was administered orally at a dose of 12 mg/daily (for bodyweight ≥60 kg) or 8 mg/daily (for bodyweight <60 kg). (Kudo 2018)[18]

Eligibility criteria for REFLECT included: unresectable HCC (confirmed histologically, cytologically, or clinically in accordance with American Association for the Study of Liver Diseases criteria); no previous systemic therapy for HCC; one or more measurable target lesions; Barcelona Clinic Liver Cancer stage B or C; Child-Pugh class A; and ECOG PS 0 or 1. (Kudo 2018)[18]

REFLECT was generally at low risk of bias, apart from being open-label (

Table 12). Baseline characteristics were generally well balanced between treatment groups; however, there was a higher frequency of hepatitis C aetiology in the sorafenib group, and a higher frequency of patients in the lower AFP category in the sorafenib group, than in the lenvatinib group (Kudo 2018).[18]

Table 12: QA of REFLECT (adapted from CS Appendix D and Kudo 2018)[18]

	QA by CS (CS Appendix D.3)	QA by ERG
Was the allocation sequence adequately generated?	Low - The randomisation sequence was generated by an independent statistician by the system vendor, and the investigators obtained the randomisation assignments from the system directly	Low Independent statistician via IVRS
Was the concealment of treatment allocation adequate?	Low - Allocation of treatment group was done with an interactive voice–web response system, which also functioned as the allocation concealment method	Low IVRS
Was knowledge of the allocated interventions adequately prevented from participants and personnel	High – open label	High open label
Was knowledge of the allocated interventions adequately prevented from outcome assessors	Low - Although open label design masked independent assessments were conducted	Mixed High risk for investigator assessed endpoints and PROs. Low risk for "Post-hoc exploratory tumour assessments using mRECIST and RECIST version 1.1" which were conducted by "masked central independent imaging review" [18]
Were incomplete outcome data adequately addressed?	Low - Primary and secondary endpoints reported	Low ITT analyses for effectiveness outcomes
Are reports of the study free of suggestion of selective outcome reporting?	Low - The study reports outcomes of interest as specified	Low The effectiveness, safety and HRQoL outcomes in the protocol (clinicaltrials.gov/ct2/show/NCT01761266) are reported in Kudo 2018[18]

Baseline characteristics of REFLECT and IMbrave150 were similar in terms of age, sex, ECOG PS, BCLC stage, and participants were Child Pugh class A in both trials (

Table 13). REFLECT had a higher proportion of patients from the Asia-Pacific region than IMbrave150, and the trials different differentiations of AFP category imply lower AFP in the REFLECT population than in IMbrave150. (Kudo 2018)[18]

Table 13: Baseline characteristics IMbrave150 and REFLECT (adapted from CS Table 5, and Kudo 2018[18])

	IMbrave150	**IMbrave150**	**REFLECT**	**REFLECT**
	A+B n=336	**Sorafenib n=165**	**Sorafenib n=476**	**Lenvatinib n=478**
Median age, years	64.0	66.0	62.0 (range 22-88)	63.0 (range 20-88)
Male, n (%)	227 (82.4)	137 (83.0)	401 (84%)	405 (85%)
Geographic region	Asia (excl. Japan) 133 (39.6) Rest of World 203 (60.4)	Asia (excl. Japan) 68 (41.2) Rest of World 97 (58.8)	Asia-Pacific 319 (67%) Western 157 (33%)	Asia-Pacific 321 (67%) Western 157 (33%)
ECOG PS, n (%)				
0	209 (62.2)	103 (62.4)	301 (63%)	304 (64%)
1	127 (37.8)	62 (37.6)	175 (37%)	174 (36%)
BCLC stage at study entry, n (%)				
A1	5 (1.5)	3 (1.8)	0	0
A4	3 (0.9)	3 (1.8)	0	0
B	52 (15.5)	26 (15.8)	92 (19%)	104 (22%)
C	276 (82.1)	133 (80.6)	384 (81%)	374 (78%)
Aetiology of HCC				
HBV	164 (48.8)	76 (46.1)	228 (48%)	251 (53%)
HCV	72 (21.4)	36 (21.8)	126 (26%)	91 (19%)
Non-viral	100 (29.8)	53 (32.1)	122 (26%)*	136 (28%)*
Extrahepatic spread and/or macrovascular invasion present at study entry Yes	258 (76.8)	120 (72.7)	336 (71%)	329 (69%)
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
Weight n(%)				
<60kg	72 (21%)	41 (25%)	146 (31%)	153 (32%)
≥60kg	264 (79%)	124 (75%)	330 (69%)	325 (68%)
AFP category at screening, ng/mL	<400 210 (62.5) ≥400 126 (37.5)	<400 104 (63.0) ≥400 61 (37.0)	<200 286 (60%) ≥200 187 (39%)	<200 255 (53%) ≥200 222 (46%)

*alcohol/other/unknown

The median time on study treatment was 5.7 months for patients in the lenvatinib group and 3.7 months for the sorafenib group (Kudo 2018).[18] For information, this was relatively similar to the sorafenib group of IMbrave150, for whom median time on study treatment was 2.8 months (CS Section B.2.10).

Median overall survival in the lenvatinib group was 13·6 months (95% CI 12·1, 14·9), and in the sorafenib group median OS was 12·3 months (95% CI 10·4, 13·9). Lenvatinib was non-inferior to sorafenib (HR 0·92, 95% CI 0·79, 1·06) with respect to a non-inferiority margin of 1.08. (Kudo *et al.* 2018)[18]

For information, the sorafenib group in REFLECT had a similar median OS (12.3 months), to the sorafenib group in IMbrave150 which had an estimated median OS of 13.2 months.[1] The REFLECT authors speculated that the sorafenib group had a higher median OS than in previous trials partly due to the subsequent therapy after discontinuation of study treatment, with post-sorafenib treatment of systemic treatment (39% patients) or non-systemic treatment (27% patients).[18] In IMbrave150, 44.2% of the sorafenib group had subsequent HCC systemic therapy (CS Section B.2.3.3).

Lenvatinib showed statistically significant advantages over sorafenib for the secondary endpoints PFS, TTP and ORR. Median PFS assessed by masked review according to RECIST 1.1, was 7·3 months (95% CI 5·6, 7·5) for the lenvatinib group, and 3·6 months (95%CI 3·6, 3·9) for the sorafenib group. The HR for PFS was 0·65 (0·56, 0·77) $p<0·0001$. TTP assessed by masked review according to RECIST 1.1 produced a HR 0·61 (0·51, 0·72) $p<0·0001$, median TTP was 7·4 months (95%CI 7.3, 9.1) for the lenvatinib group, and 3·7 months (95% CI 3·6, 5.4) for the sorafenib group. Objective response rate assessed by masked review according to RECIST 1.1 produced a HR of 3.34 (2.17, 5.14) $p<0·0001$ was 18.8% (95% CI 15.3, 22.3) for the lenvatinib group, and 6.5% (95% CI 4.3, 8.7) for the sorafenib group.[18]

AEs were experienced by 99% of patients in each group, and grade 3+ adverse events were experienced by 67% of the sorafenib group, and 75% of the lenvatinib group.[18]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

In the absence of head-to head evidence for all treatments of interest, a network meta-analysis (NMA) was performed to estimate the relative treatment effect of lenvatinib and sorafenib compared to A+B. An SLR identified twenty-three studies (including IMbrave150), which formed a connected network for inclusion into the SLR (Figure 6 of the CS). After exclusions, three studies were included in the base case evidence network: IMbrave150 (A+B vs. sorafenib),[19] REFLECT (lenvatinib vs. sorafenib)[20] and CheckMate 459 (nivolumab vs. sorafenib).[21] In response to clarification question A9, the company

justified the inclusion of nivolumab by stating that "*when the NMA was being developed, it was unclear whether Nivolumab would be approved or not. In addition, the NMA covers all systemic therapies with information published in 1L in HCC since the sorafenib approval in 2007*." In addition, the company provided results showing that removing CheckMate 459 (an RCT of nivolumab versus sorafenib) from the network did not affect the results.

The base case NMAs were conducted using a Bayesian random effects model of log HRs. The HR for OS was 0.63 (95% Credible Interval [CrI]: 0.32, 1.25) for A+B compared to lenvatinib, and 0.58 (95% CrI: 0.35, 0.99) for A+B compared to sorafenib. Hence, there was uncertainty whether A+B is superior to lenvatinib; the ERG assumes that the posterior probability that A+B is superior to lenvatinib reported in Table 18 of the CS is an error; the probability the A+B is superior to lenvatinib is given as 0.94 in Table 18 of the CS and yet the upper limit of the 95% CrI is 1.25. The HR for PFS was 0.91 (95% CrI: 0.23, 3.65) for A+B compared with lenvatinib, and 0.59 (95% CrI: 0.23, 1.58) for A+B compared with sorafenib.

There are no feedback loops in the evidence base so it is not possible to formally assess inconsistency in the evidence base (i.e. there is only direct evidence specific to each trial). Biased estimates of treatment effect would arise if there was an imbalance in the distribution of treatment effect modifiers across studies comparing difference pairs of treatments.

With limited studies, it was necessary to incorporate external information about the between-study standard deviation in the random effects models. However, the company did not report posterior estimates of the between-study standard deviations. Furthermore, the company only reported summaries of the mean of the random effects distributions, although it is recommended to also present summaries of predictive distributions of effects in new studies. In addition, posterior predictive distributions of effects in new studies are what is recommended to use to characterise uncertainty in economic models to account for heterogeneity.

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, and it is inconsistent to generate the lenvatinib survival function using hazard ratios; this is discussed further in Section 4.3.4.2.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work related to clinical effectiveness was undertaken by the ERG.

3.6 Conclusions of the clinical effectiveness section

The ERG believes that no RCTs of A+B meeting the inclusion criteria of the final scope have been missed by the CS. The search for clinical evidence reflected the decision problem set out in the final scope, but did not include best supportive care (BSC), and had a broader selection of active comparators. The ERG believes this allowed identification of relevant sorafenib and lenvatinib studies. Clinical effectiveness evidence was available from one RCT, IMbrave150, that compared A+B to sorafenib. Safety data were available from IMbrave150 and the phase 1b study GO30140.

IMbrave150 randomised adults with adults with locally advanced or metastatic and/or unresectable hepatocellular carcinoma (HCC), who had no previous systemic treatment for HCC, to A+B (atezolizumab 1200 mg IV infusions every three weeks, and bevacizumab 15 mg/kg every three weeks, n=336) or sorafenib (400 mg orally twice per day n=165). The quality of the IMbrave150 RCT was assessed using well-established and recognised criteria. IMbrave150 was an open label trial, but was of otherwise good methodological quality.

According to clinical advice, the demographics of the IMbrave150 trial population were broadly representative of the UK population eligible for A+B treatment, although there are a smaller proportion of Asian patients, and patients with an aetiology of hepatitis B in the UK than in the trial, and more patients in the UK would have aetiology of alcohol or non-alcohol related fatty liver disease, than in the trial. Prior treatments in IMbrave150 were broadly similar to a UK population, although prior radiotherapy is rare in the UK, whereas 10% of trial patients received prior radiotherapy.

OS was statistically significantly higher for A+B, than for sorafenib HR (stratified) 0.58 (95% CI 0.42, 0.79) p=0.0006. Median OS for A+B was not estimable (NE), median OS for sorafenib was 13.2 months (95% confidence interval [CI] 10.4, NE). There was a statistically significant treatment group difference for PFS HR (stratified) 0.59 (95% CI 0.47, 0.76) p<0.0001. Median PFS was 6.8 months (95% CI 5.6, 8.3) in the A+B group, and 4.3 months (95% CI 4.0, 5.6) for the sorafenib group.

The majority of A+B treated patients experienced at least one AE of any severity (98.2%). The most common AEs of any grade in the A+B group were hypertension (29.8), fatigue (20.4%) and proteinuria (20.1%). The most common NCI-CTCAE Grade 3 or 4 AEs experienced in the A+B group were hypertension (10.3%), aspartate aminotransferase increased (4.3%) and proteinuria (2.7%). The most common Grade 3 or 4 AEs in the sorafenib group were hypertension (9.0%), palmar-plantar erythrodysaesthesia syndrome (8.3%), diarrhoea (3.8%), decreased appetite (3.8%),

hypophosphataemia (3.2%), fatigue (3.2%), aspartate aminotransferase increased (2.6%), blood bilirubin increased (2.6%) and rash (2.6%).

There was a longer time to deterioration for A+B over sorafenib in three of the HRQoL domains measured: Global Health Status/quality of life; physical functioning; and role functioning.

4 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company to support the cost effectiveness of A+B for untreated locally advanced metastatic HCC patients.

The company present a systematic literature review (SLR) of relevant economic evidence and then present a *de novo* economic evaluation. The company also provided an electronic version of their economic model developed in Microsoft Excel.

4.1 ERG's comment on company's review of cost-effectiveness evidence

4.1.1 Objective of cost effectiveness review

The company performed systematic literature searches for: i) published cost-effectiveness studies in the first-line treatment of patients with unresectable HCC (CS Appendix G); ii) HRQoL and health state utilities in patients with HCC in the first-line setting (CS Appendix H), and iii) cost and healthcare resource use of first-line HCC (CS Appendix I)**.**

An extensive range of databases, HTA conference websites and grey literature sources were searched by the company. In the economic SLR search (CS Appendix G), the following sources were searched: MEDLINE [via Ovid], MEDLINE In-Process, Epub Ahead of Print and Daily [via Ovid], Embase [via Ovid], Cochrane Database of Systematic Reviews [via EBM Reviews], Cochrane Central Register of Controlled Trials [via EBM Reviews], The Health Technology Assessment [via EBM Reviews]), and Database of Abstracts of Reviews of Effects [via EBM Reviews], American College of Physicians [via EBM Reviews], Cochrane Clinical Answers [via EBM Reviews], Cochrane Methodology Register [via EBM Reviews], and EconLit [via Ovid] in October 2019. The ERG notes that in contrast to the clinical effectiveness SLR (Section 3.1), the company did not attempt to update the search so eligible studies post 2019 would be excluded in the review.

A comprehensive list of intervention and comparator search terms combined with an economic search filter was applied in the company's MEDLINE and Embase search. As seen in the EconLit database search, a more sensitive strategy and approach would be obtained by combining HCC terms with an economic search filter (CS Appendix G Table 18, page 54). However, the ERG acknowledges that the number of records retrieved may have been unmanageable for the company to review.

Supplementary searches by the company include searching several conference abstract websites in the last three years (2017-2019): American Society of Clinical Oncology, European Society for Medical Oncology, American Association for Cancer Research, International Society for Pharmacoeconomics

and Outcomes Research: European Meeting, Health Technology Assessment International, Society for Medical Decision Making (Appendix G, page 89).

The company also searched several HTA websites for previous technology submissions: NICE, the Scottish Medicines Consortium, the All Wales Medicines Strategy Group, the Pharmaceutical Benefits Advisory Committee, the Canadian Agency for Drugs and Technologies in Health including the pan-Canadian Oncology Drug Review.

Supplementary searches in several HTA databases and the Research Papers in Economics (via EconPapers) were undertaken by the company for published literature. The ERG notes that there is significant overlap of coverage of content indexed in the International Network of Agencies for Health Technology Assessment, the University of York Centre for Reviews and Dissemination and the National Institute for Health Research HTA database. However, the ERG is unable to confirm whether the searches were applied consistently across these sources as the search strategies were absent in the CS. In addition, the company's purpose for searching Google Scholar was not explicitly stated.

For the HRQoL and health state utilities studies searches, the company searched the same sources as in the cost-effectiveness review but with the inclusion of two web sources: the EuroQol website and the University of Sheffield ScHARRHUD database (CS Appendix H). The company's searches were comprehensive (HCC population combined with a recognized and published HSU search filter) with no observable and consequential errors in the strategies.

In the economic, cost and healthcare resource and humanistic burden searches of first-line HCC (CS Appendix I), the company searched the same sources as those reported in the cost-effectiveness SLR. The company's searches were comprehensive (HCC population combined with cost and resource terms) with no observable and consequential errors in the strategies.

4.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion criteria used by the company to facilitate study selection are presented in

Table 14. The ERG considers the inclusion criteria to be appropriate to capture recent and relevant published evidence.

Table 14: Inclusion/exclusion criteria for the company's economic review

Category	Inclusion criteria
Population (P)	Aligned with patients enrolled in the IMbrave150 study: Age: adults aged ≥18 years Gender: any Race: any Disease: patients with locally advanced or metastatic HCC who have received no prior systemic therapy for HCC
Intervention (I)	A+B
Comparators (C)	Any pharmacological intervention whether single agent or in a combination including sorafenib, nivolumab, TACE, radiotherapy, other investigational agents, and others being examined in ongoing studies.
Outcome (O)	Cost-effectiveness estimates (costs, health outcomes, and ICERs)
Study design	- Cost-effectiveness analysis - Cost-utility analysis - Cost-minimisation analysis - Cost-benefit analysis
Language	English language publications or non-English language publications with an English abstract.

HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; TACE, transarterial chemoembolisation

4.1.3 Findings of the cost effectiveness review

Fifty-seven studies were identified that were relevant to the decision problem (27 full publications, 22 conference abstracts, and eight previous HTA submissions); however, none of these included A+B as an option. The majority of studies were cost-utility analyses reporting incremental cost per QALY gained with most of the models using a Markov approach. Table 30 in the CS summarises the evidence found in the 27 full publications identified.

4.1.4 Conclusions of the cost effectiveness review

As the company's searches did not identify any relevant studies of A+B, they developed a *de novo* health economic model.

4.2 **Summary of the company's submitted economic evaluation**

4.2.1 Population

The population included in the company's health economic analysis reflects adult patients with locally advanced or metastatic HCC who have not received prior systemic treatment. The modelled patient characteristics reflect those of the full patient population within the IMbrave150 study[1] with a mean age of 63.4 years, and 18% of the population are assumed to be female. The mean baseline body weight was 71.7 kg and the mean baseline body surface area was 1.82 m^2.

In response to clarification question B2, the company provided separate subgroup analyses for the IMbrave150 population excluding Asia (except for Japanese patients).

4.2.2 Interventions and comparators

Atezolizumab is provided at a fixed dose of 1200mg whereas bevacizumab is given at a weight-based dose of 15mg/kg. Both drugs are administered intravenously every 3 weeks until loss of clinical benefit, disease progression, or unacceptable toxicity. Both atezolizumab and bevacizumab can be given separately if patients became intolerant to the other intervention.

In line with the final NICE scope, the included comparators were sorafenib and lenvatinib. Both are administered orally at a fixed dose of 400 mg, twice daily, for sorafenib, and a weight-dependant dose, once daily, for lenvatinib (12 mg for patients ≥60 kg and 8 mg for patients <60 kg).

