Medicinrådet

Bilag til Medicinrådets anbefaling vedr. durvalumab i kombination med tremelimumab til førstelinje-behandling af voksne med fremskreden eller ikke-resektabel hepatocellulært karcinom (HCC)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. durvalumab i kombination med tremelimumab
2. Forhandlingsnotat fra Amgros vedr. durvalumab i kombination med tremelimumab
3. Ansøgers endelige ansøgning vedr. durvalumab i kombination med tremelimumab

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

22.11.2024

Draft assessment report regarding durvalumab (Imfinzi) in combination with tremelimumab (Imjudo) indicated for the first-line treatment of adults with unresectable hepatocellular carcinoma (uHCC)

AstraZeneca would like to thank you for the assessment of durvalumab in combination with tremelimumab (STRIDE) for first-line treatment of adults with unresectable hepatocellular carcinoma (uHCC) and appreciate the opportunity to comment on the draft report.

Overall, AstraZeneca find the DMC report to be balanced and thorough. However, we have one remark regarding the cost analysis and the assumed treatment duration that we would like to comment further upon.

The assessment report concludes that the MAIC analysis performed in the application shows that there are no differences in OS outcomes despite of differences in PFS between STRIDE and atezolizumab + bevacizumab. The 5-year follow-up OS data from the latest update of the HIMALAYA study further confirms the OS benefit of STRIDE.

Regarding PFS, the indirect comparison estimated an HR of 1.73 (95% CI; 1.30, 2.32) for STRIDE compared with atezolizumab + bevacizumab. In the DMC assessment report, this difference in PFS is acknowledged to be due to a difference in the mode of action, where the effect of STRIDE occurs by an indirect activation of the immune system and not directly on the tumor cells as is the case with bevacizumab. This difference means that the response of STRIDE is developing gradually (and more slowly), and therefore the effect to a greater extent will be reflected in long-term survival. Based on this it is concluded that the PFS is not as relevant an endpoint as OS in determining clinical equivalency between the two treatments, and therefore the focus in the assessment report is on the evaluation on OS.

Both STRIDE and atezolizumab + bevacizumab are administered until disease progression or intolerable adverse events according to the SmPC's. Consequently, we assume that the treatment duration is equal to PFS in the cost analysis. Data from the clinical studies show the median time on treatment was 5.5 months for STRIDE in HIMALAYA and 8.4 months for atezolizumab + 7.0 months for bevacizumab in IMbrave150.

In the assessment report, the main cost analysis assumes equal treatment duration between the two treatments, due to an assumption on equivalent efficacy. However, with the difference in PFS estimated in the MAIC analysis, and the differences observed in the respective clinical studies regarding median time on treatment, the results from the main analysis will most likely lead to an underestimation of the total treatment cost related to atezolizumab + bevacizumab compared to the real-life costs. As a consequence, a sensitivity analysis is presented in the assessment report where the difference in PFS is taken into consideration for the cost analysis and presented in the summary of the assessment report.

In conclusion, AstraZeneca would like to highlight that when evaluating the total costs, it is important to include differences in treatment duration, as this would likely be a more accurate reflection of the cost observed in clinical practice. Therefore, we would like to encourage DMC to account for the differences in treatment duration and put their main emphasis on the sensitivity analysis when evaluating STRIDE for uHCC patients in Denmark.

As a final note, STRIDE has demonstrated a clear OS benefit for patients with uHCC in the HIMALAYA trial, which showed that one in five patients was alive with STRIDE at the 5-year OS analysis, the longest follow-up in a phase 3 study within uHCC to date, and substantially longer than the 15.6 months follow-up for atezolizumab + bevacizumab in the IMBrave150 study. We hope that STRIDE will be made available for Danish patients with uHCC, so they can benefit from this treatment in the future.

Kind regards,

Mette Lange
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26.11.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.12.2024
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab) i kombination med Imjudo (tremelimumab)
Ansøgt indikation	Durvalumab i kombination med tremelimumab er indiceret til førstelinjebehandling af voksne med fremskreden eller ikke-resektabel hepatocellulært karcinom (HCC)
Nyt lægemiddel / indikationsudvidelse	Imfinzi, indikationsudvidelse/Imjudi, nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Imjudo (tremelimumab):

Tabel 1: Forhandlingsresultat Imjudo

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Imjudo	20 mg/ml	15 ml	155.726,82	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Imjudo, indkøbes lægemidlet til følgende SAIP:
[redacted]

Amgros har følgende aftalepris på Imfinzi (durvalumab):

Tabel 2: Aftalepris Imfinzi

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP, (DKK)	Rabatprocent ift. AIP
Imfinzi	50 mg/ml	10 ml	17.307,33	[redacted]	[redacted]
Imfinzi	50 mg/ml	2,4 ml	4.179,6	[redacted]	[redacted]

Aftaleforhold

Amgros har indgået en aftale med leverandøren, som gælder fra den 19.12.2024 til den 31.12.2025. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Aftalen på Imjudo gælder i samme periode som aftalerne på de øvrige immunterapier.

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler jf. Medicinrådet vurderingsrapport.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient for et års behandling

Lægemiddel	Styrke	Paknings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Imjudo	20 mg/ml	15 ml	300 mg IV på dag 1 i cyklus 1	[redacted]	[redacted]
Imfinzi	50 mg/ml	10 ml	1.500 mg IV hver 4. uge	[redacted]	[redacted]
Pris for kombinationsbehandling					[redacted]
Tecentriq	1.200 mg	1 stk.	1.200 mg IV hver 3. uge	[redacted]	[redacted]
Bevacizumab	25 mg/ml	16 ml	15 mg*/kg IV hver 3. uge	[redacted]	[redacted]
Pris for kombinationsbehandling					[redacted]

*Patientens vægt er 82 kg jf. Medicinrådets vurderingsrapport

Tabel 4: Sammenligning af lægemiddeludgifter pr. patient baseret på behandlingsvarighed baseret på PFS

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift (SAIP, DKK)
Imjudo	20 mg/ml	15 ml	300 mg IV på dag 1 i cyklus 1	[redacted]	[redacted]
Imfinzi	50 mg/ml	10 ml	1.500 mg IV hver 4. uge	[redacted]	[redacted]
Pris for kombinationsbehandling					[redacted]**
Tecentriq	1.200 mg	1 stk.	1.200 mg IV hver 3. uge	[redacted]	[redacted]
Bevacizumab	25 mg/ml	16 ml	15 mg/kg* IV hver 3. uge	[redacted]	[redacted]
Pris for kombinationsbehandling					[redacted]***

*Patientens vægt er 82 kg jf. Medicinrådets vurderingsrapport
**Behandlingsvarighed på 5,5 måneder jf. Medicinrådets vurderingsrapport
***Behandlingsvarighed på 8,4 måneder for Tecentriq og 7 måneder for bevacizumab jf. Medicinrådets vurderingsrapport

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Under vurdering	Link til vurdering

Konklusion

[redacted]

Application for the assessment of Imfinzi (durvalumab) in combination with Imjudo (tremelimumab) for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC).

Submitted by AstraZeneca: June 21st 2024
Re-submitted by AstraZeneca: August 3rd 2024
Re-submitted by AstraZeneca: September 2nd 2024

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

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Abbreviations

Abbrevation	Definition	Abbreviation	Definition
1L	First-line	LY	Life years
2L	Second-line	MAIC	Matching Adjusted Indirect Comparison
ADA	Anti-Drug Antibody	MHC	Major Histocompatibility Complex
AE	Adverse Event	mOS	Median Overall Survival
AFP	Alpha-Fetoprotein	MRI	Magnetic resonance imaging
ALBI	Albumin-bilirubin score	NAFLD	Non-Alcoholic Fatty Liver Disease
Atezo-bev	Atezolizumab with bevacizumab	OR	Odds Ratio
BIC	Bayesian information criterion	ORR	Overall Response Rate
BID	Bis In Die, dosing twice a day	OS	Overall Survival
CD	Cluster of Differentiation	PD	Progressed disease
CI	Confidence Interval	PD-L1	Programmed Death-Ligand 1
CNS	Central Nervous System	PF	Progression Free
CR	Complete Response	PFS	Progression Free Survival
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein-4	PPE	Palmar-Plantar Erythrodysesthesia (hand-foot syndrome)
CP	Child-Pugh score	PR	Partial Response
CT	Computerized tomography	PS	Performance Status
DCO	Data Cut-Off	PSP	Pharmacy Selling Price
DOR	Duration Of Response	Q4W	Dosing (Quaque) every 4 weeks

ECOG PS	Eastern Cooperative Oncology Group Performance Status	QALY	Quality-adjusted life years
EHS	Extra Hepatic Spread	RECIST	Response Evaluation Criteria in Solid Tumors
EMA	European Medicines Agency	SD	Standard Deviation
EPAR	European Public Assessment Report	SMQ	Standardised MedDRA Queries
ESMO	European Society for Medical Oncology	SOC	Standard of Care
FAS	Full Analysis Set	STRIDE	Single Tremelimumab Regular Interval Durvalumab regimen
GI	Gastrointestinal	TACE	Trans Arterial Chemoembolization
GP	General practitioner	TARE	Trans Arterial Radioembolization
HCC	Hepatocellular Carcinoma	TCR	T cell receptor
HBV	Hepatitis B Virus	TAI	Trans Arterial Infusion
HVC	Hepatitis C Virus	TARE	Trans Arterial Radioembolization
HR	Hazard Ratio	TEAE	Treatment Emergent Adverse Events
HTA	Health Technology Assessment	TRAE	Treatment-Related Adverse Events
ICER	Incremental cost-effectiveness ratio	TKI	Tyrosine Kinase Inhibitor
IgG1κ	Immunoglobulin G1-kappa	Treg	T regulatory cell
INR	International normalized ratio	TTD	Time to treatment discontinuation
IO	Immuno-Oncology	TTP	Time To Progression
ITC	Indirect Treatment Comparison	TTR	Time To Response
IV	Intravenous	uHCC	Advanced or unresectable Hepatocellular Carcinoma
KM	Kaplan–Meier	VEGF	Vascular Endothelial Growth Factor

1. Regulatory information on the medicine

Overview of the pharmaceutical – Imfinzi and Imjudo	
Proprietary name	Imfinzi + Imjudo. Dosing regimen named STRIDE
Generic name	**Imfinzi**: Durvalumab **Imjudo:** Tremelimumab
Therapeutic indication as defined by EMA	Imfinzi in combination with Imjudo is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
Marketing authorization holder in Denmark	**Imfinzi**: AstraZeneca AB SE-151 85 Södertälje Sverige **Imjudo**: AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	Imfinzi: L01FF03 (2) Imjudo: L01FX20 (3)
Combination therapy and/or co-medication	Imfinzi in combination with Imjudo
(Expected) Date of EC approval	Imfinzi: January 30th 2023: https://ec.europa.eu/health/documents/community-register/html/h1322.htm Imjudo: February 20th 2023:

Overview of the pharmaceutical – Imfinzi and Imjudo	
	https://ec.europa.eu/health/documents/community-register/html/h1713.htm
Has the pharmaceutical received a conditional MA?	**Imfinzi:** No **Imjudo**: No
Accelerated assessment in the EMA	**Imfinzi:** No **Imjudo:** No
Orphan drug designation	**Imfinzi**: No **Imjudo:** No
Other therapeutic indications approved by EMA	**Imfinzi:** **Biliary Tract Cancer (BTC)** • Imfinzi in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). **Non-Small Cell Lung Cancer (NSCLC)** • Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. • Imfinzi in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. **Small Cell Lung Cancer (SCLC)** Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). **Hepatocellular carcinoma (HCC)** Imfinzi as monotherapy is indicated for the first line treatment of adults with advanced or unresectable HCC. **Imjudo:** **Non-Small Cell Lung Cancer (NSCLC)** Imjudo in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.
Other indications that have been evaluated by the DMC (yes/no)	**Imfinzi:** yes **Biliary Tract Cancer (BTC) - completed** Imfinzi in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC. **Non-Small Cell Lung Cancer (NSCLC) - completed** Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. **Imjudo:** No
Dispensing group	**Imfinzi**: BEGR **Imjudo**: BEGR

Overview of the pharmaceutical – Imfinzi and Imjudo	
Packaging – types, sizes/number of units and concentrations	Imfinzi: 2.4 ml or 10 ml concentration 50 mg/ml Imjudo: 15 ml concentration 20 mg/ml

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Durvalumab in combination with tremelimumab for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
Dosage regiment and administration:	Tremelimumab (300 mg) is administered as a single intravenous dose (for 1 hour) in combination with intravenous infusion of durvalumab 1500 mg at cycle 1 (day 1) followed by durvalumab monotherapy every 4 weeks. Regimen named STRIDE.
Choice of comparator	Atezolizumab in combination with Bevacizumab (henceforth referred to as atezo-bev)
Prognosis with current treatment (comparator)	The median overall survival is approx. 20 months after chemoembolization, approx. 19 months after atezo-bev, 10-12 months after sorafenib treatment and 3-6 months for patients in supportive treatment(1, 4).
Type of evidence for the clinical evaluation	Indirect comparison (MAIC)
Most important efficacy endpoints	Landmark OS, OS hazard ratio
Most important serious adverse events for the intervention and comparator	STRIDE: The most common grade 3 or 4 adverse events with STRIDE were increased lipase (6.2%), and increased aspartate aminotransferase (5.2%).(5) Atezo-bev: The most common grade 3 or 4 adverse events with atezo-bev were hypertension (12%) and increased aspartate aminotransferase (5%).(1)
Impact on health-related quality of life	Clinical documentation: Positive trend only
Type of economic analysis that is submitted	Type of analysis: cost-minimizing for STRIDE vs atezo-bev. Type of model: partitioned survival model
Data sources used to model the clinical effects	HIMALAYA study(5) https://evidence.nejm.org/doi/10.1056/EVIDoa2100070

Summary	
Data sources used to model the HRQoL	HIMALAYA study
Life years gained	N.A.
QALYs gained	N.A.
Incremental cost per patient	DKK –106 109 (STRIDE cost saving vs. atezo-bev)
ICER (DKK/QALY)	N.A.
Uncertainty associated with the cost estimates	• We have assumed equal treatment durations. With treatment duration based on hazard ratio for PFS according to the indirect treatment comparison, the cost savings with STRIDE would be larger. • There is some uncertainty in long-term extrapolations of progression-free and overall survival.
Number of eligible patients in Denmark	HCC patients: • Incidence: 598 (in 2022) • Prevalence: 33.8 per 100 000 (as of 2021) HCC patients eligible for any systemic treatment • Incidence: 85 HCC patients eligible for dual IO (STRIDE) or atezo-bev: • Eligible: 68 (in the first year)
Budget impact (in year 5)	Cost increase of DKK 0.2 million

3. The patient population, intervention, choice of comparators and relevant outcomes

Table 1. Summary of PICO

Patient population	Patients (aged ≥18 years) with unresectable advanced or metastatic HCC receiving systemic treatment in the 1st line setting
Intervention	Durvalumab in combination with tremelimumab
Comparator	• **Atezo-bev** is the relevant comparator for patients in the ITT population.
Outcomes	• Overall survival • Progression-free survival • Adverse events • HRQoL

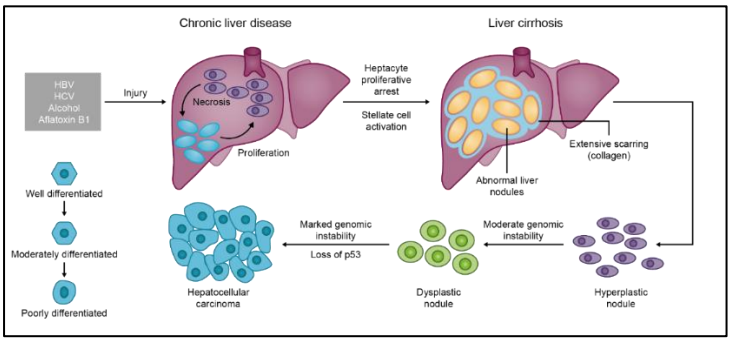
3.1 The medical condition

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for 80-90% of all liver cancer cases, and represents the sixth most common cancer and the third leading cause of cancer death worldwide.(6, 7). Incidence of HCC is three to four times higher in men compared to women and in older adults, with the highest age-specific incidence reported in individuals aged >70 years old.(7-10) The strongest risk factor for HCC development is cirrhosis of any aetiology, viral hepatitis, as well as diabetes or obesity related non-alcoholic steatohepatitis (NASH), chronic alcohol consumption, and exposure to aflatoxin B1(7, 11). From 2017-2021 about 500 new cases of liver cancer was diagnosed in Denmark each year(12), however, the incidence increased to 598 liver cancer patients in 2022, with an incidence rate of 11.8/100 000 for men and 4.3/100 000 for women in 2022(13). 70-80% of patients diagnosed with HCC have a history of cirrhotic liver (14), where the most frequent cause of cirrhosis (approx. 65%) in Denmark is excessive alcohol consumption(15). However, there seems to be a decrease in alcoholic cirrhosis and Hep B and C infections these years, while fatty cirrhosis has an increasing trend(14).

Pathophysiology

HCC development is a complex process, it usually occurs through a multistep biological process which results in the malignant transformation of normal hepatocytes.(16) In general, various HCC-inducing aetiologies give rise to continuous rounds of hepatocyte death and regeneration, which eventually leads to chronic liver disease and cirrhosis.(17) Cirrhosis is characterized by abnormal liver nodule formation, collagen deposition, and scarring of the liver.(17) Cirrhosis then leads to the formation of hyperplastic nodules, pre-malignant dysplastic nodules, and ultimately HCC, which has the capacity to invade the surrounding fibrous stroma and vessels, and occasionally has metastatic potential.(17) See Figure 1 for a summary of the molecular progression and features associated with HCC.(17)

Figure 1. Histopathological progression and molecular features of HCC



Source: Adapted from Farazi and DePinho (2006).(17)

Clinical presentation

HCC generally presents with non-specific symptoms such as right upper abdominal or epigastric pain, early satiety, weight loss, and malaise(6). As a result of these non-specific symptoms, HCC diagnosis is often delayed, and the majority of patients with HCC are diagnosed with advanced disease, which precludes the use of potentially curative

interventions.(6) In cirrhosis, liver failure symptoms such as ascites (body fluid in the abdominal cavity), bone oedema, icterus (yellowish or greenish pigmentation of the skin) and gastrointestinal bleeding are more common than in non-cirrhotic patients(18). 70-80% of patients diagnosed with HCC have a history of cirrhotic liver (14). Fever, however, is more common in patients without cirrhosis (18).

Prognosis for current treatment option

Five-year survival is 40-70% after potentially curative treatment (surgery, radiofrequency ablation or transplantation), but the median overall survival is approx. 20 months after chemoembolization, approx. 19 months after atezo-bev treatment(1), 10-12 months after sorafenib treatment and 3-6 months for patients in supportive treatment(4).

Influence of the condition on the patients' functioning and health-related quality of life

Patients with HCC experience a substantial humanistic burden, as a result of the signs and symptoms of HCC, comorbidity from their underlying liver disease, as well as treatment-related toxicity.(19) In Denmark, 85% of patients have underlying diseases(20). Furthermore, patients with intermediate and advanced-stage disease require informal caregiving to manage daily living, often provided by an unpaid family member, which has been associated with physiologic, psychological, and social burdens to the caregiver.(21) Hence, there remains an unmet need for novel treatment options that can reduce this burden, improve quality of life (QoL) and extend survival for patients at all stages of HCC.

3.2 Patient population

In 2021, the prevalence of HCC was 671 men and 322 women, corresponding to 33.8 per 100.000, see Table 2(12). According to the Danish Cancer Registry, 598 patients were diagnosed with liver cancer in 2022, 424 men and 174 women(13). The incidence has been slightly increasing from 490 in 2018 to 598 in 2022, Table 2. While the incidence has been stable for women, the incidence of HCC has increased in men.