4.2.3 Perspective, time horizon and discounting

The base case model adopts an NHS and Personal Social Services (PSS) perspective. The base case model uses a 20-year time horizon; shorter time horizons were included in the company's scenario analyses. Both costs and quality-adjusted life years (QALYs) were discounted at 3.5% per annum as recommended by NICE.[22]

4.2.4 Model structure

As part of its submission to NICE, the company developed a fully executable partitioned survival model (PSM) in Microsoft® Excel that included three mutually exclusive and exhaustive health states: (i) progression-free survival (PFS); (ii) progressed disease (PD); and (iii) death. The model is similar to that of other treatments for advanced/metastatic cancer previously submitted to NICE as part of the STA process. The model structure is shown in

Figure 5. A weekly cycle length was used, and half-cycle correction was implemented.

Figure 5: The company's model structure (reproduced from Figure 9 of the CS)

All patients are assumed to enter the model in the progression-free health state and remain there until progression or death. As with a standard PSM, the health state membership for A+B and sorafenib is inferred via survival functions fitted to the IMbrave150 study PFS and OS data. As lenvatinib was not included in IMbrave150, the company undertook an NMA to estimate HRs for PFS and OS for patients treated with lenvatinib compared to those treated with A+B. The lenvatinib HRs were then applied to the A+B PFS and OS functions.

Parametric survival models were fitted to time to treatment discontinuation (TTD) data from the IMbrave150 study for atezolizumab, bevacizumab and sorafenib separately. The company assumed that time to treatment discontinuation on lenvatinib is equivalent to time to progression as TTD was not explicitly reported in REFLECT.[18]

4.2.5 Evidence used to inform the company's model parameters

The main groups of the company's base case model parameters and the evidence sources used to populate these are summarised in

Table 15. These are discussed in further detail in the subsequent sections.

Table 15: Evidence sources used to inform model parameters in the company's base case

Parameter type	Parameter	Source(s)
Time-to-event parameters	PFS – A+B	The IMbrave150 study[1]
	PFS – sorafenib	The IMbrave150 study[1]
	PFS – lenvatinib	HRs from the company's ITC[23] applied to A+B data
	OS – A+B	The IMbrave150 study[1]
	OS – sorafenib	The IMbrave150 study[1]
	OS – lenvatinib	HRs from the company's ITC[23] applied to A+B data
	TTD – A+B	The IMbrave150 study[1]
	TTD – sorafenib	The IMbrave150 study[1]
	TTD – lenvatinib	Assumed the same as the lenvatinib PFS
Adverse event rate (grade 3+ experienced by at least 5% of the patients)	A+B	The IMbrave150 study[1]
	Sorafenib	The IMbrave150 study[1]
	Lenvatinib	The REFLECT study[18]
HRQoL	Two sets of health utilities (on/off treatment), each has four utility values defined in terms of proximity to death	EQ-5D-5L questionnaires collected in The IMbrave150 study[1]
Resource use and costs	A+B acquisition cost (including PAS)	The CS by Roche[23]
	Sorafenib and lenvatinib acquisition cost (list prices)	The British National Formulary (BNF)[24]
	Drug dosing as planned per individual characteristics in the IMbrave150 study	The IMbrave150 study[1]
	A+B subsequent therapy %	Assumed to be 0%
	Sorafenib subsequent therapy %	Assumed that 44.2% of patients on sorafenib who went on to receive subsequent therapy, would only receive regorafenib
	Lenvatinib subsequent therapy %	Assumed to be 0%

	Subsequent therapy acquisition costs (list prices)	The British National Formulary (BNF)[24]
	Drug administration costs	NHS Reference costs 2018-19[25]
	Medical resource use for progression-free and progressed health states	Expert elicitation
	Adverse event costs	NHS Reference costs 2018-19[25]
	End of life care costs	Costs were sourced from Georghiou and Bardsley[26] and inflated using PSSRU HCHS indices[27]

A+B, atezolizumab plus bevacizumab; CS, company's submission; HCHS, Hospital and Community Health Services; HR, hazard ratio; HRQoL, health-related quality of life; ITC, indirect treatment comparison; NHS, National Health Services; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; PSSRU, Personal Social Services Research Unit; TTD, time to treatment discontinuation

4.2.5.1 Treatment effectiveness and extrapolation in the base case

The data for the full ITT population from IMbrave150 were used to model PFS and OS independently in the A+B and sorafenib arms in the company's base case. At the time of data cut-off (29th August, 2019), 71% of the patients on A+B were still alive compared to 61% on sorafenib. Approximately 41% of patients were still progression-free on A+B compared to 34% on sorafenib.

The company followed guidance for fitting and selecting survival models based on NICE Decision Support Unit Technical Support Document 14.

The company investigated the use of a range of parametric survival models: exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions fitted independently to each treatment arm. The company also incorporated in the model the option of using the KM survival functions directly from IMbrave150 and extrapolating beyond the duration of follow-up using one of the six aforementioned models.

4.2.5.1.1 Estimating OS

The company considered independently fitted parametric distributions (i.e. for each treatment arm separately) in the economic model. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values were compared to assess relative goodness-of-fit to the observed data. For the fit to the A+B OS data, the generalised gamma was the distribution with the lowest BIC, although there was little to distinguish between this and log-normal and log-logistic distributions as the difference in BIC values were below 2. For the fit to the sorafenib OS data, the log-normal was the distribution with

the lowest BIC, although there was little to distinguish between this and the log-logistic and generalised gamma distributions as the difference in BIC values were below 2. There was positive, but not strong evidence that the generalised gamma distribution was a better fit to the observed data than the Weibull distribution.

AIC and BIC values are presented in Table 16; the company chose the exponential distribution for its base case. The clinical advisor to the ERG did not rule out that the hazard of a death could be constant throughout the patient's life and proportional for each treatment.

Table 16: Goodness-of-fit of parametric models to OS data observed in IMbrave150

	A+B		Sorafenib		Summed Totals*	
Parametric distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	547.24 (6)	551.06 (5)	325.09 (5)	328.20 (5)	872.33 (6)	879.26 (5)
Weibull	538.43 (4)	546.06 (4)	322.36 (4)	328.57 (4)	860.79 (4)	874.63 (4)
Log-normal	534.56 (2)	542.19 (2)	**320.63 (1)**	**326.84 (1)**	**855.19 (1)**	**869.03 (1)**
Generalised Gamma	**534.55 (1)**	**542.19 (1)**	322.26 (3)	331.57 (3)	856.81 (2)	873.76 (3)
Log-logistic	536.30 (3)	543.93 (3)	320.88 (2)	327.09 (2)	857.18 (3)	871.02 (2)
Gompertz	544.90 (5)	552.53 (6)	325.28 (6)	331.49 6)	870.18 (5)	884.02 (6)

*Calculated by the ERG. Rounding errors may be present
Numbers in brackets provide the rank ordering of each distribution. The best-fitting distribution to the observed data is highlighted in bold.

An HR of [redacted] (Table 18 of the CS) was applied to the selected A+B parametric model to estimate OS survival function for lenvatinib. The company stated that they deemed it appropriate to apply HRs from the NMA to an accelerated failure time model. The ERG does not agree that a HR should be applied to models that are not proportional hazard models. Furthermore, the ERG does not accept that it is appropriate to use hazard ratios to estimate a survival function or to estimate the effect of lenvatinib from a different model to one estimating the effect of sorafenib. These issues are discussed in Section 4.3.4.2.

The company then assessed the tails of the parametric distributions for their clinical plausibility using judgements from six UK clinicians. The aim was for clinicians to ensure that the survival functions estimated in the populations defined by the IMbrave50 and REFLECT studies were consistent with what is seen in UK clinical practice. The clinicians concluded "*that only the exponential model and the Generalised Gamma model represented clinically plausible estimates, as the remaining four models*

projected a higher OS for sorafenib than lenvatinib, which is not aligned with the REFLECT trial clinical data which showed lenvatinib OS to be non-inferior to sorafenib." (page 99 of the CS)

The clinicians considered that the exponential model represented the most realistic survival rates at 12, 24, 36, 48 and 60 months for both sorafenib and lenvatinib but noted that it might under-estimate the long-term proportion of patients surviving when treated with A+B. The company selected the exponential distribution in its base case and explored the impact of a generalised gamma distribution in scenario analyses.

Figure 6 presents the selected exponential models for the three treatment arms and their respective KM survival functions which have been marked academic-in-confidence by the company. Comparisons between IMbrave150 and REFLECT represent a naïve indirect comparison. The full range of parametric models are presented in Figure 16 of the CS for A+B and in Figure 17 of the CS for sorafenib.

In response to clarification question A7, as described in Section 3.4, the company also fitted a first-degree Bayesian fixed effect fractional polynomial NMA to allow for time-varying HRs for OS. The impact of this model was explored as a scenario analysis.

Additionally, the company's economic model offered the option to maintain the treatment effect until a user-selected time point after which the probabilities of death on A+B are assumed to be the same as that of sorafenib.

Figure 6: The company's base case OS extrapolation (adapted from the company's model)

4.2.5.1.2 Estimating PFS

The company fitted six parametric models to the A+B and sorafenib data independently. AIC and BIC values were compared to assess relative goodness-of-fit to the observed data and are presented in Table 17. The log-normal distribution produced the smallest BIC (highlighted) for both treatment arms and was the model used in the company base case.

Table 17: Goodness-of-fit of parametric models to PFS data observed in IMbrave150

	A+B		Sorafenib		Summed Totals*	
Parametric distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	841.34 (5)	845.16 (5)	381.53 (6)	384.64 (6)	1222.87 (6)	1229.80 (5)
Weibull	836.71 (4)	844.34 (4)	370.46 (4)	376.67 (4)	1207.17 (4)	1221.01 (4)
Log-normal	815.65 (2)	**823.28 (1)**	**360.21 (1)**	**366.42 (1)**	1175.86 (2)	**1189.70 (1)**
Generalised Gamma	**813.19 (1)**	824.64 (2)	362.19 (2)	371.50 (2)	**1175.38 (1)**	1196.14 (2)
Log-logistic	825.06 (3)	832.70 (3)	364.08 (3)	370.29 (3)	1189.14 (3)	1202.99 (3)
Gompertz	843.11 (6)	850.75 (6)	378.92 (5)	385.14 (5)	1222.03 (5)	1235.89 (6)

*Calculated by the ERG. Rounding errors may be present

Numbers in brackets provide the rank ordering of each distribution. The best-fitting distribution to the observed data is highlighted in bold.

As for OS, the company assessed the tails of the parametric distributions for their clinical plausibility based on judgments from six UK clinicians "*to ensure the curves represented UK clinical practice*." (page 106 CS) In addition, the company assessed whether the fitted lenvatinib PFS survival function is in line with the lenvatinib KM survival function from REFLECT. The company ruled out the generalised gamma distribution as it exceeded the OS exponential models selected in the company's base case. The company excluded the Weibull and Gompertz distributions because they did not produce "*a lenvatinib PFS curve in line with lenvatinib KM data from the REFLECT trial*."

In addition to being the model that represented the observed PFS survival functions best, the log-normal distribution was selected by the company for its base case as it was used in the lenvatinib submission to extrapolate PFS. The impact of using exponential and log-logistic distributions was explored in scenario analyses.

Figure 7 presents the fitted lognormal models for the three treatment arms and their respective KM survival functions.

An HR of [redacted] (Table 21 of the CS) was applied to all of the A+B parametric models to estimate the PFS survival function for lenvatinib. The company stated that they deemed it appropriate to apply HRs

from the NMA to an accelerated failure time model. The ERG does not agree that a hazard ratio should be applied to models that are not proportional hazard models. Furthermore, the ERG does not accept that it is appropriate to use hazard ratios to estimate a survival function or to estimate the effect of lenvatinib from a different model to one estimating the effect of sorafenib. These issues are discussed in Section 4.3.4.2.

Additionally, the company's economic model includes an option to maintain treatment effect for A+B until a user-selected time point after which the probabilities of progression associated with sorafenib were applied.

Figure 7: The company's base case PFS extrapolation (adapted from the company's model)

4.2.5.2 Duration of treatment

In IMbrave150 patients were allowed to receive atezolizumab until loss of clinical benefit or unmanageable toxicity meaning that patients could receive the regimen following disease progression. Treatment duration data were collected in the IMbrave150 study and TTD KM survival functions were estimated separately for each of atezolizumab, bevacizumab and sorafenib. TTD data were not available for lenvatinib; hence, the company assumed that the PFS survival function for lenvatinib was a proxy for the TTD survival function of lenvatinib in the economic model.

Based on the KM survival function at 16 months 30% of patients on A+B were still receiving at least one of the two treatments compared to 12% of patients on sorafenib. The company decided that the TTD data were relatively complete and used parametric survival modelling only to extrapolate beyond 14 months. In a similar approach to that used for OS and PFS, the company fitted the six parametric distributions to TTD data. Goodness-of-fit statistics are provided in Table 38 of the CS.

Based on AIC and BIC, the generalised gamma and Weibull distributions represented the data best for both atezolizumab and bevacizumab. For sorafenib, the lognormal distribution gave the best fit based on BIC. However, the company stated that the '*Weibull, Log-Normal and Log-Logistic provided poor fit to the observed data and very long unrealistic tails. The Gompertz and Exponential reported the same values. Therefore, the Exponential parametric distribution is used in the base case for the extrapolation of TTD, because whilst it does not provide the best statistical fit, it does demonstrate the best visual fit out of all potential distributions, as well as clinical validity.*'

The company decided that because "*the observed TTD data for Atezo+Bev and sorafenib in IMbrave150 are relatively complete, it was deemed appropriate to use the TTD KM curve followed by the Exponential distribution, as this was the parametric model showing the best visual fit to the observed data, for atezolizumab, bevacizumab and sorafenib*." The company used the KM survival function, without allowing for uncertainty, for the first 14 months, and extrapolated beyond that timepoint using an exponential distribution. The time point of 14 months was said to '*to ensure robustness in terms of patient numbers at risk*' although no comment was made on why 14 months was deemed preferable to 13 or 15 months but this value could be changed in the model.

Figure 8 shows the base case TTD survival functions used in the company's economic model.

Figure 8: The company's base case TTD estimation

4.2.5.3 Treatment safety

In the model, AEs were associated with additional costs. All grade 3, 4 or 5 AEs were included in the model where at least 5% of patients experienced them in at least one of A+B and sorafenib within

IMbrave150. The clinical advice provided to the ERG indicated that there were no known, rare, AEs that would have a high clinical burden or large cost.

For lenvatinib the rates within the lenvatinib NICE submission[28] were used which represents a naïve indirect comparison. In its response to clarification question A5, the company acknowledged that the '*rate of lenvatinib adverse events would be lower as the length of follow-up in the REFLECT trial is much longer than in the IMbrave150 trial. This would result in a more accurate rate of lenvatinib adverse events, as the current naive indirect comparison relies on the assumption that time doesn't determine the relative frequency of adverse events, as well as comparability of populations.*' This approach is therefore unfavourable to lenvatinib.

The incidence rates used to inform the economic model are presented in Table 39 of the CS. The company applied the impact of adverse events on costs for each cycle to patients still on treatment after converting the incidence rates into weekly probabilities. The costs per AE are discussed in Section 4.2.5.5.5.

In the base case the company did not include the impact of AEs on health-related quality of life (HRQoL) assuming that any disutility due to an AE was already captured in the EQ-5D data collected in the study and incorporating extra disutility could be considered double counting. In the clarification response (question A6), the company stated that '*A regression analysis was carried out to determine if the EQ-5D questionnaire was measured whilst an adverse event was active. The results show that adverse events did have a statistically significant impact on the EQ-5D measurement (-0.04 - this is for any AE), but this impact is not considered clinically significant.*' Thus, it appears that the EQ-5D did capture AEs that were being experienced when the questionnaire was completed, which was on treatment administration and three-monthly thereafter for one year. The average duration of adverse events was provided in Table 3 of the clarification response to indicate the likelihood that AEs would be experienced when the EQ-5D was completed. The company also presented a scenario analysis where an additional disutility was applied; this had little impact on the model results.

4.2.5.4 Health related quality of life

The SLR carried out by the company identified 23 unique HRQoL studies relevant to the technology appraisal; however, only 15 of these were presented as full publications. The company identified only two publications that fully met NICE reference case, where utilities were derived directly from patients using the preferred EQ-5D tool and the UK tariff was used to value the resulting health states; however, both were hepatitis C virus (HCV)-related. The first study (Chong *et al.*) reported an EQ-5D-3L utility value of 0.65 [95% CI 0.44-0.86] and was collected from 15 HCV-related HCC patients.[29] The second

publication was an HTA report examining health benefits of antiviral therapy for mild chronic HCV and sourced the utility value (0.45) for HCC from a prospective multi-centre UK trial.[30, 31]

HRQoL data were collected using the EQ-5D-5L within IMbrave150 at each visit prior to treatment administration (i.e. every 3 weeks) or at each follow-up visit every 3 months for one year following disease progression or treatment discontinuation. The Van Hout *et al*[32] crosswalk mapping algorithm was applied to these data to estimate the corresponding EQ-5D-3L values as recommended in the NICE position statement on the EQ-5D-5L.[32, 33]

The company explored four different approaches to include the mapped mean utility values in the model: i) an on/off treatment approach where three sets of utility scores were derived for patients on A+B, patients on sorafenib, and patients off treatment; ii) a pre- and post-progression approach where also three sets of utility scores were derived for progressed-free patients on A+B, progressed-free patients on sorafenib, and progressed patients; iii) a pre- and post-progression including AE disutility approach where the analysis performed in ii included a covariate for grade 3 or higher AEs; and iv) a proximity to death approach where a mixed linear model was constructed using treatment status and proximity to death as covariates.

The utility values produced by the four approaches are presented in Table 18. The time to death approach was used in the company's base case assuming that it was the most relevant to the population under consideration reflecting the decline in HRQoL of cancer patients as they approach death.

It is noted that a utility value of 0.78 would be associated with that of a population aged 60 years. In response to clarification question B34 the company stated that "*Assuming a higher utility for patients on treatment more than 15 weeks from death than for the IMbrave 150 age-matched general population is a plausible assumption. This is because the age-matched general population are also composed of observations that are closer to the death of the patient, which have a negative impact on the general utility level (the brazier regression does not include any time coefficients that may control for this effect). This means that a patient who is more than 15 weeks from death can have a higher utility than the general population average.*" The ERG was not convinced that, on average, this would be correct.

Additionally, the ERG noted that in the time to death approach, the difference in midpoint utility estimate increases as the proximity to death increases, with a large difference when a patient is within 5 weeks of death. The ERG does not know whether this is a true finding, although comments that the duration of time associated with this utility is relatively small.