Table 2. Incidence and prevalence in the past 5 years

Year	2018	2019	2020	2021	2022
Incidence in Denmark(13)	490	518	494	568	598
Prevalence in Denmark per 100.000(12)	29.6	30.0	30.4	33.8	N/A

- The total incidence of HCC in Denmark accounts for about 80% of all liver cancers or 478 HCC patients ((7), (22) and AstraZeneca Market Research).
- 70% of the HCC patients are diagnosed at the advanced stage of the cancer or 334 patients per year (20, 23, 24).
- Patients with a preserved liver function, with a Child-Pugh class A score, are eligible for systemic treatments according to national treatment guidelines and expert interviews (18). Those patients account for about 30% of advanced HCC patients or 100 patients.
- A good performance status is a prerequisite for systemic treatment administration (18) and only those patients with an ECOG performance status (PS) of 0-1 are eligible for

systemic therapy, while those patients with ECOG PS 2+ are referred to palliative care unit. 85% of the patients who have Child-Pugh class A score have ECOG PS of 0-1 (in total 85 patients) and are therefore eligible for systemic treatment.

Table 3. Estimated number of patients eligible for treatment

	Proportion	Number of patients per year
Liver cancer incidence incl. iCC (13)	100%	598
HCC (20)	80%	478
Advanced HCC (20) (23, 25, 26)	70%	334
Child-Pugh A* (20, 24)	30%	100
PS 0-1* (20)	85%	85
Patients eligible for any systemic treatment	100%	85

Footnotes: * supported by expert interviews.

Table 4. Estimated number of patients eligible for treatment in the coming year

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for systemic treatment in the coming years	85	85	86	86	86

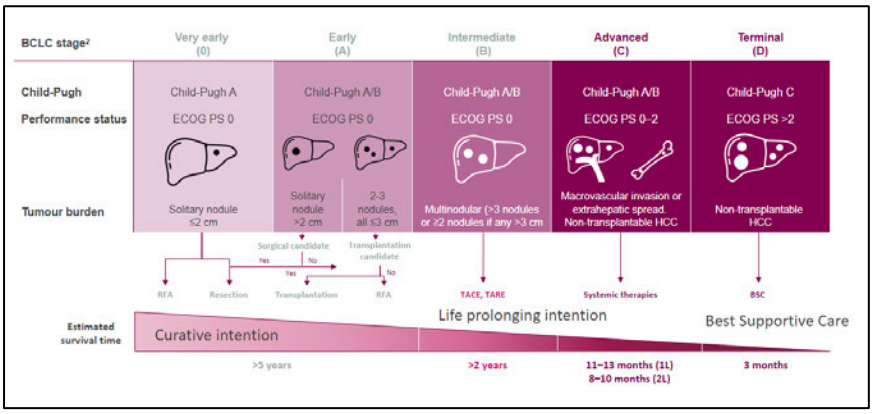
*Assuming 0.5% population growth and otherwise stable incidence.

Not all patients will be eligible to receive a dual immunotherapy (STRIDE). The patient flow and patient numbers who would be treated with STRIDE are summarized in Section 13.

3.3 Current treatment options

HCC constitutes a disease continuum for which the Barcelona Clinic Liver Cancer (BCLC) staging system is used in staging of the disease and to decide which treatment the patient would benefit from. The BCLC principle assesses tumor spread, liver function (Child-Pugh, CTP) and general condition (ECOG PS) (27, 28). The BCLC staging system divides patients into five groups, of which groups 0 and A are potentially curable, groups B and C are suitable for active palliative treatment with life-prolonging intent, while group D can only be given symptomatic treatment. (27, 28). The HCC national clinical guidelines are described by the Danish Liver-Biliary Tract Cancer Group (DLGCG) and were last updated March 1st 2023(14) based on the BCLC staging and treatment system(14, 29), illustrated in Figure 2. The Danish clinical guidelines differ from the BCLC guideline as they describe specific treatment strategies according to cirrhosis status in HCC.

Figure 2. BCLC staging and treatment strategy (27, 28)



Current treatment of advanced HCC

In patients with advanced-stage HCC, systemic treatment is considered the most appropriate treatment option. Current first-line treatments for advanced-stage HCC include a combination of atezolizumab (PD-L1 inhibitor) and bevacizumab (VEGF inhibitor) as well as tyrosine kinase inhibitors (TKIs) sorafenib and lenvatinib (30-34).

Atezolizumab and bevacizumab

Recently the combination of atezolizumab and bevacizumab has become the SOC for advanced HCC patients without contraindications to either immune checkpoint inhibitors or anti-angiogenic therapy. Atezo-bev has been approved by the European Commission in the first-line setting following the phase 3 IMbrave150 study, which demonstrated significant and clinically meaningful improvements in the co-primary endpoints of OS and PFS compared to sorafenib(35), results are presented in Chapter 6. Despite becoming the first-line SOC for patients with advanced HCC, atezo-bev may not be suitable for patients with bleeding risks(36). As a consequence of patients' underlying liver disease and high incidence of portal hypertension, patients with advanced HCC are at a particularly high risk of GI-bleeding, a risk which may be exacerbated by antiangiogenic agents such as bevacizumab, for which bleeding is a known safety concern(37, 38). In the EPAR of atezolizumab (39), screening for and subsequent treatment of esophageal varices was recommended as per clinical practice prior to starting treatment with the combination of atezolizumab and bevacizumab. The assessment report concluded that despite attempts to exclude all patients with prior bleeding due to esophageal and/or gastric varices within 6 months prior to study treatment and perform esophagogastroduodenoscopy (EGD) on all patients in order to treat all size varices, a considerable number of patients experienced gastrointestinal bleedings in the atezo-bev arm in study IMbrave150. Patients treated with bevacizumab have an increased risk of hemorrhage, and cases of severe gastrointestinal hemorrhage, including fatal events, were reported in patients with HCC treated with atezo-bev. In 2021 the DMC approved atezolizumab in combination with bevacizumab as first line treatment for unresectable HCC patients with preserved liver function and good performance status(40). There has not yet been published any real-world evidence studies in a Danish setting.

Sorafenib

In the advanced-stage HCC setting, sorafenib (a multireceptor TKI) was until recently the only treatment option shown to significantly extend survival compared with placebo. The

efficacy and safety were shown in the global, randomised, double-blinded, placebo-controlled Phase III SHARP-study. However, sorafenib failed to offer patients a long-term survival beyond one year (one-year landmark survival of 44%)(41). Sorafenib is also associated with high toxicity, with ~15% of patient's intolerant to treatment and a further 35% requiring dose reduction(42). Clinical outcomes for patients receiving treatment with sorafenib are associated with patients' liver function, and patients with well-preserved liver function (Childs-Pugh A) had considerably longer OS than patients with poor liver function (Childs-Pugh B/C)(43). As the majority of advanced-stage HCC patients present with chronic cirrhosis, poor liver function, and compromised functional status, there is an unmet need for additional well-tolerated and effective treatment options to extend survival in this patient group. Sorafenib has been available in Denmark since 2007. A nationwide study from 2012 showed that the median OS for sorafenib in Danish patients was 5.4 months compared to 10.7 months in the original clinical study, SHARP.(41, 44)

Lenvatinib

Lenvatinib is another multi-receptor TKI which when approved in 2018 represented the first new drug approved in the first-line advanced HCC setting for over ten years(45). Lenvatinib demonstrated non-inferiority compared with sorafenib in the Phase III REFLECT study (45). Based on these results, lenvatinib has been positioned as an alternative to sorafenib in the treatment of advanced-stage HCC, however, there are some limitations to treatment with lenvatinib. Firstly, Grade 3 or higher treatment-emergent adverse events (TEAEs) occurred at similar rates in the lenvatinib and sorafenib arms(45). Additionally, patients enrolled in the REFLECT trial could not have >50% liver involvement, clear bile duct invasion or main portal vein invasion, which may suggest that this trial population is not fully representative of the wider advanced HCC population. In a real-world study, however, the results were aligned with the pivotal study and the authors raised lenvatinib as a choice for patients ineligible for immune-oncology (IO) therapies(46).

2L and 3L

According to the Danish clinical guidelines sorafenib, lenvatinib or regorafenib can be used as 2nd and 3rd line in patients with preserved liver function(14). However, regorafenib remains the only drug approved by the Danish Medicines Council for second line treatment in Denmark for patients with hepatocellular carcinoma with performance status 0-1 and with liver function corresponding to Child Pugh A, which is previously treated with and have tolerated sorafenib(47).

<u>Unmet need</u>

As concluded by EMA authorities in the IMJUDO EPAR (48), despite recent advances in treatment options, patients with uHCC continue to have a short life expectancy and the underlying liver disease and portal vein hypertension increase the risk of gastrointestinal bleeding, which can be potentially life-threatening. 1L treatment with immunotherapy atezolizumab in combination with bevacizumab (atezo-bev) showed superior effect vs. the TKI sorafenib in the IMbrave150 study, and thus immune-combination therapy remains the first choice for patients who are expected to tolerate immunotherapy. As presented in chapter 6, STRIDE has also shown superior OS-effect vs. sorafenib in the HIMALAYA trial, but has potential advantages compared to both atezo-bev and sorafenib as STRIDE has a toxicity profile with clinically important differences. STRIDE is also the only

immunotherapy that have shown long-term (beyond 4 years) survival gains for these patients versus sorafenib. TKIs are alternative treatments for patients who are ineligible for anti-VEGF bevacizumab, or where immunotherapy in general is contraindicated (e.g. active autoimmune diseases and transplanted patients). TKIs like sorafenib are associated with severe side effects like myocardial ischaemia and infarction, gastrointestinal perforations, drug induced hepatitis, haemorrhage (including gastrointestinal, respiratory tract and cerebral haemorrhage) and hypertensive crisis. Common, troublesome side effects includes diarrhoea, fatigue, alopecia, infections, palmar plantar erythrodysaesthesia (PPE) syndrome and rash (49, 50).

In conclusion, there is a clear unmet medical need for better and more tolerable treatment options for patients with uHCC (48).

Future treatment of advanced HCC

In the 2022 update of the BCLC strategy, tremelimumab in combination with durvalumab, as well as atezo-bev are currently considered first-line treatment options in patients suitable for systemic treatment, as they confer a superior survival benefit compared to sorafenib (29). Furthermore, the American NCCN guidelines recommend the combination of tremelimumab and durvalumab as first-line option for advanced HCC(34). The European Society for Medical Oncology (ESMO) has recently granted the highest score 5 for the combination of tremelimumab and durvalumab in the first-line treatment of advanced hepatocellular carcinoma in the Magnitude of Clinical Benefit Score ESMO-MCBS (51), however, ESMO guidelines haven't been updated since 2021.

3.4 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Imfinzi in combination with Imjudo is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
Method of administration	Imfinzi and Imjudo intravenous injection
Dosing	STRIDE: Imfinzi 1500 mg administered in combination with 300 mg Imjudo as a single dose at Cycle 1/Day 1, followed by Imfinzi 1500 mg as monotherapy every 4 weeks. Patients are treated until disease progression or unacceptable toxicity.
Dosing in the health economic model (including relative dose intensity)	STRIDE: Imfinzi 1500 mg administered in combination with 300 mg Imjudo as a single dose at Cycle 1/Day 1, followed by Imfinzi 1500 mg as monotherapy every 4 weeks. Patients are treated until disease progression or unacceptable toxicity.
Should the pharmaceutical be administered with other medicines?	Imfinzi in combination with Imjudo
Treatment duration / criteria for end of treatment	**Imfinzi**: 1500mg every 4 weeks until progression or unacceptable toxicity, start day 1 cycle 1 **Imjudo**: 300 mg one dose at day 1 cycle 1
Necessary monitoring, both during administration and during the treatment period	No

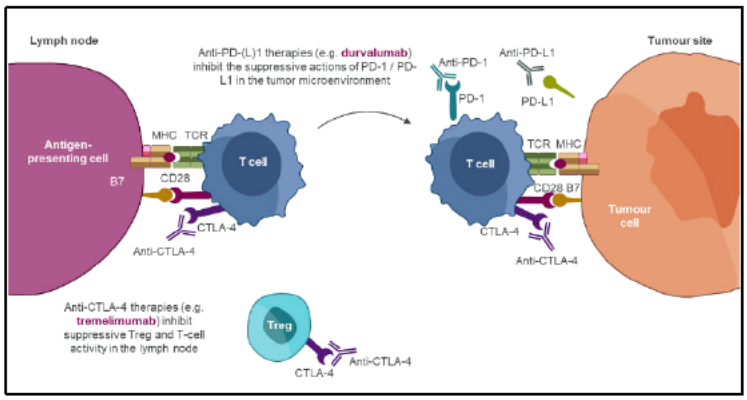
Overview of intervention	
Need for diagnostics/other tests	No
Package size(s)	**Imfinzi**: 2.4 ml or 10 ml concentration 50 mg/ml **Imjudo**: 15 ml concentration 20 mg/ml

Mechanisms of action

Durvalumab is a fully human, immunoglobulin G1-kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction between PD-L1 and PD-1 and CD80, respectively which enhances antitumor immune responses and increases T-cell activation(52). Durvalumab has been engineered to eliminate the potential induction of antibody dependent cell-mediated cytotoxicity (ADCC) on effector T cells following the expression of PD-L1 on activated T cells, thereby preventing T-cell depletion.(53, 54)

Tremelimumab is a selective and fully human IgG2 antibody that blocks CTLA-4 to interact with CD80 and CD86. This leads to enhanced T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumor activity(52). Pre-clinical and clinical evidence suggests that anti-tumor activity following PD-L1 blockade by durvalumab is strengthened by the non-redundant inhibition of CTLA-4 by tremelimumab, acting via distinct mechanisms (Figure 3) (55). Tremelimumab primarily acts early in the T-cell response, increasing activation to create a diverse T-cell response (55, 56). Conversely, durvalumab mainly acts during the effector phase within the tumor, eliciting cytotoxic activity on both exhausted and activated lymphocytes response (55, 56). Therefore, the simultaneous blockade of PD-L1 and CTLA-4 pathways by durvalumab and tremelimumab, can result in complementary, longer-lasting immune effects, enhanced anti-tumor activity and ultimately improved patient outcome(56).

Figure 3. Mechanism of action: PD-L1 and CTLA-4 blockade.



Source: Figure adapted from(55).

3.4.1 The intervention in relation to Danish clinical practice

Imjudo and Imfinzi are expected to be used within its indication and in accordance with Danish clinical practice. The mean doses in clinical practice are expected to be similar to the dose in the HIMALAYA trial.

3.5 Choice of comparators

Imjudo (tremelimumab) in combination with Imfinzi (durvalumab) is indicated as first line treatment of adults with advanced or unresectable hepatocellular carcinoma (uHCC). The dosing regimen is called STRIDE (**S**ingle **T**remelimumab **R**egular **I**nterval **D**urvalumab). As stated above, the Danish clinical guidelines recommend atezo-bev to be used as first line treatment (taking into account their contraindications).

In accordance with the recommendations in the Danish clinical guidelines, for HCC patients in the Himalaya ITT population atezolizumab-bevacizumab is the relevant comparator.

Table 5. Overview of comparator

Overview of comparator –	Atezolizumab + bevacizumab
Generic name	Atezolizumab + bevacizumab
ATC code	L01FF05 + L01FG01
Mechanism of action	Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. 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.
Method of administration	Intravenous
Dosing	Atezolizumab: 1 200 mg every 3rd week Bevacizumab 15 mg/kg every 3rd week
Dosing in the health economic model	Atezolizumab: 1 200 mg every 3rd week Bevacizumab 15 mg/kg every 3rd week
Should the pharmaceutical be administered with other medicines?	Atezolizumab in combination with bevacizumab
Treatment duration/ criteria for end of treatment	Until loss of clinical benefit or unmanageable toxicity.
Need for diagnostics or other tests	Screening for and subsequent treatment of oesophageal varices should be performed as per clinical practice prior to starting treatment with the combination of atezolizumab and bevacizumab. Diabetes mellitus can occur during treatment with atezolizumab in combination with bevacizumab. Physicians should monitor blood glucose levels prior to and periodically during treatment with atezolizumab in combination with bevacizumab as clinically indicated.
Package sizes	Atezolizumab: 840 mg or 1200 mg Bevacizumab: 25 mg/ml in vials of 4 ml or 16ml

3.6 Cost-effectiveness of the comparator(s) – Health economic evaluation

Atezo-bev has been assessed in HCC and was recommended by DMC in June 2021.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application.

Table 6. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) **Median OS** **Landmark OS** [Included study HIMALAYA and IMBRAVE150]	23rd Jan, 2023	OS is defined as the time from randomization to death from any cause. OS was defined as the time from the date of randomization until death due to any cause, regardless of whether the participant withdrew from randomized therapy or received another anticancer therapy. Any participant not known to have died at the DCO date was censored based on the last recorded date on which the participant was known to be alive. If the last known date alive or if the date of death was after the DCO date, participants were censored at the DCO date. The median survival is based on the KM estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	For landmark analysis: percentage of participants who were alive at fixed time points (18, 24, and 36 months) after randomization. The estimated percentage of survival along with the 95% confidence interval were calculated using Kaplan-Meier technique on the full analysis set.
PFS based on investigator assessment. [Included study HIMALAYA and IMBRAVE150]	27th August 2021	PFS (per Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1] using Investigator assessments) was defined as the time from the date of randomization until the date of objective disease progression or death by any cause in the absence of progression, regardless of whether the patient withdrew from study treatment or received another anticancer therapy prior to progression. Progression (i.e., PD) was defined as a at least 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of	Tumor scans performed at baseline, every 8 weeks for the first 48 weeks following randomization, and every 12 weeks thereafter until RECIST 1.1-defined progression. Assessed up to DCO

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		diameters (nadir) - this includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm from nadir.	
PFS BICR [Included study HIMALAYA and IMBRAVE150]	August 2020	PFS based on BICR is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression via BICR according to RECIST Version 1.1 or death due to any cause.	Tumor scans performed at baseline, every 8 weeks for the first 48 weeks following randomization, and every 12 weeks thereafter until RECIST 1.1-defined progression. Assessed up to DCO
ORR [Included study HIMALAYA and IMBRAVE150]	27th August 2021	Time from the date of first documented confirmed response (complete or partial response) until the first date of documented progression or death in the absence of disease progression. Complete response (ie., CR) was defined as disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm. Partial response (ie., PR) was defined as at least a 30% decrease in the sum of the diameter of TL, taking as reference the baseline sum of diameters.	From the date of first documented response until the first date of documented progression or death, assessed until the final analysis DCO
HRQoL [Included study HIMALAYA and IMBrave150]	27th August 2021	European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30): Global health status/QoL, functioning (physical), multi-term symptom (fatigue)	EORTC QLQ-C30

Validity of outcomes

The most persuasive outcome to demonstrate efficacy in anticancer trials is OS and possible primary efficacy endpoints include PFS, and patient-reported outcomes (57). Data on ORR, DoR, time to progression (TTP)/PFS and confirmed ORR are considered suitable markers of anti-tumor activity. Additionally, in DMC´s evaluation of Tecentriq® ((document 115538)) for the same indication, the committee pre-specified OS, PFS, ORR and QoL (assessed via the EORTC QLQ-C30) as critical or important efficacy measures. All of these outcome measures were defined as endpoints in the HIMALAYA trial. Further, the cost-minimization model was directly based on the key outcomes of the HIMALAYA trial, which directly represent treatment goals for HCC in Denmark: OS, PFS and QoL.

4. Health economic analysis

4.1 Model structure.

4.1.1 Cost minimization analysis STRIDE vs atezo-bev

There are no head-to-head clinical trials that enable a direct comparison between STRIDE and the combination of atezo-bev as treatments for uHCC. To investigate the comparative effectiveness, Indirect Treatment Comparisons (ITCs) have been conducted. Given that imbalances between patient populations were identified between the IMbrave150 and the HIMALAYA trials, a Matching Adjusted Indirect Comparison (MAIC) was chosen as methodology to compare the two treatments (a more detailed description of the analysis is provided in section 7). The results of the MAIC together with pharmaceutical, administration, and monitoring costs have been used to inform a cost minimization analysis. Patient time and transportation costs were also included in the cost per patient analysis. The features of the economic model are described in Table 7.