Table 18: Utility values produced by each of the four methods

Category	Utility (95% CI)	Utility (95% CI)
On/Off treatment		
On treatment: A+B	0.79 (0.777, 0.803)	
On treatment: Sorafenib	0.75 (0.734, 0.771)	
Off treatment: Pooled	0.68 (0.666, 0.702)	
Pre- and post-progression		
Pre-progression: A+B	0.78 (0.765, 0.792)	
Pre-progression: Sorafenib	0.77 (0.749, 0.786)	
Post-progression: Pooled	0.74 (0.723, 0.753)	
Pre- and post-progression including AE disutility		
Pre-progression: A+B	0.74 (0.728, 0.764)	
Pre-progression: Sorafenib	0.72 (0.695, 0.744)	
Post-progression: Pooled	0.72 (0.700, 0.735)	
Time to death approach	On Treatment	Off Treatment
≤ 5 weeks before death	0.64 (0.573, 0.713)	0.37 (0.303, 0.430)
> 5 & ≤ 15 weeks before death	0.73 (0.702, 0.759)	0.62 (0.572, 0.658)
> 15 & ≤ 30 weeks before death	0.78 (0.750, 0.805)	0.66 (0.585, 0.722)
> 30 weeks before death	0.80 (0.763, 0.834)	0.71 (0.607, 0.816)

The company's model additionally allowed for a scenario analysis adjusting utilities according to age as per Ara and Brazier,[34] although this did not have a marked impact on the ICER.

4.2.5.5 Resources and costs

The costs and resource use included in the base case model comprised: drug acquisition costs; post-discontinuation subsequent therapy costs; drug administration costs; medical resource use (MRU) associated with progression status; AE costs; and end of life care costs. These are discussed in the following sections.

4.2.5.5.1 Drug acquisition costs

Atezolizumab is available as a 1,200 mg vial at a price of £3807.69 ([redacted] when incorporating the Patient Access Scheme (PAS) discount). Bevacizumab is available in two vial sizes; 400 mg and 100 mg vial at a cost of £924 and £242.66 respectively ([redacted] and [redacted] when incorporating the PAS discount). The costs for A+B are planned to be incurred every 3 weeks. Sorafenib is available in packs of 112 x 200 mg tablets (this represents a supply of 28-days) at a cost of £3,576.56, whereas lenvatinib is supplied as a package of 30 x 4 mg capsules (this represents 15 days' supply for patients weighing <60kg and 10 days' supply otherwise) at a cost of £1,437. As requested by NICE, the company's economic model did not include the PAS discounts for either sorafenib or lenvatinib. The results when these PASs are included are contained in a confidential appendix. All costs were sourced from the British National Formulary (BNF).[24]

Atezolizumab has a fixed IV dose of 1,200 mg, whereas bevacizumab is weight-based, being administered as 15 mg/kg every 3-week cycle. Sorafenib is administered at a dose of 400 mg twice daily, whilst lenvatinib is given at a dose of 8 mg if a patient weighs less than 60kg or 12 mg once daily otherwise.

Following the clarification process, three dosing approaches were considered in the company's economic model.

(i) The base case approach used individual patient characteristics to calculate the planned dose per patient and compute the mean dose per the whole IMbrave150 population

(ii) The second approach used the mean actual dose, considering patient characteristics (mainly weight) and the dose intensity observed in the in IMbrave150. ([redacted] (atezolizumab), [redacted] (bevacizumab), and [redacted] (sorafenib) as reported in the CSR [3]

(iii) The third approach (planned mean dose) replicated the second approach but assumed 100% relative dose intensity (RDI).

For atezolizumab, the base case approach yielded a mean of one vial per patient every three weeks - the third approach provided the same result. Applying the RDI of atezolizumab in the actual dosing approach gave a mean of 0.951 vials every three weeks. The ERG believes that using the reduced RDI (approach (ii) is reasonable given that dose modification was not allowed in the study.

For bevacizumab, the base case approach generated a mean planned dose of 1076.16 mg (2.43 400 mg vials plus 1.49 100 mg vials). Applying the RDI of bevacizumab generated an actual dose of 1047.34 mg (2.27 400 mg vials plus 1.39 100 mg vials) in the second approach. The third approach used the mean weight of IMbrave150 cohort (71.74 kg) and resulted in the same dose as in the first approach albeit using a slightly different number of vials (2 400 mg vials plus 3 100 mg vials) as calculations were done on the mean dose requirements and not individual dose requirements.

For sorafenib, the base case approach yielded a mean daily dose of 400 mg which was the same as in the third approach. In the second approach the actual mean dose was 335.2 mg when the sorafenib-specific RDI was applied. For sorafenib the RDI approach may be less reasonable as it assumes that all reductions in RDI were due to planned reductions rather than patients not being able, or forgetting, to take a tablet intermittently.

For lenvatinib, the base case approach resulted in a planned mean daily dose of 11.10 mg (equating to 2.77 tablets), which was the same as for as the second approach given that the company assumed an RDI of 1 for lenvatinib. However, the third approach considered only the mean weight of the population,

which was above 60 kg, leading to a mean daily dose of 12 mg equivalent to 3 tablets per day. When asked about the assumption of an RDI of 1 for lenvatinib, clarification question B26, the company responded that that the "*RDI for lenvatinib was assumed to be 1.00 in the absence of trial information. The RDI for lenvatinib can easily be updated to equal the sorafenib RDI (83.8%), or alternatively a value of 88% can be applied, sourced from Kudo et al*.[18]" As with sorafenib, using an RDI-based approach for lenvatinib would be less reasonable than for vial-based treatments such as atezolizumab.

The company assumed that 5% of patients shared vials although did not provide justification for this value. In addition, the company assumed that a vial would not be opened if the patient requires less than 5% of its content, in line with NHSE bevacizumab dose banding table. Clinical advice to the ERG suggested that this was appropriate. Scenario analyses undertaken by the company suggested that the ICER would increase slightly if these assumptions were removed. Given the small increase in the ICER these issues have not been explored further by the ERG.

Table 19 summarises the total drug acquisition costs for all the comparators every 3-week cycle using the three dosing approaches and assuming that a vial would not be opened if a patient required less than 5% of it. Drug acquisition costs were applied to the TTD distributions every three weeks for A+B and were adjusted for sorafenib and lenvatinib to be applied every week.

Table 19: Drug acquisition costs every 3-weeks using the three dosing approaches considered in the company's model and assuming a vial would not be opened if a patient required less than 5% of it

Comparator	Approach 1: Planned individual patient dosing (base case)	Approach 2: Actual mean dosing	Approach 3: Planned mean dosing
Atezolizumab	[redacted]	[redacted]	[redacted]
Bevacizumab (5% vial sharing)	[redacted]	[redacted]	[redacted]
Bevacizumab (no vial sharing)	[redacted]	[redacted]*	[redacted]
Sorafenib	£2,682.42	£2,247.87	£2,682.42
Lenvatinib	£2,790.81	£2,790.81	£3,017.70

* The resulting discrepancy (£609.13 being lower than £609.28 with vial sharing) is because the company did not amend all model sheet cells following their response to clarification questions

4.2.5.5.2 Post-discontinuation subsequent therapy costs

Upon discontinuation of A+B or sorafenib, patients in IMbrave50 were allowed to receive a range of subsequent therapies. These are presented in Appendix 1. A summary of these subsequent-line therapies is provided in Table 20.

Table 20: Subsequent therapies observed in IMbrave150 (reproduced from Table 44 of the CS)

	Sorafenib n=165	A+B n=336
Number of patients with at least 1 systemic treatment	[redacted]	[redacted]
Therapy type		
Tyrosine Kinase Inhibitors	[redacted]	[redacted]
Angiogenesis Inhibitors	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Others	[redacted]	[redacted]

Currently, the only recommended second-line therapy in the UK is regorafenib, which is only recommended for use after sorafenib. This means that patients on A+B would not receive expensive subsequent therapies, and those who received sorafenib would only receive regorafenib. Therefore, IMbrave150 was not in line with UK clinical practice. The company performed a Cox regression analysis to examine how subsequent therapies administered in IMbrave150 affected the OS on both treatment arms. The detailed results produced by the Cox regression analyses were not provided by the company. It is unclear whether there was sufficient follow-up post-progression or events within the study for differences in underlying survival rates to be observed. Consequently, the survival functions estimated from the data in IMbrave50 might not reflect the survival functions that might have been estimated if patients had been treated according to UK clinical practice.

The company initially explored three approaches to account for second-line treatment in the economic model. The OS models were not changed for any change in assumptions related to subsequent treatment. Regorafenib is supplied as 84 x 40 mg tablets at a cost of £3,744 at list price. It is administered at a dose of 160 mg once daily for 21 days every 28-day treatment cycle as was assumed to be taken for 13.3 weeks based on IMbrave150 data. The PAS for regorafenib is excluded from the company analysis, as recommended by NICE, but included in the confidential appendix by the ERG. Within all approaches, costs of post-discontinuation subsequent therapies were applied as a one-off cost for patients once they discontinue their first-line treatment.

The first approach, which was used in the company's base case, assumed that the 44.2% of patients on sorafenib who received subsequent systemic treatments would receive regorafenib (and thus incur its associated costs), whereas patients on either A+B or lenvatinib were assumed to receive no further treatments and incur no further treatment costs. This led to a second-line treatment cost of £6,745 for patients on sorafenib.

The second approach altered the proportion of patients who received sorafenib arm who would get regorafenib to be 20%, based on advice provided to the company by clinical experts at an advisory board. This led to a second-line treatment cost for sorafenib patients of £3,052.

The third approach used the IMbrave150 study data to account for immunotherapy (nivolumab) and tyrosine kinase inhibitors (TKIs) administered as a second-line option. For A+B, 1.2% of patients received nivolumab and 18.8% received TKIs; for sorafenib 18.8% of patients received nivolumab and 26.1% received TKIs. TKIs were costed as the weighted mean of sorafenib, lenvatinib, and regorafenib. Further details are provided in Tables 46 and 47 in the CS, although there is a typographical error in Table 46 of the CS as the duration of TKI therapy after A+B was 14.4 weeks, not 13.4 weeks (Clarification response C5). This approach resulted in subsequent treatment acquisition costs of £1,641 for A+B and £6,152 for sorafenib. Patients on lenvatinib were assumed to have the same costs of subsequent therapies as for patients on A+B; based on the use of subsequent treatments in REFLECT, which provides information relating to the relative efficacy of sorafenib and lenvatinib, this assumption appears reasonable.

Following the clarification process the company undertook, at the request of the ERG, three further analyses relating to the use of subsequent treatments. These were: assuming that the full costs for subsequent treatments were costed for both A+B and sorafenib; using statistical analyses to adjust OS removing treatments not recommended in England, and not including costs for subsequent treatments. The ERG acknowledges that the third scenario is not plausible but might provide useful information to the committee in understanding the sensitivity of the ICER to assumptions related to subsequent treatments. The ERG comments that no details were provided on the statistical methods used to adjust OS for removing treatments and as such, the results of this analysis should be treated with caution.

4.2.5.5.3 Drug administration costs

The costs for IV administration were sourced from NHS Reference costs 2018-19 (codes SB14Z (for A+B) and SB15Z (for nivolumab, when costed). Oral chemotherapy delivery costs were sourced for sorafenib, lenvatinib (code SB11Z).[25] A+B administration costs (£371) were applied every three weeks

while nivolumab was provided every two weeks with administration costs of £332. For sorafenib and lenvatinib, administration costs (£195) were applied only once in the first cycle of the model.

4.2.5.5.4 Medical resource use associated with progression status

MRU costs included visits to different health care practitioners, various laboratory tests and scans, and hospitalisation. In the company's base case MRU data were estimated based on consultation with 6 UK clinical experts treating patients with HCC. Experts gave their views on the proportion of patients in need of a resource with the associated frequency per month required. MRU varies according to progression status, and MRU was estimated separately for progression-free and progressed health states. Table 50 of the CS shows the elicited values for MRU in the company's base case.

The company explored a scenario analysis where MRU estimates were sourced from lenvatinib NICE submission[28] as was shown in Table 51 of the CS. Unit costs were estimated using NHS Reference costs 2018-19[35] and Personal Social Services Research Unit 2018-19[27] as presented in Table 49 in the CS. Table 21 summarises the MRU weekly costs applied in the economic model.

Table 21: MRU costs per week used in the economic model

Approach	Base case (company's expert elicitation)	Scenario (lenvatinib submission data)
MRU costs/week for progression-free patients	£129.91	£137.52
MRU costs/week for progressed patients	£131.07	£299.14

4.2.5.5.5 AE costs

The rationale and frequency for the AEs included in the model is provided in Section 4.2.5.2.3. The costs associated with each AE were primarily sourced from NHS Reference Costs 2018-19.[25] Table 53 in the CS presents the costs associated with the management of a single occurrence for each AE. This resulted in mean weekly costs of £4.68, £11.62 and £19.10 to resolve AEs associated with A+B, sorafenib, and lenvatinib, respectively for patients whilst on treatment. No costs were considered for AEs after cessation of the first treatment, which is likely to underestimate AEs.

4.2.5.5.6 End of life care costs

End of life care costs (health and social care costs) for HCC patients reported within Georghiou and Bardsley were considered in line with lenvatinib NICE submission.[26, 28] Table 52 in the CS provides the itemised costs and the inflated costs that were derived for the model using Hospital and Community Health Services (HCHS) indices.[36] This resulted in a one-off cost of £8,186 which was applied for all patients upon entry to the 'Dead' health state.

4.2.6 Model validation and face validity check

The company validated its economic model using two approaches. The first was via *"a number of UK clinical experts"* who validated the key aspects and assumptions of the model. The second approach was an internal quality control of the company's model by a third party.

4.2.7 Cost effectiveness results

Following the clarification process, the company submitted a revised version of the model that included updated estimates of the cost-effectiveness of A+B. All the results presented in this section and in Section 4.2.8 use the revised model and include the increased PAS for atezolizumab and the list prices for sorafenib, lenvatinib, and regorafenib. A confidential appendix presents the same results with the PAS considered for all of the five treatments.

Table 22 shows the results of the company's base case analysis based on the deterministic and probabilistic versions of the company's revised model. The probabilistic sensitivity analyses (PSA) results are based on 2,000 iterations run by the ERG. Based on the probabilistic version of the model, A+B is expected to generate [redacted] additional QALYs at an additional cost of [redacted], compared with sorafenib. The corresponding ICER is £22,419 per QALY gained. The deterministic version of the company's model produces a similar ICER of £22,267 per QALY gained. A+B dominated lenvatinib, generating [redacted] more QALYs at a reduced cost of [redacted] based on the probabilistic version of the model.

Figure 9 shows the cost-effectiveness acceptability curves (CEAC) for all three options based on a re-run of the PSA by the ERG. Figure 10 plots the PSA results on the cost-effectiveness plane.

Figure 11 presents the resultant survival functions for the first 12 years of the company's model.

Table 22: Company's base case results

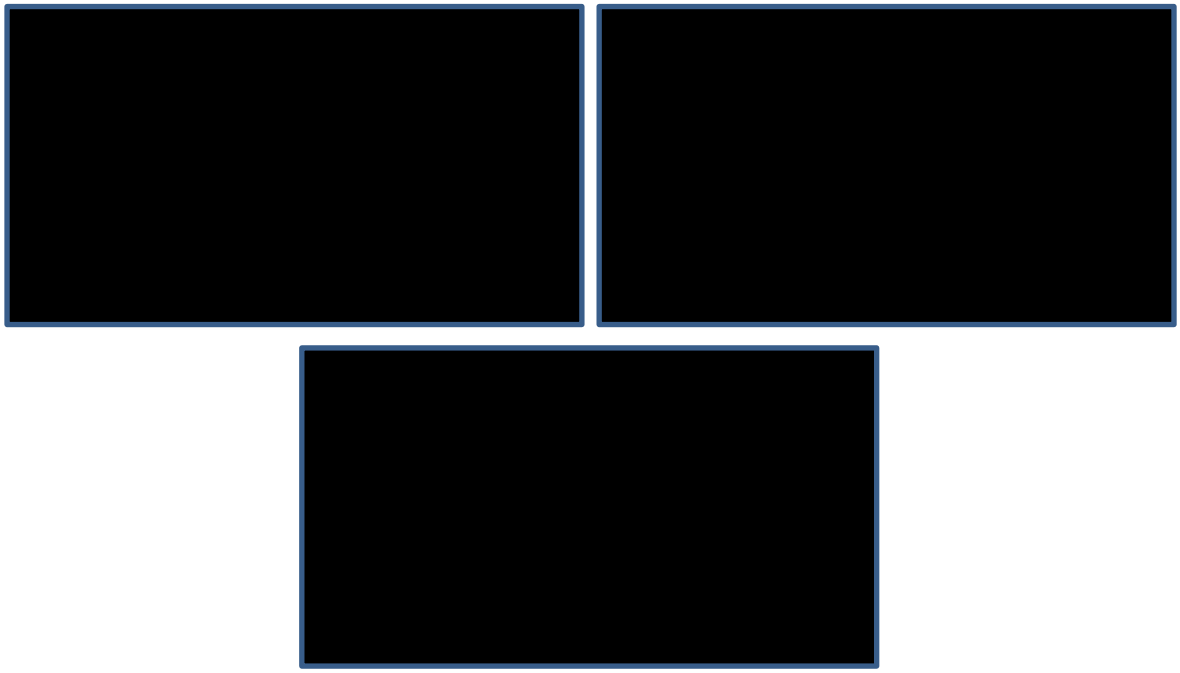
Treatment	Total QALYs	Total Costs	Incremental QALYs	Incremental costs	ICER (£ per QALY gained)
Deterministic					
Sorafenib	1.05	£44,983	-	-	
Lenvatinib	1.13	£62,580	[redacted]	[redacted]	Dominated
A+B	[redacted]	[redacted]	[redacted]	[redacted]	£22,267
PSA (run by the Evidence Review Group)					
Sorafenib	1.05	£45,002	-	-	
Lenvatinib	1.19	£63,557	[redacted]	[redacted]	Dominated
A+B	[redacted]	[redacted]	[redacted]	[redacted]	£22,419

A+B, atezolizumab plus bevacizumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Figure 9: Company's base case cost-effectiveness acceptability curves

Figure 10: Company's base case cost-effectiveness plane

Figure 11: Company's base case survival functions (model traces) – A+B (top left), sorafenib (top right) and lenvatinib (bottom)



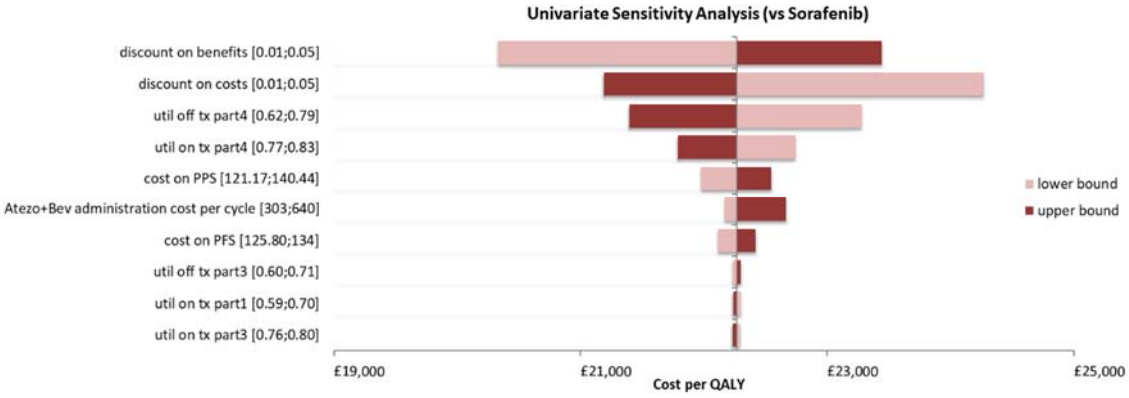
4.2.7.1 Tornado diagrams

A tornado plot showing the ten most influential parameters in terms of impact on the ICER of A+B and sorafenib is presented in

Figure 12. Within this analysis, all parameters were varied between the upper and lower bounds of the 90% percentile values obtained from the distributions used in the PSA. If such distributions were not available, the parameter was varied by ±20%. The tornado plots were reproduced by the ERG from the revised model. The ERG notes that the relative efficacy for sorafenib and lenvatinib were not included in the tornado diagram which is a limitation given that the CrIs suggest that lenvatinib could be more efficacious than A+B (see Section 3.4).

The most influential parameters, of those explored, on the ICER of A+B versus sorafenib were related to the discount rates applied and utility values used for patients with more than 30 weeks to die. None of the ICERs on the tornado plot exceeded £25,000 per QALY gained. A+B dominance of lenvatinib remained for all parameter changes and thus a tornado diagram has not been presented.

Figure 12: Tornado diagrams of A+B versus sorafenib



4.2.8 Sensitivity analyses

The company conducted a range of scenario analyses, which included the effects of using alternative survival models and parameter inputs on the results.

4.2.8.1 Scenario and subgroup analyses

The ERG updated the results of the scenarios outlined in Table 57 of the CS and added those conducted by the company in response to clarification questions. These are provided in Table 23.

Table 23: The company's scenario analyses results

No.	Scenario	ICER versus sorafenib	ICER versus lenvatinib
Base case		22,267	A+B dominant
1	5-year time horizon	24,470	A+B dominant
2	10-year time horizon	22,531	A+B dominant
3	15 - year time horizon	22,296	A+B dominant
4	Atezo+Bev OS - Generalised Gamma	18,657	A+B dominant
5	Atezo+Bev OS - Log-logistic distribution	21,443	A+B dominant
6	Sorafenib OS - Generalised Gamma distribution	24,054	A+B dominant
7	Sorafenib OS - Log-logistic distribution	28,073	A+B dominant
8	Atezo+Bev PFS – Exponential distribution	22,283	5,950
9	Atezo+Bev PFS - Log-logistic distribution	22,261	A+B dominant
10	Sorafenib PFS – Exponential distribution	22,266	A+B dominant
11	Sorafenib PFS - Log-logistic distribution	22,271	A+B dominant
12	Atezo TTD – Exponential distribution	21,029	A+B dominant
13	Atezo TTD – Weibull distribution	29,111	4,625
14	Discount rate – costs - 0%	25,153	A+B dominant
15	Discount rate – costs - 5%	21,192	A+B dominant

16	Discount rate – effects - 0%	19,565	A+B dominant
17	Discount rate – effects - 5%	23,441	A+B dominant
18[†*]	Stopping rule – Yes	15,827	A+B dominant
19	Treatment duration: Until progression	16,465	A+B dominant
20	Dose: Planned ind. dose without vial sharing	22,299	A+B dominant
21	Utilities: IMbrave150 (On/Off treatment)	22,303	A+B dominant
22	Utilities: IMbrave150 (Off/On progression)	22,532	A+B dominant
23	Utilities: IMbrave150 (Off/On progression)+ AE3+	23,078	A+B dominant
24	Modelling sorafenib using HRs from ITC rather than IMbrave150 study data	21,376	A+B dominant
25	Resource use estimates: TA551[28]	27,516	6,351
26	Subsequent therapy: IMbrave150 study data	23,064	A+B dominant
27	Subsequent therapy: Sorafenib arm only receive regorafenib (clinical expert opinion)	27,626	A+B dominant
28[†]	Modelling sorafenib and lenvatinib: Fractional polynomial NMA	21,813	A+B dominant
29[†]	Lenvatinib dose prescribed assuming all patients weigh ≥ 60kg	22,267	A+B dominant
30[†]	Lenvatinib dose prescribed assuming all patients weigh < 60kg	22,267	16,391
31[†*]	All patients receive full recommended dose of bevacizumab (i.e. no vial use threshold)	22,308	A+B dominant
31[†]	Subsequent therapy: IMbrave150 study data (all treatments are costed in)	A+B dominant	A+B dominant
32[†]	OS adjusted excluding subsequent treatments not recommended in England	20,307	A+B dominant
33[†]	Subsequent therapy: no costs are applied	32,054	A+B dominant

A+B, atezolizumab plus bevacizumab; AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison, NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TA, technology appraisal, TTD, time to treatment discontinuation

[†]Reported in the clarification response

[*]The ERG could not reproduce the results reported by the company

Most scenarios produced ICERs that were similar to the company's base case ICER. All ICERs for A+B versus sorafenib were less than £30,000 per QALY gained, except when subsequent therapies were assumed to have zero cost (Scenario 33).

Similarly, A+B dominated lenvatinib in all but four scenarios; Scenario 8, where the PFS of A+B (and also lenvatinib because of the use of a HR) is decreased as PFS was used as a proxy for TTD for lenvatinib; Scenario 13, where the TTD of A+B was increased; Scenario 25 where resource use associated with TA 551 was used; and Scenario 30, where all patients weigh < 60kg and the cost per patient of lenvatinib is reduced. However, none of the resulting ICERs were above £20,000.

Additionally, the ERG asked for a subgroup analysis for IMbrave150 population excluding patients from Asia (except Japan); the results of this analysis are presented in Table 24. The rationale for this request was that in the NICE appraisal of sorafenib,[37] data from the SHARP study[38], in which 70% of patients were European, was preferred to that from the Asia Pacific study[39] which recruited patients from China, Korea and Taiwan and where there was endemic HBV.

Table 24: The company's subgroup results for IMbrave150 population excluding Asia (except Japan)

Option	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
A+B	[redacted]	[redacted]	-	-	-
Sorafenib	44,802	1.05	[redacted]	[redacted]	22,368
Lenvatinib	59,103	1.04	[redacted]	[redacted]	Dominant

A+B, atezolizumab plus bevacizumab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

4.3 Critique of company's submitted economic evaluation by the ERG

4.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model and discussion of issues identified amongst the members of the ERG.
- Verification of the implementation of the company's model.
- Examination of the correspondence between the description of the model reported within the CS and the company's executable model.
- Re-running the scenario analyses and PSA presented within the CS.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.2 Adherence of the company's model to the NICE reference case

Table 25 compares the company's economic evaluation with the NICE reference case.[22]

Table 25: Adherence of the company's model to the NICE reference case

Element	Reference case	ERG comments
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is in line with the NICE reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company used a time horizon of 20 years which was sufficiently long to meet the NICE reference case. The number of patients alive in the model at 20 years was effectively zero.
Synthesis of evidence on health effects	Based on study outcome data and systematic review	The company used data directly drawn from IMbrave150 to model the relative effectiveness of A+B and sorafenib. An ITC, albeit with some limitations, was undertaken to assess the relative effectiveness of lenvatinib with A+B and sorafenib.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	The model uses the EQ-5D measure as preferred in the NICE reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L data reported by patients were collected in IMbrave150. This meets the NICE reference case.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The company followed advice by NICE regarding mapping of the EQ-5D-5L to 3L and meets the NICE reference case. The company adopted a '*proximity to death*' approach which involved the use of a mixed linear model which had theoretical limitations (See Section 4.3.4.4).
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company's model is in line with the NICE reference case, although the company makes a case for the end of life criteria being met.
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	The company's model is in line with the NICE reference case.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	The company's model is in line with the NICE reference case.

4.3.3 ERG Critique of the modelling performed by the company

4.3.3.1 Model verification

The ERG checked and verified the implementation of the model and the methods for generating results in the model submitted after the clarification process. Only small errors were identified which are detailed in Section 4.3.4.1.

The ERG could not replicate the scenario analyses on two occasions (see Table 23) for unknown reasons.

4.3.3.2 Correspondence of the model inputs and the original sources of parameter values

The ERG is satisfied that, where checked, model parameters corresponded with their original source values. These were in line also with the parameter values reported in the CS.

4.3.4 Issues identified from the ERG's critical appraisal

Box 1 summarises the issues identified within the company's health economic model. These points are discussed in the following subsections. Where possible, the ERG has performed exploratory analyses as described in Section 4.4 with the impact on the ICER being provided in Section 5.

Box 1: Summary of the issues identified within the company's health economic model

- Perceived modelling errors
- Limitations in the estimation of time-to-event data and choice of distribution used to estimate OS
- Actual dosage not considered in the company's base case
- Insufficient wastage of oral chemotherapy considered
- Inappropriate use of utility values for patients with unresectable HCC that were greater than average age and gender-matched patients
- Using a naïve indirect comparison to estimate AEs associated with lenvatinib
- Underestimating the relative efficacy of lenvatinib
- Lack of details associated with the analyses removing treatments not recommended by NICE from IMbrave150

4.3.4.1 Perceived modelling errors

The ERG identified three modelling errors in the calculations for bevacizumab dose after receiving the company's response to clarification questions. The first error was related to question B18. The company amended the formulae in cells Q30:S30 in the 'Dosing' worksheet which related to calculations for bevacizumab without vial sharing. However, the same formulae in cells U30:V30 were not amended. This resulted in the discrepancy shown in Table 19, whereby the cost of the 'vial sharing' approach was more than that of the 'no vial sharing' approach.

The second error was related to calculating the number of bevacizumab number of vials needed per patient. In its response to clarification question B16, the company did not account for the 5% vial use threshold stated in response to question B5. Accordingly, the model calculations assumed that a patient gets a vial even if they require less than 5% of the vial's amount which is not in line with NHSE bevacizumab dose banding table.

4.3.4.2 Limitations in the estimation of time-to-event data and choice of distribution used to estimate OS.

The ERG considers the following issues to be limitations with the survival modelling:

- It is inappropriate to estimate the relative treatment effects of lenvatinib versus A+B using an HR from a random effects NMA, whilst estimating the effect of sorafenib versus A+B using arm-based parametric survival models

- There is no reason to assume proportional hazards for the comparison of lenvatinib versus A+B and to do so when hazards are not proportional will generate a biased estimate of the lenvatinib absolute survival function and population mean survival.
- Furthermore, the Cox HR from REFLECT would not have the same numerical value as a hazard ratio that would be estimated by fitting a parametric model to both treatment arms. If it is believed that a particular parametric model correctly represents the underlying data-generation process and proportional hazards is accepted, then there is no reason to not use the parametric model to estimate the relative treatment effect.
- Overlaying the HR from one analysis onto a baseline arm from a different analysis will overstate the uncertainty in the analysis because the covariation between baseline and treatment effect that would be expressed in a single coherent analysis is lost, resulting eventually in an incorrect characterisation of the uncertainty in incremental net benefit.
- When the proportional hazards assumption does not hold, then the HR obtained from a Cox model is meaningless, and applying it to a parametric form for the baseline survival function will give incorrect inference.
- Not all parametric distributions, such as the log-logistic distributions, can be parameterized as a proportional hazards model and yet the company generated survival functions for lenvatinib in such cases.
- The company used a random effects NMA to estimate the relative effect of lenvatinib versus A+B but used a different model to estimate the effect of sorafenib versus A+B, effectively treating the effect of sorafenib versus A+B as fixed. Consequently, the uncertainty associated with the two estimates of treatment effect is modelled differently and allows for greater uncertainty for the relative effect of lenvatinib than for the relative effect of sorafenib.
- The underlying hazard functions may vary between treatments for various reasons including differences in the mechanism of action of treatments. Nevertheless, the company has sought to find a single standard parametric model that can be used to model the time-to-event data for each treatment. In response to clarification question A11 the company stated, "*More flexible survival models such as spline models were not deemed necessary due to the good fit of the data to standard distributions. More flexible survival models are more commonly used when the survival curves do not follow a specific distribution and the data is slightly more complex to extrapolate. That was not the case when fitting the IMbrave150 data or the ITC data to parametric distributions*." The ERG notes that no standard parametric distribution is likely to be the true model and that interest is not only in identifying a model that is a reasonable representation of the sample data but also one that provides plausible predictions. While the ERG is aware that spline models

generally require many events to estimate parameters and make assumptions about the extrapolation phase, they do provide a way of relaxing the assumption of a single underlying standard parametric model for each treatment. In response to clarification question A15, the company justified their choice of model for the data based on the shape of the survival functions rather than the underlying hazard functions and stated that "*the tail of the curve OS would naturally differ due to the different mechanism of action between an immunotherapy and a TKI, as one may expect a prolonged tail of patients who have not relapsed on Atezo+Bev therapy. Nevertheless, it was agreed that as extrapolated survival curves are based on assumptions, it is justified to assume the same hazard function for all treatments, and it was deemed a conservative approach by the clinical community*."

- At the clarification stage, the ERG asked the company to perform network meta-analyses allowing for time varying treatment effects (i.e. not necessarily HRs) for different survival models including all treatments of interest and referred the company to methods proposed by Ouwens *et al*. for standard parametric models[40] and Jansen for fractional polynomials.[41] The methods require the same reconstruction of KM product limit estimates as sample data from KM survival functions. In response, clarification question A7, the company used a first-degree Bayesian fixed effect FP NMA to analyse OS data. However, the company did not present fitted survival functions or make an assessment of the relative goodness-of-fit of this model to the original models, and did not comment on the clinical plausibility of the extrapolations. In addition, it is not clear why the company used a fixed effect model rather than a random effects model as it did in the original NMA. Consequently, the ERG is not able to assess the credibility of this analysis.
- In response to clarification question A7, the company stated that "*the Ouwens approach was unfeasible, as that also required individual patient level data.*" It is not clear to the ERG why the company was not able to fit time-varying models as described by Ouwens *et al* given that it used the same likelihood function for FPs.
- If the company had performed random effects meta-analyses allowing for time-varying treatment effects and FPs, then the appropriate input to the economic model would be samples from the posterior predictive joint distribution of the effects of treatments in a new study; this would generate greater uncertainty than has currently been allowed for.
- At the clarification stage, and in response to clarification question A7, the company stated that the "*FP NMA was unattainable for PFS due to the different methodologies in data collection in the REFLECT and Imbrave150 trials, mRECIST and RECIST 1.1, respectively."* The ERG notes that this issue also applies to its base case using HRs.
- The company claims that *"the exponential model and the Generalised Gamma model represented clinically plausible estimates, as the remaining four models projected a higher OS for sorafenib*

than lenvatinib, which is not aligned with the REFLECT trial clinical data which showed lenvatinib OS to be non-inferior to sorafenib." This ignores several important issues that the ERG believe affects the company's choice of survival model:

- Non-inferiority of lenvatinib versus sorafenib in REFLECT was judged according to an HR estimated over an approximately 40-month study period assuming no treatment by time interaction. While an HR is a convenient summary in clinical trials, survival functions may not be proportional in practice and they are not particularly relevant in HTA allowing for the observed and extrapolated (i.e. approximately another 40 months in the case of lenvatinib based on Figure 9 of the CS) periods.
- Non-inferiority of proportional hazards model means that the true lenvatinib survival function could be worse than sorafenib. Indeed, the conclusion regarding non-inferiority was based on a 95% CI for the HR (0.79, 1.06), an average treatment effect over the observed study period, which suggests that lenvatinib could be worse than sorafenib, and even worse than indicated by the upper limit of the 95% CI.

- Patients in IMbrave150 and REFLECT were not treated according to UK clinical practice post--progression. Consequently, the survival functions estimated from the data in IMbrave50 and REFLECT might not reflect the survival functions that might have been estimated if patients had been treated according to UK clinical practice. This may lead to biases in survival in favour of A+B and lenvatinib because subsequent therapies not approved in UK clinical practice were allowed in IMbrave150 and REFLECT, respectively, whereas patients receiving sorafenib can receive regorafenib, if sufficiently fit.
- The ERG has concern with the process use to elicit judgements of experts:
  - The process is not transparent, including a lack of clarity regarding the evidence that each expert was familiar with and the questions that were asked.
  - The ERG is concerned that experts' judgements are sought "*to ensure the curves represented outcomes seen in UK clinical practice*". It is the opinion of the ERG that this could be misleading. The survival functions estimated in the studies reflect the mix of patients defined by the inclusion/exclusion criteria of the studies and not necessarily the target population when treatments are used in clinical practice.
  - The ERG notes that clinical trials provide a sample estimate of a survival function not the true survival function. We expect sampling variation and differences in the central estimates of survival functions in different studies even if a study is repeated under identical circumstances and the clinicians are not required to account for sampling variation or parameter uncertainty when expressing their judgements.

An additional potential problem with the use of an HR for lenvatinib is that it has been assumed to be maintained throughout the time horizon of the model and does not take into account the actual time on A+B and lenvatinib treatment.

In accordance with usual practice, the baseline survival function for the target population is taken from the A+B arm of the IMbrave150 study. The ERG notes that the mix of patients in clinical trials may be different to that in clinical practice and the two baseline survival functions may differ. This would affect the expected absolute survival functions for all treatments and the estimate of incremental survival, although it is not possible to say whether this would be smaller or larger in this case.

4.3.4.2.1. Estimation of OS survival functions

Refer to Section 4.3.4.2 for detailed comments.

The company choose to model OS using an exponential distribution despite it not being one of the better fitting models, and it being associated with a constant hazard of death for the lifetime of patients and a constant treatment effect. The ERG was not convinced by the reasons given by the company for discarding other survival model and undertook further modelling using log-normal, generalised gamma and log-logistic models.

4.3.4.2.2. Estimation of PFS survival functions

No exploratory analyses were undertaken by the ERG relating to PFS as this was shown to only have a small impact on the ICER in the company's scenario analyses and the company's choice of base case model appeared appropriate.

4.3.4.2.3. Estimation of TTD survival functions for A+B and sorafenib

The company fitted the same set of models to TTD data that it used to analyse OS and PFS data. The ERG does not know whether the use of the 14-month cut-off point for switching between the KM survival function and the parametric distribution is optimal, but changes to this time point does not change the ICER markedly.

4.3.4.3 Actual dosage not considered in the company's base case

The company provided three analyses relating to the dosage (and costs) of interventions as shown in Table 19. The ERG believes that in addition to Approach 2, which considers the actual RDI used in IMbrave150, another informative scenario would be to use the RDI for atezolizumab, which is vial-based but planned dosage for sorafenib, as it is plausible that savings on unused tablets are not recouped (termed Approach 2b). The correct dosages for decision making are likely to lie between Approach 2 and Approach 2b.