4.2 Model features.

Table 7. Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with unresectable HCC not been previously treated with systemic therapy. IMbrave 150 patient population compared to HIMALAYA patient population restricted and reweighted in the ITC. However, in the model the results from the full HIMALAYA population are used.	Imbalances between patient populations was observed. HIMALAYA patient population was adjusted to match IMbrave 150 patient characteristics.

Model features	Description	Justification
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (35 years)	To capture the totality of costs associated with the treatments. Different horizons are considered in scenario analysis
Cycle length	1 week	A 1-week cycle length is used to adequately capture transitions and allowing drug cycles to be accurately costed. A 1-week cycle length ensures that the model can consider the different dosing schedules across the comparator arms
Half-cycle correction	No	Due to the short cycle length, half-cycle correction is not applied in the base case; it is implicitly assumed that all patient transitions, health outcomes, and costs occur at the beginning of each cycle
Discount rate	3.5 %	According to DMC and recommendations from the Finance Ministry
Included costs	• Pharmaceutical costs • Administration costs • Monitoring costs • Adverse event costs • Patient and transport costs • Subsequent therapy costs	Standard cost items
Intervention	Tremelimumab plus durvalumab (tremelimumab 300 mg for one single dose + durvalumab 1500 mg Q4W)	According to HIMALAYA study and the SmPC (EPAR)
Comparator	Atezolizumab plus bevacizumab (1200 mg of atezolizumab + 15 mg/kg of bevacizumab Q3W)	According to national treatment guideline. Validated by Danish clinical expert
Outcomes	OS, PFS, TTD	Standard outcomes in oncology models

5. Overview of literature

5.1 Literature used for the clinical assessment.

5.1.1 STRIDE vs atezo-bev

A systematic literature review (SLR) was performed with the objective of identifying publications assessing the comparative efficacy and safety of treatments approved by the HTA agencies as first line treatment in patients with advanced metastatic HCC.

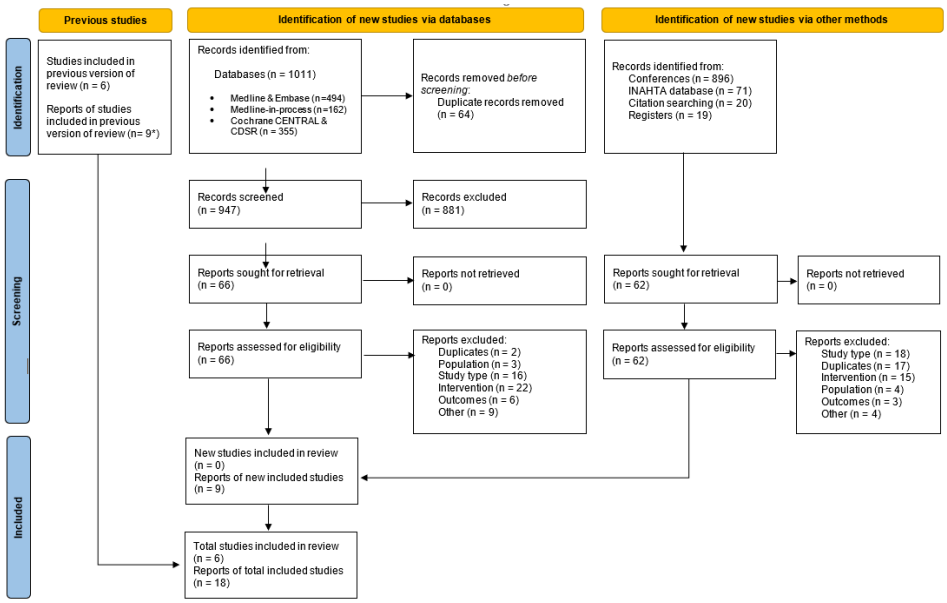
The target of the global SLR was specified using the PICOs framework (Population, Intervention, Comparator, Outcome, and Study type) which is outlined in Table 8. Based on the FDA and EMA approvals as well as the review of guidelines, four potential comparators (atezo-bev, Sorafenib, Lenvatinib and Nivolumab) were considered of interest. The outcomes to be extracted as part of the SLR were selected in accordance with the data collected in the HIMALAYA trial.

Table 8. PICOs

Component	Description
Population	Patients (aged ≥18 years) with unresectable advanced or metastatic HCC receiving systemic treatment in the 1st line setting
Intervention	Durvalumab + tremelimumab
Comparator	Atezolizumab + bevacizumab, Sorafenib, Lenvatinib and Nivolumab
Outcomes	Efficacy: DOR, OS, PFS, TTP, tumor response. Safety and tolerability: Withdrawals, specific AEs, incidence of Grade 3 and 4 AEs, serious AEs, and AEs leading to discontinuation.
Study type	Randomized controlled trials
Language	English
Publication time frame	Original review up to October 2021, but updated with further targeted searches up to October 2023
Country scope	No restriction

The PRISMA of the updated SLR is shown in Figure 4.

Figure 4. SLR strategy



Of the 18 publications identified in the SLR, 13 were relevant for the ICT, the remaining 5 focused on specific subgroups and were therefore not considered for the ICT. Three clinical trials (REFLECT, CheckMate459, IMbrave150) plus three other studies potentially of interest to connect the network were identified. No publication was available for the HIMALAYA trial at the time of the SLR update, however, data on file provided by AstraZeneca was considered for the feasibility assessment of the ITC. One additional publication (Cheng et al. 2022)(1) was identified through hand searches and was also considered for the ITC. This publication reported updated data of IMbrave150 with a longer follow-up duration.

A summary of the study design characteristics across all included studies are outlined in appendix H (Table 87). A total of six studies conducted in patients with unresectable HCC, with the addition of the AZ HIMALAYA trial, obtained from AstraZeneca's data on file, were included in the review, from 18 publications. Eight publications on the six studies from the original SLR were included. Nine publications on IMbrave 150 and one publication on CheckMate 459 were included as part of a targeted literature search to update the global SLR in October 2023. For this application, one publication on IMbrave 150 was deemed relevant for the efficacy and safety comparison, hence why only one publications is included in the local adaptation of the global SLR(1).

The study baseline characteristics differed in terms of the study site countries and regions. The regions differed as three trials had global sites, one trial excluded Asia-Pacific and two trials were performed in the Asia-Pacific region only.

For the local adaption of the SLR, the only relevant comparison would be STRIDE (Durvalumab + tremelimumab) vs. Atezo-bev (recommended by DMC).

Table 9. Relevant literature included in the assessment of efficacy and safety.

Reference	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Finn RS; Q. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. Published online 2020.(36)	IMbrave150	NCT03434379	Start: 15/03/18 Study Completion: 17/11/22 DCO: 29/08/19 DCO: 31/08/20	Atezolizumab plus bevacizumab vs sorafenib unresectable hepatocellular carcinoma
Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862-873. doi:10.1016/j.jhep.2021.11.030.(1)	IMbrave150			
Ghassan K. Abou-Alfa Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. Published June 6, 2022.NEJM Evid 2022;1(8) DOI: 10.1056/EVIDoa2100070 VOL. 1 NO. 8	HIMALAYA	NCT03298451		
Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Annals of Oncology. Volume 35, issue 5. P 448-457. May 2024(63)	HIMALAYA		Study start: 2017-10-11 completion: 2024-08-27 DCOs: August 27th 2021 and January 23rd 2023	Durvalumab + tremelimumab vs sorafenib

5.2 Literature used for the assessment of HRQoL

No health-related quality of life data was used in the cost minimization analysis of STRIDE vs atezo-bev.

Table 10. Relevant literature included for documentation of health-related QoL

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N.A.	N.A.	N.A.

5.3 Literature used for inputs for the health economic model.

5.3.1 STRIDE vs atezo-bev

No systematic literature search was carried out for inputs included in the cost-minimization analysis (CMA). Costs included in the analysis were sourced according to DMC guidelines and a more detailed description can be found in section 11.

Table 11. Relevant literature used for input to the health economic model.

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N.A.	N.A.	N.A.	N.A.

6. Efficacy

6.1 Efficacy of tremelimumab plus durvalumab compared to atezo-bev for unresectable hepatocellular carcinoma.

6.1.1 Relevant studies

The HIMALAYA trial (NCT03298451) was motivated by the positive outcome of the open-label, Phase I/II, multi-arm, multi-centre, four-part trial, Study 22 (NCT02519348), which evaluated durvalumab or tremelimumab monotherapy, or durvalumab in combination

with tremelimumab (STRIDE regimen and T75+D) or in combination with bevacizumab in 433 patients with unresectable HCC in the first- or second-line setting.) HIMALAYA is a global, multicenter open-label, Phase 3 randomized, study in patients with unresectable hepatocellular carcinoma (uHCC) not eligible for locoregional therapy and with no prior systemic therapy. (48)

The IMbrave150 trial (NCT03434379) was a global, multicenter, open-label, phase 3 randomized trial, to determine the safety and efficacy of atezo-bev as compared with sorafenib in patients with unresectable hepatocellular carcinoma who had not received systemic therapy prior to the study (36).