Further, the company assumed an RDI of 1 for lenvatinib "*in the absence of trial information.*" (Clarification question B26). The company stated that the model could be updated with the RDI observed for sorafenib (0.84) or with the value from the REFLECT study (0.88)[18] but did not perform these analyses.

4.3.4.4 Insufficient wastage of oral chemotherapy considered

The company model assumes acquisition costs for both sorafenib or lenvatinib are incurred in each weekly cycle and uses the half-cycle corrected proportion for patients on treatment to calculate acquisition costs. Wastage that occurs from patients discontinuing or dying with pills dispensed has therefore not been considered. In contrast, drug wastage was considered in the STAs of sorafenib and lenvatinib. where the Appraisal Committee for sorafenib suggested that the most plausible ICER should account for drug wastage for up to 7 days.[28, 37]

4.3.4.5 Inappropriate use of utility values for patients with unresectable HCC that were greater than average age and gender-matched patients

The utility used in the company base case (Table 15) indicate that for patients on treatment the utility could be 0.78 or higher for those who were further than 15 weeks from death. For reference, the utility associated with the age- and sex-matched population is [redacted].[34] The ERG believes it extremely unlikely that, on average, patients with unresectable HCC have a higher utility than an age- and sex-matched population.

Additionally, the ERG noted that the models used by the company to map EQ-5D-5L data to EQ-5D-3L data make the assumption of normality, effectively appealing to the Central Limit Theorem. In response to clarification question B32, the company stated that this is standard practice and estimates will be unbiased. However, the ERG notes that these data are multimodal, right bounded at 1 with a substantial gap to the next set of observations and also left bounded. These features present significant statistical challenges and it is known that standard approaches do not perform well for this reason; using standard approaches therefore introduces the possibility of bias.[42] With incremental QALYs forming the denominator of the ICER calculation, small adjustments to small values can result in significant and sometimes decision altering changes.[43] More nuanced models, such as adjusted limited dependent variable mixture models,[42] are available which address these issues. However, if the health states being considered are all well-populated with data, then a non-parametric calculation of the mean for each state (with appropriate weighting for repeated values from individuals) is also appropriate and simple to implement without introducing bias.[44]

4.3.4.6 Using a naïve indirect comparison to estimate AEs associated with lenvatinib

In response to clarification question A5, the company acknowledged that the method used for estimating the rate of AEs associated with lenvatinib treatment was a naïve indirect comparison and that if a relative frequency had been applied the rate would be lower.

4.3.4.7 Estimating the relative efficacy of lenvatinib

The main issue is that the currently the effect of lenvatinib compared to A+B is estimated inconsistently. In particular, the lenvatinib survival function is generated with respect to an HR from a random effects NMA, whereas the effect of sorafenib relative to A+B is effectively from a fixed effect arm-based comparison of survival functions from IMbrave150.

Using the HR from the NMA to generate the lenvatinib survival function (and mean survival) assumes that the A+B survival function (and mean survival) will be above that for lenvatinib over the lifetime of patients, which may not be true and is an unnecessary modelling assumption. Some indication of whether the effect of lenvatinib relative to A+B is constant over time is provided by the results of the analysis using fractional polynomials (clarification question A8) subject to the limitations discussed in Section 4.3.4.2. This shows a small but consistent increase in the time-varying hazard ratio from 0.647 at month 0.1 to 0.705 at month 75. Nevertheless, these results suggest some shrinkage in the hazard ratio towards one over the lifetime of patients. That said, the ERG is concerned with the apparent inconsistency between the average treatment effect estimated from the random effects NMA (HR of lenvatinib versus A+B: 0.63) and the time-varying HRs estimated from the model using fractional polynomials. There is no assumption of a constant treatment effects when comparing sorafenib and A+B.

Uncertainty is treated differently when comparing lenvatinib with A+B and sorafenib with A+B in that the former is from a random effects model and the latter is effectively a fixed effect comparison. The ERG would prefer to see a single random effects NMA allowing for time-varying treatment effects. The company did present results of a fractional polynomial NMA but this was from a fixed effect model rather than a random effects model and it did not sufficiently critique the results.

For further details refer to Section 4.3.4.2.

4.3.4.8 The lack of details associated with the analyses removing treatments not recommended by NICE from IMbrave150

In clarification question B30, the company were asked to provide a scenario analysis which attempted to use statistical methods to exclude treatments not recommended in England. The company provided

a set of analyses but with no explanation of the method undertaken. As such, the ERG cannot critique these values and believes that these results should be treated with caution. The ERG cannot provide a robust opinion on the likely direction and magnitude of the bias of this scenario.

4.3.4.8 The assumption that oral chemotherapy administration costs are incurred once only

The company assumed that the costs of oral chemotherapy administration (£195) was only incurred once for each patient. Previous comments by NHS England staff suggests that this could be incurred with each prescription. Communication with NICE staff has indicated that the is not a standard NICE position on this.

4.4 **Exploratory analyses undertaken by the ERG**

This section details the exploratory analyses undertaken by the ERG.

Where possible, the ERG undertook exploratory analyses to address the limitations listed in Box 1. The following two limitations could not be addressed by the ERG within the timescales of producing the report: (1) additional analyses relating to the inconsistent modelling of the relative efficacy of lenvatinib compared with A+B, and (2) assessing the appropriateness of the statistical methods used to attempt to remove the impact of subsequent treatments not recommended in England. Additionally, the ERG undertook exploratory analyses that was also performed by the company to show the impact of these given other changes made by the ERG.

4.4.1 Correction of perceived modelling errors.

The ERG amended the formulae used to calculate the number of bevacizumab vials in the actual dose approach in the 'with vial sharing' cells to be consistent with the 'no vial sharing' calculations. Accordingly, the ERG implemented the same equations of cells R30:S30 in cells U30:V30 in the 'Dosing' sheet.

In addition, the ERG amended the formulae used to calculate the number of vials per patient in the 'planned individual dosing' to take into account the 5% vial threshold. Hence, if a patient required less than 5mg of a 100mg vial, they would not receive it. For example, after implementing the correction, the patient in row 49, who is in need of 903mg of bevacizumab, is correctly receiving 2 vials of 400mg bevacizumab and 1 vial of 100mg bevacizumab (instead of 2 vials of 400mg bevacizumab and 2 vials of 100mg bevacizumab)

4.4.2 Exploratory analyses relating to the estimation of time to event data

Two exploratory analyses were undertaken which are described in the following sub-sections.

4.4.2.1 Exploratory analyses using different assumptions relating to OS for A+B, sorafenib and lenvatinib

The following analyses were undertaken.

- Using the log-normal for both A+B and sorafenib as this was the best fitting model to the observed data when adding BICs across treatment arms
- Using the generalised gamma for both A+B and sorafenib as this was the second-best fitting model to the observed data when adding BICs across treatment arms
- Using the log-logistic for both A+B and sorafenib as this was the third-best fitting model to the observed data when adding BICs across treatment arms

The KM survivor function and the survival estimates produced by the log-normal, the generalised gamma and the log-logistic are shown in Figure 13,

Figure 14 and Figure 15 respectively.

Figure 13: Estimates of OS associated with log-normal distributions

Figure 14: Estimates of OS associated with generalised gamma distributions

Figure 15: Estimates of OS associated with log-logistic distributions

The OS function for lenvatinib changed when the A+B model was changed as the company applied an HR to the A+B OS survival function to obtain the OS survival function for lenvatinib. The ERG acknowledges that applying a HR to a baseline survival function imposes an unjustifiable constant treatment effect and that it should not be applied to models that are not proportional hazards models. However, given that the company did not conduct a coherent random effects NMA allowing for time-varying treatment effects, this is this best the ERG could do and enables some assessment of the robustness of results that may be of interest to the Appraisal Committee.

4.4.2.2 Exploratory analyses using different assumptions relating to TTD for A+B, sorafenib and lenvatinib

The ERG undertook analyses varying the time at which the exponential distribution was used rather than the KM survival function from 14 months to 13 months and 15 months. The model did not allow for uncertainty in the KM survival function to be considered.

4.4.3 Exploratory analyses relating to the dosage and acquisition costs of the interventions

4.4.3.1 Exploratory analyses using the RDI for A+B and sorafenib from IMbrave150 and the RDI for lenvatinib from Kudo *et al*.

Analyses were undertaken when the RDI for lenvatinib observed in REFLECT, 0.88, [18] was used.

4.4.3.2 Exploratory analyses using the RDI for A+B from IMbrave150 and the planned dosage for sorafenib

Analysis were performed whereby the RDI observed in IMbrave150 was used for A+B but the planned dosage was used for sorafenib. These were explored as it was not known whether the reduced RDI for sorafenib was planned or due to patients intermittently not taking a tablet.

4.4.4 Exploratory analyses incorporating seven day's wastage of sorafenib and lenvatinib when a patient discontinues treatment.

In order to account for oral chemotherapy wastage, the ERG amended the calculations for the acquisition costs of sorafenib and lenvatinib by taking the patient proportion still on treatment at the start of a given cycle (i.e. columns BV and AC instead of columns BW and AD in 'Sorafenib' and 'lenvatinib' sheets respectively) and multiplying it by the weekly acquisition costs. This accounted for an average of 3.5 days of drug wastage for patients who discontinued through this cycle. A further 3.5 days' worth of drug acquisition costs (£447.07 and £465.14 for sorafenib and lenvatinib respectively based on list prices) were added to discontinuing patients to account for a total to 7 days of drug wastage for the discontinuing proportion.

4.4.5 Exploratory analyses capping the utility of patients with unresectable HCC to that of the age- and sex-matched population.

An analysis was undertaken where it was assumed that the utility associated with patients with unresectable HCC was capped at the age- and sex-matched population value. This was implemented by limiting all utility values not to exceed the age- and sex-adjusted general population utility value calculated from Ara and Brazier.[34]

4.4.6 Exploratory analyses removing AEs for lenvatinib.

To assess the influence that the rate of AEs associated with lenvatinib had on the ICER an extreme analysis was undertaken that assumed there were no lenvatinib-related AEs.

4.4.7 Exploratory analyses assuming that oral chemotherapy administration costs are incurred at every prescription rather than once only.

The ERG has run an exploratory analysis assessing the impact of administration costs being incurred every 28 days for sorafenib and lenvatinib.

4.4.8 Exploratory analyses relating to the costs of subsequent treatments after A+B, sorafenib and lenvatinib

The ERG provided results produced under three alternative assumptions relating to the costs of subsequent treatments which were: costing only TKIs and nivolumab; costing all subsequent treatments; and costing none of the further treatments. The latter two scenarios provide the potential range in the ICER based on extreme scenarios. The first alternative is the ERG's preference, as it explicitly incorporates the most widely treatments that could impact on OS.

4.4.9 Exploratory analyses removing AEs for lenvatinib.

The actual over-estimation of AEs associated with lenvatinib is unknown. To assess the influence that the rate of AEs associated with lenvatinib had on the ICER, an extreme analysis was undertaken that assumed there were no lenvatinib-related AEs. A small change in the ICER would indicate that the over-estimation of AEs associated with lenvatinib was not a key driver of the decision problem.

5 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Sixteen modifications to the company's base case were explored. Two ERG base cases are presented both of which include the first four modifications. ERG base case A, adds scenario 5, whilst ERG base case B, adds scenario 6. Together these form the ERG's preferred ICER range.

The ERG performed subgroup analyses based on patient weight for those weighing under 60kg and for those weighing 60kg and over. This was motivated by the fact that the acquisition cost of lenvatinib differs between these subgroups, hence the relative cost-effectiveness of A+B against lenvatinib is influenced by the weight category of the patient. As the ERG did not have data by patient weight it was assumed that only costs were changed and the estimated OS for all patients was generalisable to both weight groups.

95% CIs around the mean probabilistic ICER have been calculated using the method described in Hatswell *et al*.[45] It was seen that 1,000 PSA iterations appeared sufficient to reduce Monte Carlo sampling error.

The ERG ran all results deterministically, whereas probabilistic results using 1,000 iterations were obtained for the ERG's base case and subgroup analyses. A condensed summary detailed exploratory analyses undertaken by the ERG is provided in Table 26. More detailed results are presented in Table 27 and Table 28. The confidential PASs for sorafenib, lenvatinib and regorafenib are not included; these data are considered in a confidential appendix.

In the analyses using the list prices all ICERs for A+B compared with sorafenib and lenvatinib were under £50,000 per QALY gained.

Table 26: Summary of ERG-preferred ICER (cost per QALY gained) ranges for the four scenarios

	All patients in IMbrave150		**Non-Asian plus Japanese patients in IMbrave150**	
	Sorafenib	**Lenvatinib**	**Sorafenib**	**Lenvatinib**
Costs associated with patients weighing under 60kg	£16,567 to £21,843	£83 to £3,962	£15,387 to £21,488	Dominant to £3,381
Costs associated with patients weighing 60kg or more	£21,427 to £26,653	Dominant to Dominant	£20,837 to £27,017	Dominant to Dominant

The ERG additionally explored the impact of applying adjustments 8-16, detailed in Table 29, to the ERG base case with the least favourable ICER for A+B. This base case is 'ERG base case B assuming costs for patients weighing more than or equal to 60kg excluding Asia (except Japan)', in which A+B has a deterministic ICER of £26,525 compared with sorafenib (Table 29**).**

An additional analysis was performed applying adjustments 8-16 to a favourable scenario for A+B, which was 'ERG base case A assuming costs for patients weighing less than 60kg'. The deterministic ICER for A+B compared with sorafenib was £16,296 per QALY gained (Table 28). Results of these analyses are shown in

Table 30.

These analyses provide the committee with an indication of the ICER value when assumptions other than that in the ERG's base cases are chosen.

Table 27: The ERG's exploratory model results

Analysis	Discounted costs			Discounted QALYS			ICER (A + B versus sorafenib)	ICER (A + B versus lenvatinib)
	A+B	Sorafenib	Lenvatinib	A+B	Sorafenib	Lenvatinib		
Company deterministic base case	[redacted]	£44,983	£62,580	[redacted]	1.05	1.13	**£22,267**	**A+B dominant**
1) Adjusting for perceived modelling errors	[redacted]	£44,983	£62,580	[redacted]	1.05	1.13	£22,250	A+B dominant
2) Use of log-normal functions to model OS	[redacted]	£47,739	£63,920	[redacted]	1.34	1.23	£22,066	A+B dominant
3) Including 7 days oral chemotherapy wastage on discontinuation	[redacted]	£45,865	£63,491	[redacted]	1.05	1.13	£20,969	A+B dominant
4) Capping utilities for people with unresected HCC at that of the age- and sex-matched population	[redacted]	£44,983	£62,580	[redacted]	1.03	1.10	£23,083	A+B dominant
5) Costing subsequent TKIs and nivolumab treatments	[redacted]	£47,508	£71,600	[redacted]	1.05	1.13	£23,064	A+B dominant
6) Implementing the 'actual dose' approach for A+B and using an RDI of 1 for sorafenib and lenvatinib	[redacted]	£44,983	£62,580	[redacted]	1.05	1.13	£19,849	A+B dominant
7) Implementing the 'actual dose' approach and RDI of 0.88 for lenvatinib	[redacted]	£41,761	£58,176	[redacted]	1.05	1.13	£24,593	£485
8) Use of generalised gamma functions to model OS	[redacted]	£45,765	£63,761	[redacted]	1.13	1.22	£19,537	A+B dominant
9) Use of log-logistic functions to model OS	[redacted]	£47,039	£62,582	[redacted]	1.26	1.09	£26,296	A+B dominant
10) Using MRU costs associated with the STA of lenvatinib (TA551)[28]	[redacted]	£53,654	£68,560	[redacted]	1.05	1.13	£27,516	£6,351
11) Including costs of all subsequent treatments	[redacted]	£78,863	£102,433	[redacted]	1.05	1.13	A+B dominant	A+B dominant
12) Excluding costs of all subsequent treatments	[redacted]	£38,335	£62,580	[redacted]	1.05	1.13	£32,054	A+B dominant
13) Exponential tail for modelling TTD starts at 13 months	[redacted]	£44,573	£62,580	[redacted]	1.05	1.13	£22,424	A+B dominant
14) Exponential tail for modelling TTD starts at 15 months	[redacted]	£45,494	£62,580	[redacted]	1.05	1.13	£20,598	A+B dominant
15) Excluding costs of AE for lenvatinib	[redacted]	£44,983	£62,285	[redacted]	1.05	1.13	£22,267	A+B dominant
16) Including oral chemotherapy administration costs at each prescription	[redacted]	£45,952	£64,762	[redacted]	1.05	1.13	£20,841	A+B dominant

A+B, atezolizumab plus bevacizumab; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year; RDI, relative dose intensity; TKIs, tyrosine kinase inhibitors; TTD, time to treatment discontinuation

Table 28: The ERG's base case ICERs varying dose intensity of oral chemotherapy, costs associated with body weight, and the population (all patients or non-Asian patients plus Japanese patient)

Analysis	Discounted costs			Discounted QALYS			ICER (A + B versus sorafenib)	ICER (A + B versus lenvatinib)
	A+B	Sorafenib	Lenvatinib	A+B	Sorafenib	Lenvatinib		
ERG base case A (scenarios 1 – 6) assuming costs for patients weighing less than 60kg	[redacted]			[redacted]				
• Deterministic		£50,783	£60,897		1.32	1.21	£16,296	£1,031
• Probabilistic		£50,946	£61,698		1.33	1.26	£16,567 [95% CI: £16,275 to £16,875]	£83 [95% CI: A+B dominant to £1,526]
ERG base case B (scenarios 1 – 5 plus 7) assuming costs for patients weighing less than 60kg	[redacted]			[redacted]				
• Deterministic		£47,305	£56,883		1.32	1.21	£21,372	£6,043
• Probabilistic		£47,620	£58,966		1.34	1.29	£21,843 [95% CI: £21,387 to £22,331]	£3,962 [95% CI: £2,650 to £5,225]
ERG base case A assuming costs for patients weighing less than 60kg excluding Asia (except Japan)	[redacted]			[redacted]				
• Deterministic		£49,936	£57,865		1.25	1.09	£15,036	£629
• Probabilistic		£50,197	£59,301		1.27	1.18	£15,387 [95% CI: £15,049 to £15,748]	A+B dominant [95% CI: A+B dominant to £333]
ERG base case B assuming costs for patients weighing less than 60kg excluding Asia (except Japan)	[redacted]			[redacted]				
• Deterministic		£46,484	£54,092		1.25	1.09	£21,096	£5,797
• Probabilistic		£46,716	£56,418		1.26	1.18	£21,488 [95% CI: £20,902 to £22,128]	£3,381 [95% CI: £1,956 to £4,752]
ERG base case A assuming costs for patients weighing more than or equal to 60kg	[redacted]			[redacted]				
• Deterministic		£51,252	£77,623		1.32	1.21	£20,967	A+B dominant
• Probabilistic		£51,421	£81,062		1.33	1.30	£21,427	A+B dominant