Table 12. Overview of study design for studies included in the comparison.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
HIMALAYA, NCT03298451 Ghassan K. Abou-Alfa, George Lau, Masatoshi Kudo, Stephen L. Chan, et Al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. N Engl J Med Evid 2022;1(5) Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Annals of Oncology. Volume 35, issue 5. P 448-457. May 2024(63)	Randomized, open label, sponsor blind, multicenter, global, phase III study of Durvalumab and Tremelimumab as first line Treatment in patients with unresectable Hepatocellular carcinoma.	From the date of randomization until death due to any cause, assessed up to the data cut-off date (27Aug2021, to a maximum of approximately 46 months)	Adult (aged ≥18 years) with confirmed unresectable HCC based on histopathological findings BCLC stage B (not eligible for locoregional therapy) or stage C ECOG 0 or 1 Child-Pugh Score class A	Durvalumab 1500 mg plus tremelimumab 300 mg 1 dose at Week 0, followed by durvalumab 1500 mg monotherapy starting 4 weeks after the first and final infusion of the combination therapy until confirmed PD, unacceptable toxicity, or any discontinuation criteria are met.	Sorafenib 400 mg (oral) twice daily until confirmed PD at the Investigator's discretion, unacceptable toxicity, or any discontinuation criteria are met.	Primary endpoint: OS. (27Aug2021, to a maximum of approximately 46 months). Secondary endpoint: OS at 18, 24, and 36 Months After Randomization (27Aug2021). PFS (27Aug2021, to a maximum of approximately 46 months). TTP. (27Aug2021, to a maximum of approximately 46 months). ORR. (27Aug2021, to a maximum of approximately 46 months). DCR. (27Aug2021, to a maximum of approximately 46 months). DoR. (27Aug2021, to a maximum of approximately 46 months). OS by PD-L1. (27Aug2021, to a maximum of approximately 46 months). EORTC QLQ-C30 Time to Global Health Status/QoL Deterioration. (At baseline and

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						every 8 weeks for the first 48 weeks and then every 12 weeks thereafter until death or the final analysis DCO (27Aug2021), assessed up to approximately 46 months). EORTC QLQ-HCC18 Time to Symptom (Abdominal Pain) Deterioration (At baseline and every 8 weeks for the first 48 weeks and then every 12 weeks thereafter until death or the final analysis DCO (27Aug2021), assessed up to approximately 46 months). EORTC QLQ-HCC18 Time to Symptom (Shoulder Pain) Deterioration. (At baseline and every 8 weeks for the first 48 weeks and then every 12 weeks thereafter until death or the final analysis DCO (27th Aug 2021), assessed up to approximately 46 months). EORTC QLQ-HCC18 Time to Symptom (Abdominal Swelling) Deterioration. (At baseline and every 8 weeks for the first 48 weeks and then every 12 weeks thereafter until death or the final analysis DCO (27Aug2021), assessed up to approximately 46 months).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						Presence of ADA for Durvalumab. (Samples were collected on Day 1 (Week 0), Week 12 and at 3 months after the last dose of durvalumab. Assessed until the final analysis DCO (27Aug2021, to a maximum of approximately 46 months)). Presence of ADA for Tremelimumab. (Samples were collected on Day 1 (Week 0), Week 12 and at 3 months after the last dose of tremelimumab. Assessed up to approximately 46 months after the first randomization). Summary of Durvalumab Concentration Over Time (PK). (Samples were collected pre-dose at week 4 and week 12 and post-dose at week 12. Assessed at the final analysis DCO (27Aug2021)).
IMBrave150 NCT03434379 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–905(36) Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data	Randomized, open label, phase III study of Atezolizumab in Combination With Bevacizumab Compared	From randomization to death from any cause up to the clinical cut off date (CCOD) of 29Aug2019 (up to approximately	Adult (aged ≥18 years) with confirmed unresectable HCC based on histopathological findings ECOG 0 or 1	Atezolizumab will be administered by IV, 1200 mg on day 1 of each 21 day cycle Bevacizumab will be	Sorafenib 400 mg (oral) twice daily until disease progression or unacceptable toxicity.	Primary endpoint: OS in the Global Population (**29Aug2019 (up to approximately 18 months) and 31Aug2020 (up to approximately 30 months) PFS-IRF (29Aug2019 (up to approximately 18 months) Secondary endpoint:

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862-873. doi:10.1016/j.jhep.2021.11.030.(1)	With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma.	18 months) and 31Aug2020 (up to approximately 30 months	Child-Pugh Score class A.	administered by IV, 15 mg/kg on day 1 of each 21-day cycle Treated until disease progression or unacceptable toxicity.		ORR-IRF in the Global Population (29Aug2019 (up to approximately 18 months). ORR-IRF (***mRECIST) in the Global Population (29Aug2019 (up to approximately 18 months). ORR-INV in the Global Population (29Aug2019 (up to approximately 18 months). DOR-IRF in the Global Population (29Aug2019 (up to approximately 18 months)). DOR-IRF Per HCC mRECIST in the Global Population (29Aug2019 (up to approximately 18 months)). DOR-INV in the Global Population (29Aug2019 (up to approximately 18 months)). PFS-IRF Per HCC mRECIST in the Global Population (29Aug2019 (up to approximately 18 months)) PFS-INV in the Global Population (29Aug2019 (up to approximately 18 months)) TTP-IRF in the Global Population (29Aug2019 (up to approximately 18 months))

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						TTP-IRF Per HCC mRECIST in the Global Population (29Aug2019 (up to approximately 18 months)) TTP-INV in the Global Population (29Aug2019 (up to approximately 18 months)) OS by Baseline AFP in the Global Population (29Aug2019 (up to approximately 18 months)) PFS-IRF by Baseline AFP in the Global Population (29Aug2019 (up to approximately 18 months)) PFS-INV by Baseline AFP in the Global Population (29Aug2019 (up to approximately 18 months)) TTD in the Global Population (29Aug2019 (up to approximately 18 months)) Percentage of Participants With Adverse Events (AEs) in the Global Population (Up to end of study (up to approximately 40 months)) Maximum Serum Concentration (Cmax) of Atezolizumab at Cycle 1 in the Global Population (Post-dose on Day 1 of Cycle 1 (cycle length = 21 days)) Trough Serum Concentration (Cmin) of Atezolizumab in the Global Population (Pre-

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						dose on Day 1 of Cycles 2, 3, 4, 8, 12 and 16 (cycle length = 21 days)) Percentage of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab in the Global Population (Baseline and post-baseline on Day 1 (pre-dose) of Cycles 2, 3, 4, 8, 12, 16 (cycle length = 21 days) and treatment discontinuation visit (up to approximately 30 months))

Footnote: *27AUG2021: Final analysis DCO August 27th 2021. **29Aug2019: clinical cut off date (CCOD) August 29th 2019.
mRECIST: ***mRECIST (Hepatocellular Carcinoma (HCC) Modified RECIST (mRECIST))

6.1.2 Comparability of studies

Eligibility criteria between HIMALAYA and IMbrave150 trials were overall similar in terms of restriction on prior therapy, HCC etiology, ECOG PS, Child Pugh score, and presence of ascites. Regarding HCC diagnosis, both trials required a confirmed histological diagnosis, with IMbrave150 also requiring the AASLD criteria for diagnosis. HIMALAYA also included BCLC as an eligibility criterion, restricting enrolment to stage B or C patients. For parameters related to the disease progression both HIMALAYA and IMbrave150 employed the RECIST v1.1 criterion. For prior bleeding events, the time window between the latest bleeding event and study enrolment or randomization varied between studies. HIMALAYA excluded patients who had had bleeding events within the 12 months preceding enrolment while IMbrave150 excluded patients who had experienced bleeding events in the six months preceding study entry. A schematic and more detailed overview of eligibility criteria is outlined in Table 13.

Table 13. Eligibility criteria comparison

	HIMALAYA	IMbrave 150
Age	Adults (≥18 years)	Adults (≥18 years)
Population	Advanced HCC	Locally advanced or metastatic and/or unresectable HCC
Diagnosis	Histologically confirmed	By histology/ cytology or clinically by AASLD criteria in cirrhotic patients
Prior therapy	No prior systemic therapy for HCC No locoregional therapy	No prior systemic therapy for HCC No curative surgical and/or locoregional therapies or that had progressed thereafter. Patients who received prior local therapy were eligible provided the target lesion(s) have not been previously treated with local therapy
Etiology	HBV, HCV, Uninfected	HBV, HCV, Uninfected
BCLC stage	B-C	Not reported as eligibility criterion. Based on baseline characteristics: ~ 97% stage B-C / ~ 3% stage A
ECOG	0-1	0-1
Child Pugh score	A	A
Ascites	No clinically meaningful ascites	No moderate or severe ascites
Measurable disease	At least one untreated target lesion measurable according to RECIST v1.1	At least one untreated target lesion measurable according to RECIST v1.1
Additional exclusion criteria	Hepatic encephalopathy Main portal vein tumor thrombosis Active or prior documented autoimmune or inflammatory disorders Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC HIV infection History of, or current, brain metastases or spinal cord compression	History of hepatic encephalopathy Uncontrolled tumor-related pain Known active tuberculosis Active or history of autoimmune disease or immune deficiency No coinfection with HBV and HCV ***Bleeding-related criteria*** Prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding

	No coinfection (HBV and HCV, or HBV and HDV) ***Bleeding-related criteria*** Active or prior GI bleeding within 12 months (esophageal varices or ulcer bleeding) For patients with GI bleeding >12 months or high risk, adequate endoscopic therapy required §	Endoscopy: Patients must undergo an EGD (esophagogastroduodenoscopy) prior to enrollment.

§ For patients with a history of GI bleeding for more than 12 months or assessed as high risk for esophageal variceal by the Investigator, adequate endoscopic therapy according to institutional standards is required Patients must undergo an upper GI endoscopy (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.

6.1.2.1 Comparability of patients across studies

Baseline characteristics were compared across the trials of interest. The main findings are summarized below in Table 14.

Table 14. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety.

	HIMALAYA		IMbrave150	
	STRIDE	Sorafenib	Atezolizumab + bevacizumab	Sorafenib
Sample size	393	389	336	165
Age (mean)	65	64	64	65
Gender (% male)	83%	87%	82%	83%
Macrovascular invasion (%)	26%	26%	38%	43%
Extrahepatic spread (%)	53%	52%	63%	56%
Alpha fetoprotein (% of patients above AFP threshold)	37%	32%	38%	37%
HBV (%)	31%	31%	49%	46%
HCV (%)	28%	27%	21%	22%
ECOG 0 (%)	37%	38%	38%	38%
Child Pugh A (%)	98%	97%	100%	100%
BCLC C (%)	80%	83%	82%	80%

	HIMALAYA		IMbrave150	
	STRIDE	Sorafenib	Atezolizumab + bevacizumab	Sorafenib
BCLC B (%)	20%	17%	15%	16%
BCLC A (%)	0%	0%	2%	4%

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Patient characteristics for the ITT population were sourced from the HIMALAYA clinical trial and compared to the Danish population during the interview conducted with the Danish clinical expert. While age, weight, and proportion of male of in the Danish population are comparable to those from the HIMALAYA trial, Danish patients are on average expected to be taller than in the HIMALAYA trial (see Table 15). Values from the HIMALAYA trial were used in the base case.