							[95% CI: £21,009 to £21,871]	[95% CI: A+B dominant to A+B dominant]
ERG base case B assuming costs for patients weighing more than or equal to 60kg • Deterministic • Probabilistic	[redacted]	£47,717 £47,919	£71,602 £73,641	[redacted]	1.32 1.33	1.21 1.27	£26,071 £26,653 [95% CI: £26,056 to £27,289]	A+B dominant A+B dominant [95% CI: A+B dominant to A+B dominant]
ERG base case A assuming costs for patients weighing more than or equal to 60kg excluding Asia (except Japan) • Deterministic • Probabilistic	[redacted]	£50,405 £50,609	£73,586 £76,195	[redacted]	1.25 1.26	1.09 1.18	£20,432 £20,837 [95% CI: £20,286 to £21,438]	A+B dominant A+B dominant [95% CI: A+B dominant to A+B dominant]
ERG base case B assuming costs for patients weighing more than or equal to 60kg excluding Asia (except Japan) • Deterministic • Probabilistic	[redacted]	£46,897 £47,330	£67,927 £70,954	[redacted]	1.25 1.28	1.09 1.17	£26,525 £27,017 [95% CI: £26,177 to £27,940]	A+B dominant A+B dominant [95% CI: A+B dominant to A+B dominant]

A+B, atezolizumab plus bevacizumab; CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 29: Assessing the impact of ERG's exploratory model results to ERG base case B for patients weighing more than 60kg and excluding Asian patients (except Japanese: deterministic results)

Analysis	Discounted costs			Discounted QALYS			ICER (A + B versus sorafenib)	ICER (A + B versus lenvatinib)
	A+B	Sorafenib	Lenvatinib	A+B	Sorafenib	Lenvatinib		
ERG base case B assuming costs for patients more than or equal to 60kg excluding Asia (except Japan)	[redacted]	**£46,897**	**£67,927**	[redacted]	**1.25**	**1.09**	**£26,525**	**A+B dominant**
8) Use of generalised gamma functions to model OS	The ERG does not believe these results are clinically plausible. See accompanying text							
9) Use of log-logistic functions to model OS	[redacted]	£46,777	£66,769	[redacted]	1.23	0.97	£36,218	A+B dominant
10) Using MRU costs associated with the STA of lenvatinib (TA551)[28]	[redacted]	£57,877	£74,219	[redacted]	1.25	1.09	£32,954	£2,825
11) Including costs of all subsequent treatments	[redacted]	£78,109	£98,665	[redacted]	1.25	1.09	A+B dominant	A+B dominant
12) Excluding costs of all subsequent treatments	[redacted]	£37,786	£58,954	[redacted]	1.25	1.09	£37,449	A+B dominant
13) Exponential tail for modelling TTD starts at 13 months	[redacted]	£46,622	£67,927	[redacted]	1.25	1.09	£25,537	A+B dominant
14) Exponential tail for modelling TTD starts at 15 months	Not estimable as the KM survivor function stops at14 months for this subgroup of patients							
15) Excluding costs of AE for lenvatinib	[redacted]	£46,897	£67,631	[redacted]	1.25	1.09	£26,525	A+B dominant
16) Including oral chemotherapy costs at each prescription.	[redacted]	£47,857	£69,980	[redacted]	1.25	1.09	£24,802	A+B dominant

Table 30: Assessing the impact of ERG's exploratory model results to ERG base case A for patients weighing less than 60kg

Analysis	Discounted costs			Discounted QALYS			ICER (A + B versus sorafenib)	ICER (A + B versus lenvatinib)
	A+B	Sorafenib	Lenvatinib	A+B	Sorafenib	Lenvatinib		
ERG base case A assuming costs for patients below 60kg	[redacted]	£50,783	£60,897	[redacted]	1.32	1.21	£16,296	£1,031
8) Use of generalised gamma functions to model OS	[redacted]	£48,809	£60,738	[redacted]	1.12	1.19	£14,925	£811
9) Use of log-logistic functions to model OS	[redacted]	£50,083	£59,559	[redacted]	1.24	1.06	£18,558	A+B dominant
10) Using MRU costs associated with the STA of lenvatinib (TA551)[28]	[redacted]	£63,177	£68,111	[redacted]	1.32	1.21	£22,210	£12,667
11) Including costs of all subsequent treatments	[redacted]	£81,289	£90,881	[redacted]	1.32	1.21	A+B dominant	A+B dominant
12) Excluding costs of all subsequent treatments	[redacted]	£41,973	£52,239	[redacted]	1.32	1.21	£25,226	£8,455
13) Exponential tail for modelling TTD starts at 13 months	[redacted]	£50,374	£60,897	[redacted]	1.32	1.21	£16,500	£685
14) Exponential tail for modelling TTD starts at 15 months	[redacted]	£51,293	£60,897	[redacted]	1.32	1.21	£14,602	£175
15) Excluding costs of AE for lenvatinib	[redacted]	£50,783	£60,603	[redacted]	1.32	1.21	£16,296	£1,406
16) Including oral chemotherapy costs at each prescription.	[redacted]	£51,752	£63,098	[redacted]	1.32	1.21	£14,851	A+B dominant

As seen in Table 29 the ERG did not believe that results produced when using generalised gamma distributions for estimating OS were clinically plausible. This was because the estimated OS for Non-Asian patients plus Japanese patients crossed for A+B and sorafenib as shown in Figure 16. Figure 17 and

Figure 18 presents the OS estimates using the lognormal (ERG's base case) and the log-logistic (explored in ERG's scenario analyses) distributions for the aforementioned population respectively.

Figure 16: Estimates of OS associated with generalised gamma distributions for Non-Asian patients plus Japanese patients

Figure 17: Estimates of OS associated with lognormal distributions for Non-Asian patients plus Japanese patients

Figure 18: Estimates of OS associated with log-logistic distributions for Non-Asian patients plus Japanese patients

6 END OF LIFE

In Table 29 of the CS the company puts forward the case that A+B meets the NICE End of Life criteria. These criteria are:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company's base case model estimates mean life years to be 1.50 years for patients receiving sorafenib and 1.54 years for patients receiving lenvatinib. Both values appear to meet the short life expectancy criteria.

A+B is estimated to provide [redacted] life years resulting in estimated extensions of life of [redacted] years compared with sorafenib and [redacted] compared with lenvatinib. Both values are in excess of the three-month period specified in the end of life criterion.

The ERG's base cases did not materially affect these conclusions.

7 OVERALL CONCLUSIONS

The clinical evidence for A+B was based on one sorafenib controlled RCT, IMbrave150, which was open-label but of otherwise good methodological quality, and whose population was considered broadly generalisable to a UK population. There was a statistically significant advantage for A+B over sorafenib for OS, PFS and OR. OS was statistically significantly higher for A+B, than for sorafenib HR (stratified) 0.58 (95% CI 0.42, 0.79) p=0.0006. Median OS for A+B was not estimable (NE), median OS for sorafenib was 13.2 months (95% confidence interval [CI] 10.4, NE). There was a statistically significant treatment group difference for PFS HR (stratified) 0.59 (95% CI 0.47, 0.76) p<0.0001. Median PFS was 6.8 months (95% CI 5.6, 8.3) in the A+B group, and 4.3 months (95% CI 4.0, 5.6) for the sorafenib group.

The most common NCI-CTCAE Grade 3 or 4 AEs experienced in the A+B group were hypertension (10.3%), aspartate aminotransferase increased (4.3%) and proteinuria (2.7%).

The company's economic model indicated that the probabilistic ICER for A+B compared with sorafenib was £22,419 per QALY gained, whilst A+B was assumed to dominate lenvatinib (provided more QALYs at a lower cost). The ERG included the following five exploratory analyses in its base case: 1) correcting perceived errors; 2) using log-normal distributions for estimating OS; incorporating actual dosages rather than planned dosages; 3) including seven days of wastage when discontinuing oral chemotherapy; 4) capping utility at age- and sex-matched values; 5) costing the use of subsequent TKIs and nivolumab, and combined these with two different assumptions related to actual dosage used. An ERG-preferred range was provided as the costs associated with reduced RDI for patients receiving lenvatinib and sorafenib are uncertain, and have different implications on whether the reduced RDI was planned or unintentionally. Four subgroups encompassing combinations of patient weight, less than 60kg or not, and whether the full IMbrave150 population was considered or only non-Asian and Japanese patients were considered.

The ERG-preferred ranges are summarised in Table 26. It is seen that the cost per QALY gained for A+B never exceeded £30,000 per QALY when compared with either sorafenib or lenvatinib. Alternative assumptions, as detailed in Table 29 and

Table 30 could push the ICER higher.

These values, however, do not include PAS discounts related to sorafenib, lenvatinib or regorafenib; results including these PAS discounts contained in a confidential appendix to this report.

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9 APPENDICES

Appendix 1: Subsequent treatments used in the IMbrave150 study

Table 31: Post-discontinuation subsequent therapies used in the IMbrave150 trial (source: the company's economic model)

Category	Therapy	A+B arm (n=69 equivalent to [redacted] of patients)		Sorafenib arm (n=73 equivalent to [redacted] of patients)	
		No. of patients	Mean duration (months)	No. of patients	Mean duration (months)
Tyrosine Kinase inhibitors	Sorafenib	29	3.4	2	1.26
	Lenvatinib	20	4.08	17	3.85
	Regorafenib	7	2.32	20	3.54
	Sorafenib tosilate	9	2.38	0	0
	Lenvatinib mesilate	3	2.07	5	5.27
	Cabozantinib	2	2.48	6	4.33
	Cabozantinib s-malate	1	6.41	0	0
	Apatinib mesylate	0	0	1	0.13
Immunotherapy	Nivolumab	3	5.62	16	3.92
	Pembrolizumab	1	Not reported	5	4.98
	Atezolizumab	0	0	2	1.76
	Durvalumab	0	0	4	5.68
	IRX-2 (cytokines)	0	0	2	2.17
	Tremelimumab	0	0	4	7.37
	Sintilimab	0	0	2	2.2
	Tislelizumab	0	0	2	6.26
	Triprizumab	0	0	1	0
	Investigational drug	1	7.46	0	0
Angiogenesis inhibitors	Bevacizumab	0	0	2	2.56
	Ramucirumab	2	3.74	3	1.64
Chemotherapy	Fluorouracil	2	7.35	2	5.15
	Oxaliplatin	3	5.05	3	4.21
	Calcium folinate	1	7.46	2	5.15
	Capecitabine	1	0.46	2	1.18
	Pegylated arginine deiminase	1	7.46	1	0.59
	Bufalin/ Cinobufagin/ Resibufogenin	0	0	1	0.13
	Carboplatin	1	5.36	0	0
	Cyclophosphamide	0	0	3	1.72
	Etoposide	0	0	1	2.47
	Folinic acid	1	7.23	0	0
	Gemcitabine	0	0	1	2.33
	Gemcitabine hydrochloride	1	5.36	0	0

	Tegafur/ Uracil	0	0	1	1.87
Others	Thalidomide	0	0	2	1.63
	Generic component(s) not known	0	0	2	1.98
	Antineoplastic agent	0	0	1	0.72
	BLU-554 (FGFR4 inhibitor)	1	3.75	0	0
	Chinese traditional medicine	1	6.84	0	0
	PI3K inhibitor	0	0	1	1.71

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Friday 3 July** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Proportion of patients progression-free on sorafenib

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 52: 4.2.5.1 The proportion of patients progression-free on sorafenib is reported as 21% and should be 34%	At the time of data cut-off (29th August, 2019), 71% of the patients on A+B were still alive compared to 61% on sorafenib. Approximately 41% of patients were still progression-free on A+B compared to 34% on sorafenib.	Incorrect data – Table 21, page 104 of CSR	Text amended as suggested

Issue 2 Estimation of TTD survival functions for A+B and sorafenib

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 78: 4.3.4.2.3. The ERG suggest that TTD survival functions were not presented, and therefore could not comment on the appropriateness of the use of the KM survival function rather than a parametric distribution	The ERG could acknowledge the provided TTD curve options.	The company feel this data was provided – Figure 26 page 110 of the CS. Furthermore the curves can be changed in the CEM to look at the impact of applying different parametric distributions.	Apologies for the errant text. We have rewritten this section removing text relating to the lack of survival functions being presented.

Issue 3 NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 75 A random effects NMA was used to estimate the relative effect of both lenvatinib vs A+B and	The company used a random effects NMA to estimate the relative effect of lenvatinib compared to A+B due to the lack of head-to-head data, and used a non-proportional hazard model when comparing sorafenib and A+B,	It is currently misleading, as readers may miss the word 'effectively' and the sentence implies we conducted a parallel NMA with fixed effects,	The text has been amended to clarify the point intended. *"The company used a random effects NMA to estimate the*

sorafenib vs A+B	thereby treating uncertainty differently for lenvatinib.	which is not the case.	*relative effect of lenvatinib versus A+B but used a different model to estimate the effect of sorafenib versus A+B, effectively treating the effect of sorafenib versus A+B as fixed. Consequently, the uncertainty associated with the two estimates of treatment effect is modelled differently and allows for greater uncertainty for the relative effect of lenvatinib than for the relative effect of sorafenib."*
Page 76 and page 83 – The ERG suggest that as we did not conduct a coherent random effects NMA allowing for time-varying treatment effects, the NMA lacks validity.	Please update the following sentences: Page 76: It is not clear why the company used a fixed effect model rather than a random effects model as it did in the original NMA. Consequently, the ERG is not able to assess the credibility of this analysis. Page 83: The company did not conduct a coherent random effects NMA allowing for time-varying treatment effects	An in-house NMA expert was consulted on the implementation of the fractional polynomial (FP) NMA. They advised us to use a Fixed Effects (FE) FP NMA, as FP are computationally hard to fit, even under FE, and using random effects (RE) in the context of FP is not recommended. Furthermore, RE FP requires having at least 5 degrees of freedom to estimate the RE variance, which this network does not have, or, having informative priors on the RE variances, which are not available for FP models. Therefore, we were advised us to use a fixed effects FP NMA.	No change required. The issue of whether to use a fixed or random effects model relates to the question of interest and knowledge of the effect of treatment between studies and not about the ability to fit models from the available sample data. Although Jansen et al (2012) discusses the issue of identifiability of parameters in meta-regression FP models, this issue does not apply in this case because no attempt was made to explain heterogeneity. The issue of the degrees-of-freedom necessary with which to estimate the between-study

			standard deviation is a frequentist concept that does not apply when estimating parameters using Bayesian methods. In the absence of sufficient sample data with which to estimate parameters, a Bayesian analysis requires a prior distribution that represents reasonable prior beliefs. It is unlikely that it is reasonable to assume that the between study standard deviation is zero with probability one. The company did not conduct a coherent random effects NMA allowing for time-varying treatment effects. Clarification question A7 allowed for time-varying treatment effects to be estimated using models in addition to the fixed effect FP model used by the company. The company may have found it easier to implement a random effects model using one of the alternative parameterisations.

Issue 4 Incorrect labelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39 Figure 4: KM survival function for OS (reproduced from Figure 5 of the CS)	Please correct the label on the figure to " Evidence network for level 1 comparators reporting OS and PFS (reproduced from Figure 7 of the CS)"	Incorrect label	The legend has been amended as suggested.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
1. Distribution chosen for overall survival	• The company used independently-fitted parametric distributions (i.e. for each treatment arm separately) to model overall survival (OS). • Based on clinical expert opinion regarding the plausibility of the tails of the distributions, the company considered that only the exponential and generalised gamma models were clinically plausible (see section B.3.3.2 of the company submission). The remaining 4 models projected a higher OS for sorafenib than lenvatinib, which is inconsistent with evidence from the REFLECT trial comparing lenvatinib with sorafenib. • The company selected the exponential model for its base case and explored the impact of using the generalised gamma distribution in scenario analyses. • The ERG had reservations about the company's rationale for selecting the exponential model to extrapolate OS (see section 4.3.4.2 of the ERG report): o The exponential model is not one of the statistically better-fitting models. o It has a constant hazard of death over time and imposes a constant treatment effect. o The argument that other models predict higher OS for sorafenib than levatinib is an artefact of the way the company estimated the relative effectiveness of lenvatinib, which the ERG had separate concerns about (see issue 2). • The ERG undertook exploratory analyses using survival models selected based on their overall statistical goodness	• The case for using the exponential distribution for OS is unclear. • The log-normal model provides the best statistical fit to the data, slightly superior to the generalised gamma model, then the log-logistic model.

	of fit to the data: log-normal (1st), generalised gamma (2nd) and log-logistic (3rd). • Compared with the company's preferred exponential model, the log-normal and generalised gamma models reduce the Atezolizumab (A) with bevacizumab (B) ICERs compared with sorafenib and lenvatinib. The log-logistic model increases the A+B ICERs.	
2. Indirect treatment comparison	• There is no direct evidence comparing A+B with lenvatinib, so the company performed a random effects network meta-analysis (NMA) to estimate the relative treatment effect (see section B.2.9 of the company submission). • The company used the direct trial evidence from IMbrave150 to estimate the effect of sorafenib versus A+B. This is effectively a fixed effects analysis (see section 4.3.4.7 of the ERG report). • The ERG considers that it is inconsistent and inappropriate to estimate the relative effect of A+B versus sorafenib and lenvatinib using different methods. This random effects NMA approach allows for greater uncertainty in the relative effect of lenvatinib (see section 4.3.4.2 of the ERG report). • The ERG also considers that it is inappropriate to estimate the survival function for lenvatinib using the hazard ratio obtained from the NMA. Doing so assumes that the relative effect of lenvatinib versus A+B is constant over time (proportional hazards), which may not be the case. • The ERG would have preferred to have seen a single random effects NMA allowing for time-varying treatment effects. The results of a fractional polynomial NMA were presented by the company, but this was from a fixed effects model rather than a random effects model and it did not sufficiently critique the results.	• The results from the indirect comparison are uncertain. • The results of the NMA may have been inappropriately used to model lenvatinib survival. • Therefore, the clinical and cost-effectiveness estimates for A+B compared with lenvatinib are uncertain. • A single random effects NMA allowing for time-varying treatment effects should be explored.
3. The effect of subsequent treatments on overall survival	• Upon discontinuation of A+B or sorafenib, patients in IMbrave150 could receive a range of subsequent therapies (see section B.3.5.1 of the company submission). This is not consistent with NHS practice, where the only second-	• The statistical analysis from the company that purported to adjust OS for subsequent treatments not recommended

	line therapy currently recommended is regorafenib (after sorafenib). • At the clarification stage, the company provided an analysis to adjust survival estimates to remove the effect of treatments not recommended in England. This analysis improved the cost effectiveness of A+B relative to sorafenib. • The ERG was not able to critique the company's analysis, stating that the company provided insufficient detail (see section 4.2.5.5.2 of the ERG report). Therefore, the effect on overall survival of subsequent treatments that are not used by the NHS, and the size and direction of bias it has on cost-effectiveness estimates, are unknown.	in England cannot be considered robust. • The effect on survival and cost-effectiveness estimates is not known. This creates additional uncertainty for decision making.
4. Capping of utilities	• The company's base-case utility values, based on a time-to-death approach, suggest patients who are more than 15 weeks from death have a higher utility than the age-matched general population (Ara & Brazier, 2010). • At clarification, the company stated that this is plausible assumption because the general population includes people who are less than 15 weeks to death. • The ERG believes this higher utility is extremely unlikely (see section 4.3.4.5 of the ERG report). Its exploratory analysis capped utility at the age- and sex-matched population level. This causes a small increase in the A+B ICERs compared with the company's base-case analysis.	• It is not plausible that the average utility of people with unresectable HCC is higher than the average utility for the age- and sex-matched general population. • Utility values should be capped at the general population level.
5. Dosing assumptions	• The company's base-case model included 3 approaches to estimate drug dosing: 1) Using IMbrave150 patient characteristics to calculate the planned dose per patient (company's base case). 2) Using the mean actual dose, including observed reduced dosing intensity (RDI). 3) Using the mean actual dose, but assuming 100% dosing intensity. • The ERG proposed an alternative scenario (see section 4.3.4.3 of the ERG report):	• Scenarios 2 and 2b are the most appropriate for decision making. The 'true' dosages are likely to be in between these 2 assumptions.

	2b) Using the RDI for vial-based atezolizumab, but planned dosage for sorafenib and lenvatinib, as savings on unused tablets may not be recouped. • The ERG produced exploratory analyses using scenario 2, with lenvatinib RDI from the REFLECT trial (slightly increases the A+B ICERs), and 2b (reduces the ICERs).	
6. Wastage assumptions for oral chemotherapy	• The company's model calculates acquisition costs for sorafenib and lenvatinib on a weekly basis. It does not capture drug wastage from patients discontinuing or dying during a model cycle. • The appraisals of sorafenib (TA474) and lenvatinib (TA551) both considered the issue of drug wastage (see section 4.3.4.4 of the ERG report). In TA474, the committee concluded that most plausible ICER should capture drug wastage for up to 7 days. • The ERG accounted for oral chemotherapy wastage by using the proportion of patients still on treatment at the start of a cycle. This added 3.5 days of drug costs for discontinuing patients. A further 3.5 days of costs were added to give 7 days of drug wastage costs. • This causes a small decrease in the A+B ICERs compared with the company's base-case analysis.	• Costs associated with oral chemotherapy wastage should be included in the analysis.

7. Costing subsequent treatments	• As described in issue 3, IMbrave150 included subsequent therapies that are not consistent with NHS practice. The company's base-case model assumes that the 44% of patients on sorafenib who had subsequent systemic treatments would have regorafenib (and incur associated costs), whereas patients on either A+B or lenvatinib were assumed to have no further treatments (see section B.3.5.1 of the company submission). • The ERG considered 3 scenarios exploring the effect of different assumptions about subsequent treatment costs (see section 4.4.8 of the ERG report): 1) Including the cost of immunotherapy (nivolumab) and tyrosine kinase inhibitors (lenvatinib, regorafenib and sorafenib) only. 2) Including the cost of all subsequent treatments. 3) Excluding the cost of all subsequent treatments. • The ERG stated a preference for scenario 1. It described scenarios 2 and 3 as extreme assumptions providing the possible ICER range for A+B. • Scenario 1 does not alter cost-effectiveness conclusions compared with the company's base-case analysis. Scenario 2 dramatically reduces the ICERs. Scenario 3 slightly increases the ICERs.	• Because the ERG was not able to critique the company's analysis to adjust survival estimates to remove the effect of treatments not recommended in England, it is more appropriate to include the effect of those treatments, and also to include the cost of those that are likely to affect survival. • Therefore, the most appropriate scenario for decision making is to include the costs of subsequent immunotherapy and tyrosine kinase inhibitors only.
8. End of life criteria	• The company puts forward the case that A+B meets the NICE end of life criteria (see section B.2.1.3 of the company submission). • The ERG agrees that both criteria appear to be met (see section 6 of the ERG report).	• Both NICE end of life criteria appear to be met.

2 Questions for engagement

Distribution chosen for overall survival

1. What percentage of people would you expect to still be alive, having received sorafenib, at 2 years, 5 years and 10 years?

Indirect treatment comparison

2. Would the relative effectiveness of lenvatinib compared with A+B be expected to remain constant over time?

3. Why is it not feasible to fit time-varying random effects models as described by Ouwens et al (2010), given that it would require the same likelihood function for the fractional polynomial analysis provided by the company in response to clarification question A7? Can these now be provided?

Effect of subsequent treatments on overall survival

4. Please can full details be provided of the company's analysis conducted to adjust OS for the subsequent treatments not currently recommended in England?

Capping of utilities

5. Is it plausible that the health-related quality of life of a person with HCC would be better than the general population average for the same age and sex?

Dosing assumptions

6. To what extent can unused tablets for oral chemotherapy be reused?

Wastage assumptions for oral chemotherapy

7. Is it appropriate to consider up to 7 days wastage for oral chemotherapy treatments?

Costing subsequent treatments

8. Which of the 4 approaches to the costing of subsequent treatments outlined in issue 7 is the most appropriate?

NICE National Institute for Health and Care Excellence

Technical engagement response form

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

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Deadline for comments **4 September 2020**

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- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted

under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement 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.

About you

Your name	**Sophie Guest**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**

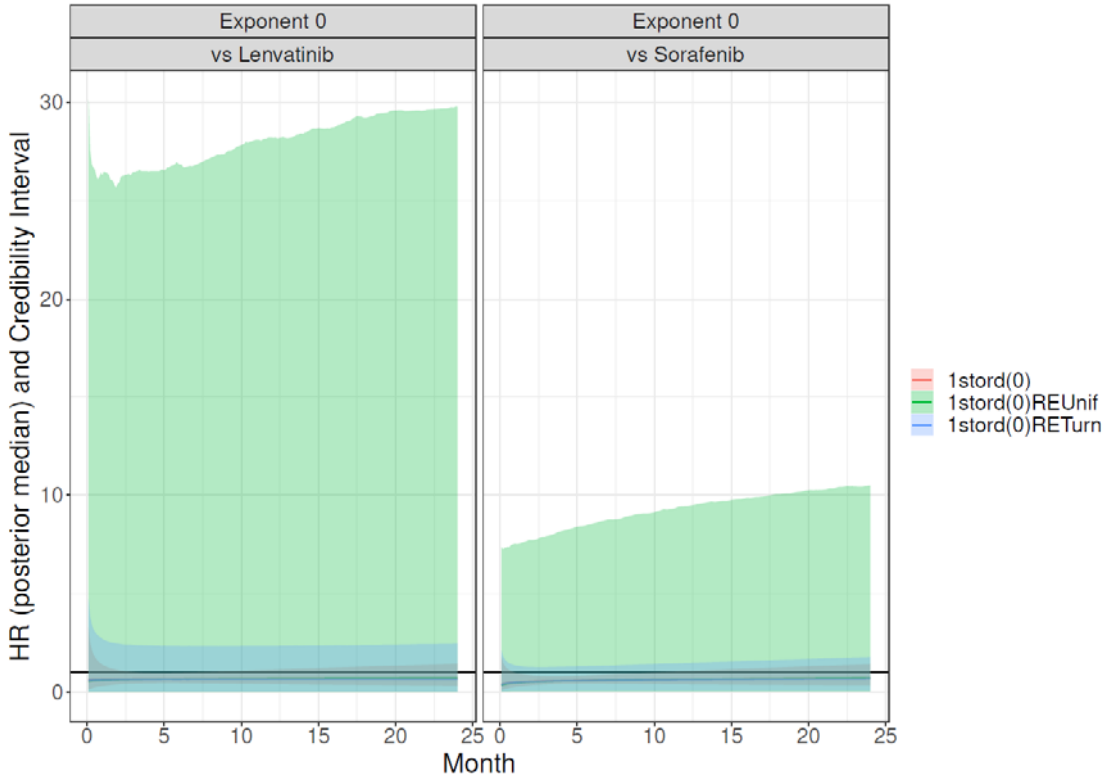
Questions for engagement

Issue 1: Distribution chosen for overall survival	
What percentage of people would you expect to still be alive, having received sorafenib, at 2 years, 5 years and 10 years?	Roche agree with the ERG and the NICE technical team that the log-normal model provides the best statistical fit to the data and is a suitable alternative to the exponential model. However, Roche consulted an HCC clinical expert to find out the 'true' proportion of patients expected to be alive after having received sorafenib at 2 years, 5 years and 10 years, as seen in clinical practice. The clinical expert confirmed that the true figures seen in clinical practice are lower than currently predicted, approximately 20% alive at 2 years, 2-4% alive at 5 years & <1% alive at 10 years. These figures are lower than the proportions predicted by both the exponential and the log-normal models, 28%, 4% and 0%, and 30%, 10% and 3%, respectively. This is most likely due to the subsequent therapy that patients received in IMbrave150, which exaggerated the OS benefit of sorafenib. If the scenario to adjust OS by removing the survival gain from subsequent therapies not approved in the UK is applied in the cost-effectiveness model, both the exponential and the log-normal models predict proportions more closely aligned with clinical practice, 22%, 2% and 0%, and 23%, 6% and 2%, respectively. In light of the above point, Roche is of the opinion that both, the exponential and log-normal extrapolation, are clinically plausible.
Issue 2: Indirect treatment comparison	
Would the relative effectiveness of lenvatinib compared with atezolizumab plus bevacizumab be expected to remain constant over time?	Clinical experts were consulted to confirm if the relative effectiveness of lenvatinib compared with Atezo+Bev would remain constant over time. In terms of overall survival, lenvatinib was only able to show non-inferiority compared to sorafenib in the REFLECT trial. Therefore, we would expect any long-term differences between lenvatinib and Atezo+Bev to be very similar to the

	difference in relative effectiveness of sorafenib compared with Atezo +Bev. As explained during the clarification stage, the initial relative effectiveness would remain constant, however over the medium or long term, the relative effectiveness may differ due to the different mechanism of action between an immunotherapy and a TKI. However, whether there is a constant or non-constant effect, as we do not have the data to reliably model the long-term treatment effect of Atezo+Bev vs lenvatinib, we cannot definitively conclude on the nature of the long-term treatment effect.
A. Why is it not feasible to fit time-varying random effects models as described by Ouwens et al (2010), given that it would require the same likelihood function for the fractional polynomial analysis provided by the company in response to clarification question A7? B. Can these now be provided?	Roche felt it was inappropriate to use a time-varying random effects model as described by Ouwens et al (2010) (1), as using random effects in the context of fractional polynomials/Ouwens method is not the same as in the context of the traditional NMA with a constant hazard ratio. Under a frequentist approach, there are not enough trials to inform the random effects. Under a Bayesian approach, there is no evidence available in terms of informative priors to use for the uncertainty of all the parameters involved, especially regarding the heterogeneity of the time coefficient. The results of the point estimates, the visual analyses and the Schoenfield residuals tests all point to the fact that there is a very small difference between a constant hazard ratio and a time-varying hazard ratio. The only differences emerge after a significant number of years, but at this point, the uncertainty around the point estimate is huge, as there is barely any information available to inform the time-varying HR, so the prediction is likely to be poor. The advantage of using a Bayesian random effects model in the traditional approach is that there are valuable informative priors like the ones from Turner et al. (2015) that can be used to inform the heterogeneity parameter (2). Despite these concerns, and as requested by the ERG and the NICE technical team, a single random effects NMA allowing for time-varying treatment effects has been added to the cost-effectiveness model as an option to model sorafenib and lenvatinib OS. The approach followed relies on assuming heterogeneity for the intersect of the fractional polynomial while assuming fixed effects for the time depending coefficients. This was done for two reasons. Firstly, to keep the uncertainty under control, as assuming heterogeneity on time depending coefficients would also involve priors on that heterogeneity and on the correlation between the parameters. This is usually implemented through a Wishart distribution, which has interesting statistical properties but is hard to interpret in terms of informative and uninformative priors. Using random effects on both intercept and slope would make uncertainty extremely big and non-practical. The second reason is that random effects only on the intercept makes the interpretation of the model fairly simple and allows to use the Turner et

al. (2015) informative priors (2). The use of this informative prior is vital to have a result that allows some inference based on the point estimates, as using uninformative priors makes any inference practically meaningless. For example, Figure 1 considers a random intercept effects model with Uniform (0,2) prior on the standard deviation (in green), the random intercept with Turner prior on the variance (in blue), and the fixed effects model (in red). The models were run for 75,000 iterations, with a burn-in of 10,000 iterations. Convergence was assessed visually based on the trace, density, autocorrelation and running mean plots.

Figure 1: Hazard Ratio and Credibility Intervals for 1st order FP with exponent 0



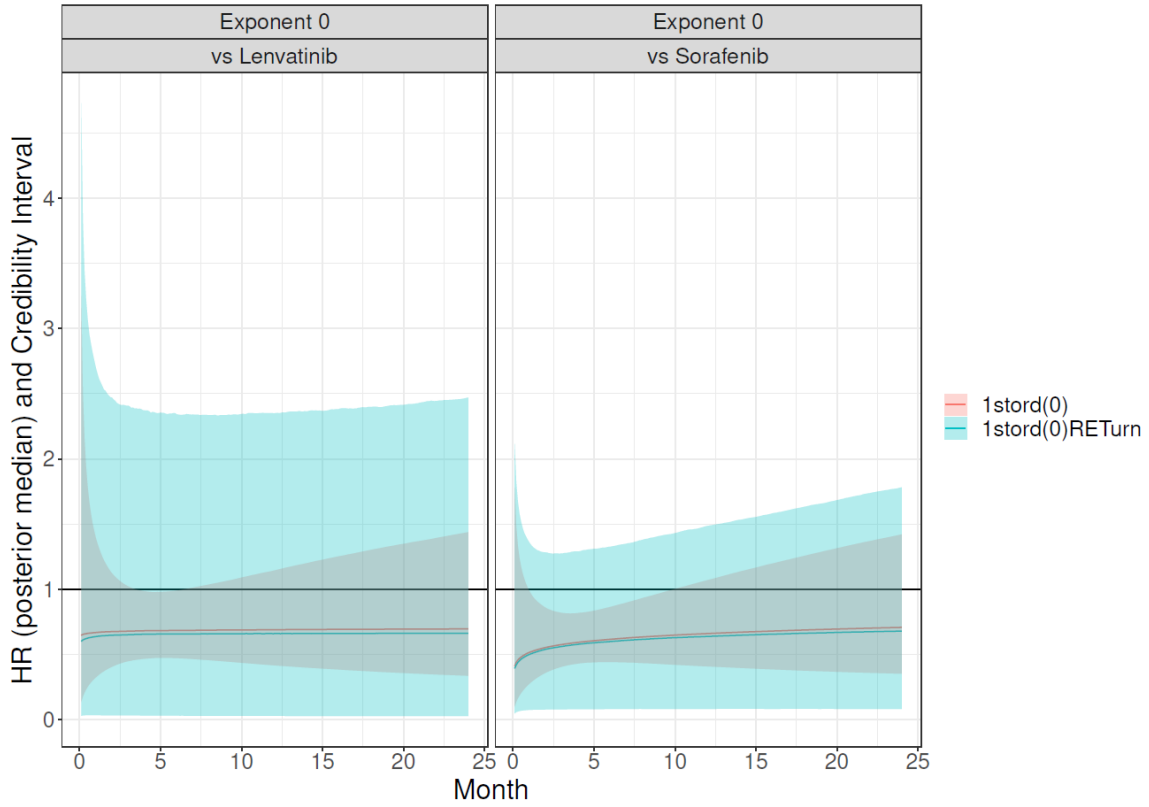
The model chosen was a first order random effects fractional polynomial with exponent equal to 0 (which would indicate that the log hazard rate has the form $\ln(h_{jkt}) = \beta_{0jk} + \beta_{1jk}\log(t)$, and this corresponds to a Weibull distribution. This decision was based on the DIC criteria among first order fractional polynomials and on the fact that second order polynomials tend to over-fit and have issues of convergence (see Table 1 for DIC results). Note the parallelism between the Weibull distribution approach from Ouwens et al. (2010) and this method (1).

Table 1: Summary of Fractional Polynomial models

Model	Order	Exponents	Random Effects (intercept)	Prior	DIC	pD	meanDev
FP (1o,0, FE)	1	0	NULL	NULL	1935.4	8	1927.4
FP (1o,1, FE)	1	1	NULL	NULL	1973.4	8	1965.5
FP (2o,01, FE)	2	0, 1	NULL	NULL	1880.5	12	1868.3
FP (2o,00, FE)	2	0, 0	NULL	NULL	1878.5	11.9	1866.6
FP (1o,0, REint, Uni)	1	0	TRUE	Uniform	1935.1	7.9	1927.4
FP (1o,0, REint, LN)	1	0	TRUE	Turner	1935.4	8	1927.4
FP (1o,1, REint, Uni)	1	1	TRUE	Uniform	1973.2	7.8	1965.6
FP (1o,1, REint, LN)	1	1	TRUE	Turner	1973.4	8	1965.4
FP (2o,00, REint, Uni)	2	0, 0	TRUE	Uniform	NaN	NaN	1866.6
FP (2o,00, REint, LN)	2	0, 0	TRUE	Turner	1878.7	12	1866.9
FP (2o,01, REint, Uni)	2	0, 1	TRUE	Uniform	1880.1	11.8	1868.3
FP (2o,01, REint, LN)	2	0, 1	TRUE	Turner	1880.7	12.3	1868.5

In this case, the results indicate that the random effects FP credibility intervals are much wider than the fixed effects FP, which makes inference ambiguous and prediction based on the point estimates less credible (see Figure 2, similar to Figure 1 but without the case of uninformative priors). The point estimate is now slightly below the one obtained through fixed effects, which improves the results for Atezo+Bev based on the point estimate (but with much higher uncertainty, as the 95% credibility interval for the hazard ratio essentially increases from 0 to higher than 2 at any point in time).

Figure 2: Hazard Ratio and Credibility Intervals for 1st order FP with exponent 0 (excluding uninformative prior)



The RE FP can be selected in the 'Model Inputs' tab cells G59, G60 and G62. Table 2 highlights the model results using the time varying random effects NMA for Lenvatinib. The scenario for sorafenib remains unchanged (uses data from the sorafenib arm in the IMbrave150 trial). Please note these results also include other updates applied to the cost-effectiveness model during the technical engagement stage (including the Log-normal model to extrapolate OS, capping of utilities, dosing adjustments, wastage of oral treatments, costing of subsequent therapy).