Table 15. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (from clinical expert interview)	Value from HIMALAYA trial	Value used in health economic model
Mean age (years)	63.1	63.1	63.1
Gender (% male)	83.7	83.7	83.7
Mean patient weight (kg)	70.9	70.9	70.9
Mean patient height (cm)	173	167.7	167.7

6.1.4 Efficacy – results per HIMALAYA

6.1.4.1 Data cut-offs and analysis sets

Two interim analyses and a final analysis were planned for the HIMALAYA study. Additionally, results from the updated analysis were recently disclosed. Final analysis: The final analysis was performed once 555 OS events occurred in the STRIDE and sorafenib arms combined (71% maturity), 46 months after the first patient was randomized (DCO3: 27th August 2021). The median follow-up time was 33.18 (CI 31.75-34.53) months in STRIDE-arm and 32.23 (30.42-33.71) months in sorafenib-arm (5). Updated analysis: The updated analysis was performed after 912 OS events in all arms (DCO4: 23rd Jan, 2023). The median follow-up time was 49.12 (CI 46.95-50.17) months in STRIDE-arm and 47.31 (45.08-49.15) months in sorafenib-arm (63).

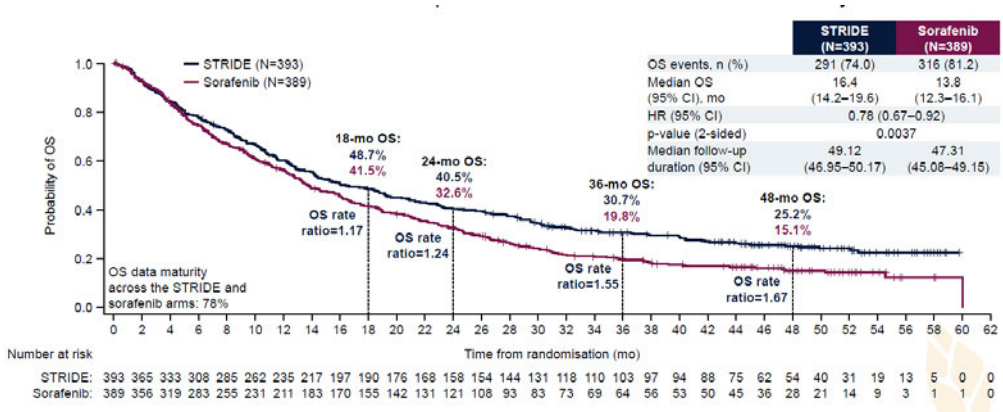
In summary:

- OS at DCO4: A statistically significant median OS improvement from 13.8 months to 16.4 months with a 22% reduced risk of death, HR 0.78 (95% CI 0.67-0.92) in favor of STRIDE.
- The median follow-up time for HIMALAYA was over 49 months at the updated analysis (DCO4). For atezo-bev, only 18 months survival rates have been published. While we do not know the long-term effect for atezo-bev, this is well documented for STRIDE.
- The OS benefit was confirmed at DCO4 (four-year update), showing that 25.2% of the patients were alive in the STRIDE arm and 15.1% in the sorafenib arm at 48 months.
- The updated four-year OS shows improvement for STRIDE vs. sorafenib regardless of etiology.

6.1.4.2 Overall survival

The HIMALAYA trial met its primary objective demonstrating a statistically significant and clinically meaningful improvement in OS for treatment with STRIDE compared to sorafenib at DCO4. Median OS improved from 13.8 months to 16.4 months with a 22% reduced risk of death, HR 0.78 (CI 0,67-0,92) with an estimated 2.7-month difference in median OS values between the two treatment arms, at DCO3 (5). The OS benefit was confirmed with the longer follow-up at DCO4 illustrated in Figure 5 below. The updated results confirmed the sustained OS benefit as durable responses from adding a single priming dose of CTLA-4 inhibitor tremelimumab to repeated dosing of the PD-L1-inhibitor durvalumab (63). The KM curves began to separate after 6 months of therapy and the improvement in OS was sustained, with a greater number of patients alive in the STRIDE treatment arm compared with the sorafenib treatment arm at all recorded timepoints (5), see Figure 5 below (63). The updated analysis was performed after a median of 49.12 months follow up with 75.0% of events in the STRIDE arm and after a median of 47.31 months with 81.2% events in the sorafenib arm, respectively (607 OS events in total) (63). Thus, the OS data are considered mature (64).

Figure 5. Four-year updated OS curve.



Source: Sangro et all 2024(63)

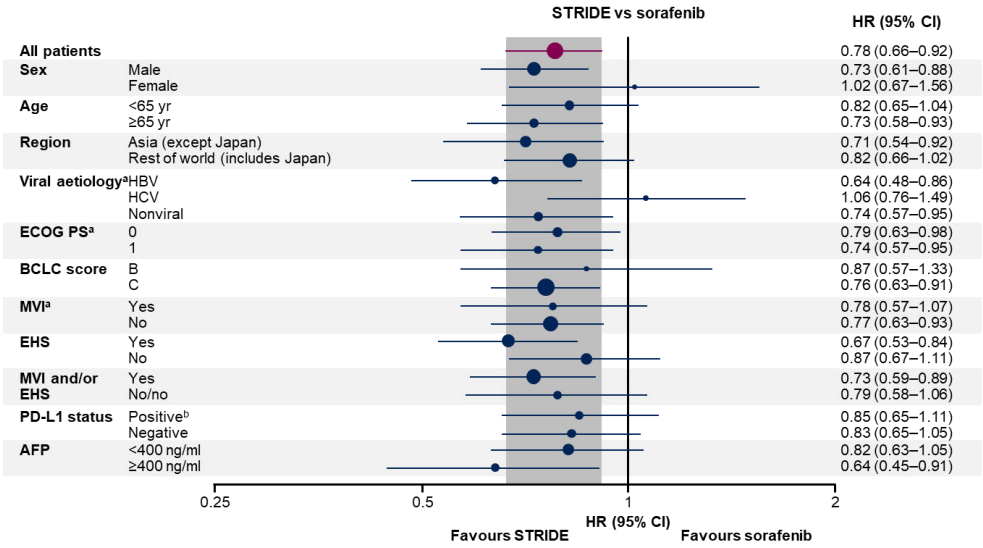
Survival rates for STRIDE vs sorafenib were 48.7% vs 41.5% at 18 months, 40.5% vs 32.6% at 24 months, 30.7% vs 20.2% at 36 months, and 25.2% and 15.1% at 48 months,

respectively, showing the development of plateau in the STRIDE-arm. In the sorafenib-arm, 17.2% of the patients received immunotherapy in second line. This is seen as longer OS survival compared to previous studies.

6.1.4.3 Subgroup analyses of OS data – STRIDE vs. sorafenib

Subgroup analyses were undertaken to assess the consistency of treatment effect across a range of important clinical and demographic characteristics (Figure 6). The OS benefit favoring STRIDE treatment vs. sorafenib treatment was consistent across most pre-specified subgroups, evidenced by the fact that the HR point estimate for each subgroup was contained within the 95% CI of the HR for the overall population. Some variability was observed, in particular for the female sex subgroup and for the subgroup of patients with confirmed HCV disease. For analysis of the female sex subgroup, this variability is likely due to the small sample size (<100 patients were enrolled in each treatment arm). For HCV, a post-hoc analysis of baseline covariates within the HCV subgroup identified potential imbalances in prognostic factors between the groups. Overall, however, the subgroup analyses demonstrate that the OS benefit observed in the intention-to-treat (ITT) population was consistent across stratification and pre-specified subgroups (5).

Figure 6. Forest plot of OS in patient subgroups for STRIDE versus sorafenib in the ITT population, DCO3 (supplementary material to (5))

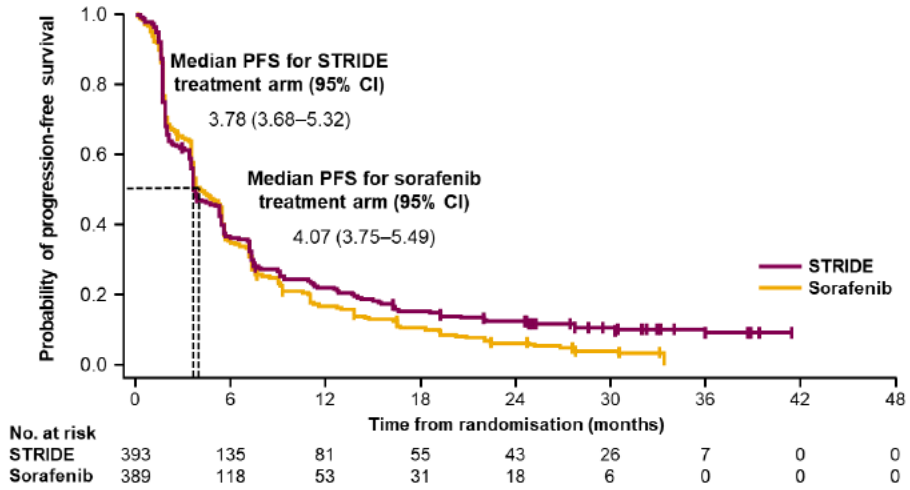


6.1.4.4 Progression free survival

Treatment with STRIDE resulted in a median time to progression of 3.78 months (3.68-5.32) compared to 4.07 months (3.75-5.49) with sorafenib (FAS: HR for PFS = 0.90 (CI 0.77-1.05), Figure 7). However, a greater proportion of patients were progression-free at final analysis (DCO 3) in the STRIDE treatment arm compared with the sorafenib-arm (12.5% vs. 4.9%). The results are aligned with the MoA of immune check-point inhibitors, where the tumor killing mechanism of action is indirect and mediated through immune system

activation instead of direct tumor killing, which is the case with chemotherapy and multikinase inhibitors (i.e. sorafenib). Thus, the response develops gradually, and the long-term benefit can be seen more clearly during the follow-up as OS benefit. The weakness of PFS measured with RECIST and not iRECIST as an efficacy endpoint in IO-trials has been acknowledged also by regulatory authorities. In the EPAR of IMJUDO it was concluded that the PFS analyses are mature with 85.2% and 84.1% events in the STRIDE and sorafenib arms, respectively, and the KM curves do not clearly separate at any time. This finding is considered consistent with the pattern of efficacy generally observed for immunotherapy, where PFS benefit is often lacking or of a small magnitude, while OS is often clinically significantly improved. Hence, this could be considered an acceptable result as the primary endpoint was OS, and that an OS benefit has been shown for the proposed treatment regimen STRIDE vs sorafenib.