Table 2: Model results using a 1st order RE FP with exponent 0 (Turner prior on the intercept)

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	50,699	1.92	1.33	[redacted]	[redacted]	[redacted]	14,978	20,354
Lenvatinib	73,772	1.75	1.25	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Issue 3: The effect of subsequent treatments on overall survival

Please can full details be provided of the company's analysis conducted to adjust overall survival for the subsequent treatments not currently recommended in England?

The method used to adjust survival estimates by removing the effect of treatments not recommended in England is a two stage accelerated failure time (AFT) model (3).

Firstly, patients that are "switching" to subsequent therapy not recommended in England are identified. PFS is then used as a second baseline to determine the time after progression until the end of subsequent therapy. The method works on the assumption that a "second baseline" can be defined for all patients in the control arm as the time when they are at risk of switching (for example at disease progression or at discontinuation of first line treatment). This second baseline should be defined by a single clinically meaningful event for all patients.

An AFT model was fitted (Weibull) to compare switchers to non-switchers, with stratification variables also included in the regression, to see the impact it has on patients depending on whether they switched or not.

Finally, the survival time of the patients that crossed over is shrunk by the estimated acceleration factor, so that the "treatment effect" of the subsequent therapy is removed. The model was fitted using the survreg package in R with region, AFP and MVI/EHS as stratification variables.

For clarity, please see the code that was used.

#This code uses a 2 stage Weibull AFT to generate adjusted survival to correct for the fact that some patients undergo subsequent therapy
#Note that this code is for the UK, so regorafenib has been excluded from this adjustment

```
rm(list = ls())


if (!require("pacman")) install.packages("pacman")
pacman::p_load(SAICE, , survival, ggplot2, dplyr, reshape2)

#Import data
initialize_connection()

adsl <-
   read_entimice(

"root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/outdata_vad/adsl.sas7bdat"
   )


adtte <-
   read_entimice(

"root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/outdata_vad/adtte.sas7bdat"
   )

adcm <-
   read_entimice(

"root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/outdata_vad/adcm.sas7bdat"
   )
close_connection()

adsl.arm <- adsl %>% select(USUBJID,ARMCD)

adtte.arm <- adtte %>% left_join(adsl.arm)

adcm.proc <- adcm %>%
```

```
  mutate(time_treat= ifelse(is.na(CMENDY) & CMENTPT=="END OF STUDY",
                            (as.numeric(as.Date(DCUTDT,"%Y-%m-%d") - as.Date(CMSTDTC,"%Y-%m-%d") +1))/30.4167,
#Time of subsequent therapy as numeric
                            (CMENDY - CMSTDY +1)/30.4167)
         ) %>%
  left_join(adsl.arm)

adcm.mindate <- adcm.proc %>%
  filter(!(CMDECOD=="REGORAFENIB" & ARMCD=="ARM_B")) %>% #Exclude all treatments not approved in
England
  filter(CMCAT %in% c("FOLLOW-UP CANCER SYSTEMIC THERAPY","FOLLOW-UP LOCAL CANCER THERAPY")
& ITTFL=="Y")%>%  #Local and systemic therapies
  group_by(USUBJID) %>%
  mutate(date.num=as.numeric(CMSTDY)) %>%
  filter(date.num==min(date.num,na.rm=T)) %>%
  select(USUBJID,CMSTDTC) %>%
  distinct()

adtte.analysis <- adtte.arm %>% left_join(adcm.mindate,by="USUBJID")




os.adtte <- adtte.analysis %>% filter(PARAMCD=="OS" & ANL01FL=="Y")%>%
  mutate(
    AVAL.SUBS=(as.Date(CMSTDTC,"%Y-%m-%d") - as.Date(STARTDT,"%Y-%m-%d")  +1) /30.4375 #construct time
of medication as numeric
    ) %>%
  mutate(
    AVAL.SUBS2 = ifelse(is.na(AVAL.SUBS),0,AVAL.SUBS),
    rx=ifelse(1- AVAL.SUBS2/AVAL<0,0,1- AVAL.SUBS2/AVAL),
    sub=as.numeric(!rx<1),
    sub2=ifelse(ARMCD=="ARM_A",1,0),
    censyrs = (as.Date(DCUTDT,"%Y-%m-%d") - as.Date(STARTDT,"%Y-%m-%d")  +1) /30.4375 #construct censoring
time as numeric
```

```
    )

#Two stage AFT

event_PFS<-  adtte.analysis %>% filter(PARAMCD=="PFSDF" & ANL01FL=="Y") %>% select(USUBJID, AVAL)
colnames(event_PFS)[2]<-"timePFS" # rename col so can be merged with dataset containing AVAL

os.adtte.pfs <- os.adtte %>% left_join(event_PFS,by='USUBJID') %>%
  mutate(switch=as.numeric(!is.na(AVAL.SUBS))) %>%
  mutate(time_from_b=AVAL - timePFS + 0.01) #construct time after baseline used

os.adtte.atez <- os.adtte.pfs %>% filter(ARMCD=="ARM_A")
os.adtte.sora <- os.adtte.pfs %>% filter(ARMCD=="ARM_B")

#Fit AFT model to control subjects to compare switchers to non-switchers
#Stratification variables are also included
Fit_AFT<- survreg(Surv(time_from_b, CNSR==0)~switch + strata(REGION2)+strata(MVI_EHS2)+strata(AFPC2),
                  data=os.adtte.atez,
                  dist="weibull")

## Survival time of those patients in control arm that crossed over is shrunk by the estimated acceleration factor
AF<-exp(-Fit_AFT$coefficient[2])

## Calculate adjusted time2 (OS time)
# If no switching the OS time is unadjusted, if switched, adjust by shrinking post switch survival time
os.adtte.atez.adj <- os.adtte.atez%>% mutate(AVAL.adj=ifelse(switch==0,AVAL,time_from_b*AF+timePFS))

##Survival analysis could be performed from this point (as for ITT above) with time2_adjusted as the response.
Fit_AFT<- survreg(Surv(time_from_b, CNSR==0)~switch + strata(REGION2)+strata(MVI_EHS2)+strata(AFPC2),
                  data=os.adtte.sora,
                  dist="weibull")

## Survival time of those patients in control arm that crossed over is shrunk by the estimated acceleration factor
AF<-exp(-Fit_AFT$coefficient[2])
```

	## Calculate adjusted time2 (OS time)
	# If no switching the OS time is unadjusted, if switched, adjust by shrinking post switch survival time
	os.adtte.sora.adj <- os.adtte.sora%>% mutate(AVAL.adj=ifelse(switch==0,AVAL,time_from_b*AF+timePFS))
	
	os.final <- rbind(os.adtte.atez.adj,os.adtte.sora.adj) %>% select(USUBJID,AVAL.adj)
	
	write.csv(os.final,file="Other_Analyses/trt_switching_subseqth/os_adj.csv", row.names = F)

Issue 4: Capping of utilities	
Is it plausible that the health-related quality of life of a person with unresectable or advanced hepatocellular carcinoma would be better than the general population average for the same age and sex?	The utility values used in the model were derived from the recent trial data whereas the population norms reported in the literature may be outdated. Nevertheless, Roche agrees that it is not plausible that the health-related quality of life of a person with HCC would be better than the general population average for the same age and sex. Therefore, the utility values have been capped at the general population level. This amendment has been included in a revised cost-effectiveness model.
Issue 5: Dosing assumptions	
To what extent can unused tablets for oral chemotherapy be reused?	Clinical experts were consulted to find out to what extent unused tablets for oral chemotherapy could reused. Current pharmacy policy states that once the treatment has been dispensed to the patient, they are not re-used. Even if the patient were to return unused oral chemotherapy back to the pharmacist, the medicine would be destroyed. Therefore, Roche are in agreement with the ERG that the most appropriate dosing scenario is to use the RDI for vial-based atezolizumab and bevacizumab, but the planned dosage for sorafenib and lenvatinib, as unused tablets cannot be reused (scenario 2b). This amendment has been included in a revised cost-effectiveness model.
Issue 6: Wastage assumptions for oral chemotherapy	

Is it appropriate to consider up to 7 days wastage for oral chemotherapy treatments?	Roche consulted clinical experts to find out if it is appropriate to consider up to 7 days wastage for oral chemotherapy treatments. This assumption is probably on the conservative side however, an appropriate assumption to make, and therefore Roche agree with the ERG and the NICE technical team that oral chemotherapy wastage should be included in the analysis. This has been included in the revised cost-effectiveness model.
Issue 7: Costing subsequent treatments	
Which of the 4 approaches to the costing of subsequent treatments outlined in issue 7 is the most appropriate?	In the absence of using the scenario to adjust OS for the use of subsequent therapies not recommended in England, Roche agree with the ERG and the NICE technical team that the most appropriate scenario for decision-making is to include the costs of subsequent immunotherapy and tyrosine kinase inhibitors only (scenario labelled 'Trial data: Imbrave 150' in the CEM'). If the scenario adjusting OS is deemed valid after the additional information has been reviewed (Issue 3), the most appropriate costing option would be to cost only the use of regorafenib (scenario labelled 'Sorafenib arm only receive regorafenib – proportion from trial').

Please see below the updated base-case results based on the above changes.

Table 3: Base case results: Post technical engagement

	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Atezo+Bev	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sorafenib	50,699	1.92	1.33	[redacted]	[redacted]	[redacted]	14,978	20,354
Lenvatinib	73,386	1.69	1.21	[redacted]	[redacted]	[redacted]	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

1. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods. 2010;1(3-4):258-71.
2. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med. 2015;34(6):984-98.
3. Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, et al. Adjusting survival time estimates to account for treatment switching in randomized controlled trials--an economic evaluation context: methods, limitations, and recommendations. Med Decis Making. 2014;34(3):387-402.

NICE National Institute for Health and Care Excellence

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- Do not use abbreviations.
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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

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About you

Your name	**Professor Tim Meyer**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Physicians**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Distribution chosen for overall survival	
What percentage of people would you expect to still be alive, having received sorafenib, at 2 years, 5 years and 10 years?	**At 2 years, published data suggests around 25% survival outside of trials (King J et al Clinical Oncology 2017, Edeline J et al E J Cancer 2017, Labeur T el al Liver International 2020. Data at 5 and 10 years but is estimated to be less than 10% at five years https://www.cancer.org/cancer/liver-cancer/detection-diagnosis-staging/survival-rates.html and less than 3% at 10 years**
Issue 2: Indirect treatment comparison	
Would the relative effectiveness of lenvatinib compared with atezolizumab plus bevacizumab be expected to remain constant over time?	**The survival for patients treated with sorafenib or lenvatinib seems to decline steadily and the number of long term survivors is very low. The survival data for Atezo/Bev is very immature and further follow-up is required to understand long term survival. However, in other tumour types, it has been observed that those patients who respond to PD1/PD-L1 inhibition can have very durable responses resulting in a significant proportion of patients at the long term tail of the survival curve. If this is the case in liver cancer, it is possible that the survival curves will become increasingly divergent. The PFS survival curves are consistent with this and show divergence with time but 20-30% seem to have progressed at 15 months and the curve is not flat so it is likely that durable responses will occur in less than 20%.**
A. Why is it not feasible to fit time-varying random effects models as described by Ouwens et al (2010), given that it would require the same likelihood function for the fractional polynomial analysis provided by the	**Not my area of expertise**

company in response to clarification question A7? B. Can these now be provided?	
Issue 3: The effect of subsequent treatments on overall survival	
Please can full details be provided of the company's analysis conducted to adjust overall survival for the subsequent treatments not currently recommended in England?	**International guidelines are currently being re-drafted in light of Atezo/Bev becoming first line and it is likely that these will recommend a TKI such as sorafenib and lenvatinib. Although the level of evidence is low, it is acknowledged that there is a scientific rational for offering TKIs with proven benefit in advanced HCC to those that have not received them. This will include those patients who progress on atezo/bev which will be the majority. So, while this not current practice in the UK, the treatment algorithm will be revised providing funding is approved. A 20-30% estimate for subsequent TKI use is reasonable if allowed in UK.**
Issue 4: Capping of utilities	
Is it plausible that the health-related quality of life of a person with unresectable or advanced hepatocellular carcinoma would be better than the general population average for the same age and sex?	Very unlikely
Issue 5: Dosing assumptions	
To what extent can unused tablets for oral chemotherapy be reused?	Once tablets are dispensed for one patient, they cannot be used for other patients.
Issue 6: Wastage assumptions for oral chemotherapy	

Is it appropriate to consider up to 7 days wastage for oral chemotherapy treatments?	It is routine for oral anti-cancer therapy to be prescribed for 4-6 weeks at a time and up to 7 days wastage is plausible.
Issue 7: Costing subsequent treatments	
Which of the 4 approaches to the costing of subsequent treatments outlined in issue 7 is the most appropriate?	

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Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
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information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement 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.

About you

Your name	**Dr Paul Ross**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**

Questions for engagement

Issue 1: Distribution chosen for overall survival	
What percentage of people would you expect to still be alive, having received sorafenib, at 2 years, 5 years and 10 years?	I agree with the ERG and the NICE technical team that the log-normal model provides the best statistical fit to the data and has previously been demonstrated to be the most appropriate distribution for extrapolating survival in patients treated with sorafenib [Muszbek et al. Curr. Med. Res. Opin. 2012; 28: 1-13]. However, all models tend to over-estimate the numbers of survivors after having received sorafenib at 2 years, 5 years and 10 years compared to that we observe in clinical practice. A secondary analysis from the RESORCE trial [Finn et al. J. Hepatol. 2018; 69: 353-358] in a population that continued to have a performance status of 0-1 and Childs-Pugh score of A at the time of disease progression on sorafenib demonstrated 2-year survival in the sorafenib-placebo sequence of 20% with a 5-year survival of 3%. In practice following sorafenib only 20 – 40% of patients are considered suitable for second line therapy. Therefore, in clinical practice the real 2-year survival is in the region of 10-15% with 5-year survival < 2% and 10-year survival <1% These figures are lower than the proportions predicted by both the exponential and the log-normal models, 28%, 4% and 0%, and 30%, 10% and 3%, respectively. This is most likely due to: 1. The requirements of the study entry being marginally more stringent than is applied in routine clinical practice; 2. Subsequent therapy that patients included in the IMbrave150 study exaggerated the OS benefit of sorafenib.

Issue 2: Indirect treatment comparison	
Would the relative effectiveness of lenvatinib compared with atezolizumab plus bevacizumab be expected to remain constant over time?	In the REFLECT trial lenvatinib was only able to show non-inferiority compared to sorafenib in the studies primary end point of overall survival. Therefore, it would be anticipated that long-term survival differences between lenvatinib and atezolizumab + bevacizumab would be similar the differences observed of survival with sorafenib compared to atezolizumab + bevacizumab. Whilst the long-term real world clinical experience is shorter with Lenvatinib than sorafenib based on the primary end-point of the REFLECT study there is no indication that 2-year, let alone 5- or 10-year survival will differ in a major way from that observed with sorafenib. In respect of atezolizumab + bevacizumab follow-up from the IMBrave 150 study is currently relatively short but given the different mechanism of action long-term follow-up may demonstrate a cohort of patients in this combination results in long -term disease control.
A. Why is it not feasible to fit time-varying random effects models as described by Ouwens et al (2010), given that it would require the same likelihood function for the fractional polynomial analysis provided by the company in response to clarification question A7? B. Can these now be provided?	This is a technical question regarding modelling and is out with my expertise.
Issue 3: The effect of subsequent treatments on overall survival	
Please can full details be provided of the company's analysis conducted to adjust overall survival for the subsequent treatments not currently recommended in England?	I am an independent Medical Adviser to Roche and do not have the details of this analysis

Issue 4: Capping of utilities	
Is it plausible that the health-related quality of life of a person with unresectable or advanced hepatocellular carcinoma would be better than the general population average for the same age and sex?	No it is not plausible that the health-related quality of life with a person with unresectable/advanced HCC would have be better than the general population average for the same age and sex. There are a number of considerations: 1. The symptoms associated with the background chronic liver disease, even when function is well controlled. Many will have some level of fatigue and other non-specific constitutional symptoms. 2. Advanced HCC can also result in similar constitutional symptoms. In addition, in some patients there may be pain associated with the primary tumour or metastases amongst other symptoms. 3. In patients remaining of relatively good performance status with well preserved liver function tyrosine kinase inhibitors contribute to the reduced quality of life due to side effects. In the clinic, even those considered to be tolerating treatment well and not requiring dose adjustments often report fatigue, altered taste, loss of appetite, weight loss and changes in bowel habit. 4. As observed in the analysis from IMBrave 150 describing patient reported outcomes these were significantly better with atezolizumab + bevacizumab compared to sorafenib.
Issue 5: Dosing assumptions	

To what extent can unused tablets for oral chemotherapy be reused?	Current pharmacy policy in the NHS states that once the treatment has been dispensed to the patient, medications are not re-used. Therefore, when a patient returns unused oral chemotherapy back to the pharmacist, the medicine would be destroyed. Changes in practice due to the COVID pandemic have resulted in an increase in virtual appointments for patients treated with tyrosine kinase inhibitors (sorafenib & lenvatinib). This is supported by drug being sent to the patients by courier. In order to mitigate the costs of the courier pharmacies in some hospitals preferring to send 2 months supply of medication at a time. This will inevitably increase the risk of drug wastage.
Issue 6: Wastage assumptions for oral chemotherapy	
Is it appropriate to consider up to 7 days wastage for oral chemotherapy treatments?	This assumption is probably on the conservative, particularly at present given some of the changes to practice described in 5. above. Therefore I agree that oral chemotherapy wastage should be included in the analysis.
Issue 7: Costing subsequent treatments	
Which of the 4 approaches to the costing of subsequent treatments outlined in issue 7 is the most appropriate?	Based on NICE guidance patients treated in the NHS with sorafenib may be offered regorafenib at the time of progression. When the choice of therapy is Lenvatinib patients treated in the NHS have no subsequent anti-cancer therapy available. Patients will be offered treatment within a clinical trial where appropriate and available or active supportive care alone.

	Data on outcomes to subsequent therapies following treatment with atezolizumab + bevacizumab has not been reported to date. Therefore, the most appropriate to scenario is that which excludes treatments not currently recommended in England.

Additional question for clinical experts following technical engagement teleconference [ID1655]

Question	Clinical expert 1	Clinical expert 2
What would you expect to happen to the risk (hazard) of death over a 10 year period for people with untreated HCC who have: 1. sorafenib? 2. lenvatinib? 3. atezolizumab with bevacizumab? For example, you might consider that the risk of death: - increases over time (e.g. as disease becomes more progressive), - decreases over time (e.g. if people who survive for longer are generally fitter, or if treatment is disease-modifying), - stays roughly constant over time, - or something else (please specify, e.g. increases then decreases).	For sorafenib and lenvatinib I would expect the HR remains relatively constant for the first 2-3 years then there will be some long term survivors so HR will reduce. For Atezo Bev I would expect the HR to reduce progressively – in other words the non-responders with progress quickly and responders will become dominant with improved survival and lower HR.	No response.