Figure 7. Kaplan-Meier plot of investigator assessed PFS in HIMALAYA (FAS), DCO 3



Source: Chan et al. (2022).

[redacted]

6.1.4.5 Interpretation of HIMALAYA efficacy results

In the HIMALAYA trial, a statistically significant and clinically meaningful improvement of the primary endpoint overall survival (OS) was shown in the STRIDE-arm compared to the sorafenib-arm, which was seen as the separation of the Kaplan-Meier curves reflecting the long-term benefit. The long-term benefit was seen in the landmark analyses as a higher proportion of patients alive at 18 months (48.7% vs 41.5%), 24 months (40.5% vs 32.6%), 36 months (30.7% vs 19.8%) and 48 months (25.2% vs 15.1%) with STRIDE compared to sorafenib (63). The dual-inhibition with immune check-point inhibitors PD-L1 and CTLA-4 has been studied in several clinical trials and experience has also been gained from post-marketing authorization use (66-69). This dual inhibition appears to activate also immunologically colder tumors (68, 69), which can be seen along the immune activation as a plateau in the Kaplan-Meier curve and the development of the so-called tail at the OS-curve. The unique dosing of STRIDE, where the single priming dose of tremelimumab is combined with durvalumab maintenance therapy, avoids the toxicity of repeated dosing dual-IO treatments while preserving the efficacy. The survival benefit from STRIDE regimen was shown in all predetermined explorative subgroups when the baseline characteristics were corrected by stratification factors. The most important subgroup analysis concerned the etiology of HCC.

The subgroup of long-term responders cannot be reliably identified from estimates based on median OS (mOS), which merely reflect the first short-term OS results, when 50% of the patients have had an event. The proportion of long-term responders is usually less than 50% and be more clearly shown as the data matures. Thus, mOS does not identify the long-term responders once it has been reached. This is essential especially with immune check-point inhibitors, where the tumor killing mechanism of action is indirect and mediated through immune system activation instead of direct tumor killing, which is the case with chemotherapy and multikinase inhibitors. Thus, the sustained response develops gradually, and the long-term benefit can be more clearly seen during the follow-up, when the mOS has been already reached. Most clearly the benefit of immune check-point inhibitors is seen after three years of follow-up. Therefore, the updated landmark OS analyses at 4 years confirms the durable responses in a long-term perspective.

6.1.5 Efficacy – results per IMbrave 150

Atezo-bev has been approved by the European Commission in the first-line setting following the phase 3 IMbrave150 study, which demonstrated significant and clinically meaningful improvements in the co-primary endpoints of OS and PFS compared to sorafenib (36, 70, 71).

Data cut-offs and analysis sets:

Patients were included to IMbrave150 between March 15, 2018, to January 30, 2019.

Primary analysis (36):

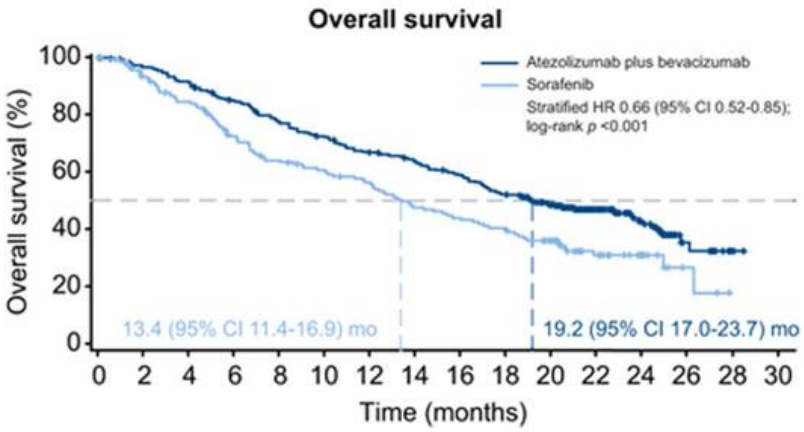
August 29, 2019: Median follow up median 8.6 months.

Updated analysis (primary analysis +12 months) (5):

August 31, 2020: Median follow up median 15.6 months. This is the latest data cut. The presented results are from the updated analysis (Aug 2020), unless otherwise is stated.

6.1.5.1 Overall survival

Figure 9. Overall survival in Imbrave150



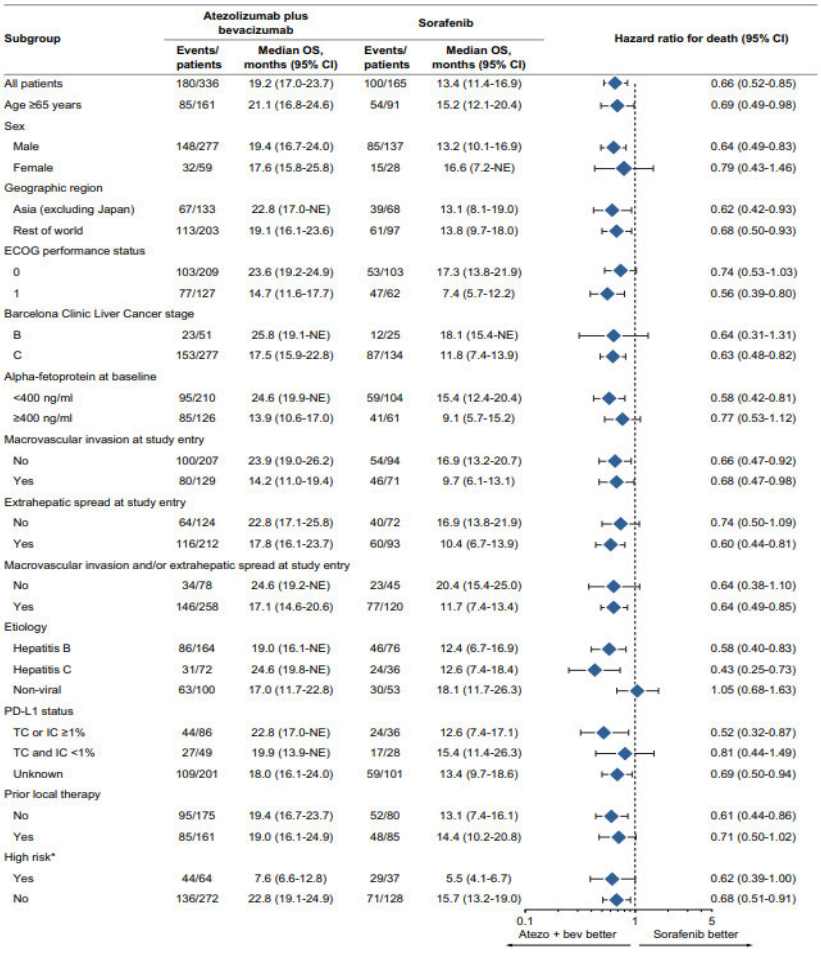
Source: Cheng, et al. (2022) (1)

The IMbrave150 study have only published OS data with a limited follow up time, median follow-up was 15.6 months with the latest data cut off (1). The median OS was 19.2 months with atezo-bev vs. 13.4 months for patients receiving sorafenib(1).

Subgroup analyses of OS data – atezo-bev vs. sorafenib

No KM curves from subgroups based on etiology are published for IMbrave150. A forest plot for OS from the last DCO have however been published (Figure 10). The evidence related to the IMbrave 150 study is thus limited.

Figure 10. Forest plot OS from IMbrave150, DCO Aug 2020 (1)



Subgroup	Atezolizumab plus bevacizumab		Sorafenib		Hazard ratio for death (95% CI)
	Events/ patients	Median OS, months (95% CI)	Events/ patients	Median OS, months (95% CI)	
All patients	180/336	19.2 (17.0-23.7)	100/165	13.4 (11.4-16.9)	0.66 (0.52-0.85)
Age ≥65 years	85/161	21.1 (16.8-24.6)	54/91	15.2 (12.1-20.4)	0.69 (0.49-0.98)
Sex					
Male	148/277	19.4 (16.7-24.0)	85/137	13.2 (10.1-16.9)	0.64 (0.49-0.83)
Female	32/59	17.6 (15.8-25.8)	15/28	16.6 (7.2-NE)	0.79 (0.43-1.46)
Geographic region					
Asia (excluding Japan)	67/133	22.8 (17.0-NE)	39/68	13.1 (8.1-19.0)	0.62 (0.42-0.93)
Rest of world	113/203	19.1 (16.1-23.6)	61/97	13.8 (9.7-18.0)	0.68 (0.50-0.93)
ECOG performance status					
0	103/209	23.6 (19.2-24.9)	53/103	17.3 (13.8-21.9)	0.74 (0.53-1.03)
1	77/127	14.7 (11.6-17.7)	47/62	7.4 (5.7-12.2)	0.56 (0.39-0.80)
Barcelona Clinic Liver Cancer stage					
B	23/51	25.8 (19.1-NE)	12/25	18.1 (15.4-NE)	0.64 (0.31-1.31)
C	153/277	17.5 (15.9-22.8)	87/134	11.8 (7.4-13.9)	0.63 (0.48-0.82)
Alpha-fetoprotein at baseline					
<400 ng/ml	95/210	24.6 (19.9-NE)	59/104	15.4 (12.4-20.4)	0.58 (0.42-0.81)
≥400 ng/ml	85/126	13.9 (10.6-17.0)	41/61	9.1 (5.7-15.2)	0.77 (0.53-1.12)
Macrovascular invasion at study entry					
No	100/207	23.9 (19.0-26.2)	54/94	16.9 (13.2-20.7)	0.66 (0.47-0.92)
Yes	80/129	14.2 (11.0-19.4)	46/71	9.7 (6.1-13.1)	0.68 (0.47-0.98)
Extrahepatic spread at study entry					
No	64/124	22.8 (17.1-25.8)	40/72	16.9 (13.8-21.9)	0.74 (0.50-1.09)
Yes	116/212	17.8 (16.1-23.7)	60/93	10.4 (6.7-13.9)	0.60 (0.44-0.81)
Macrovascular invasion and/or extrahepatic spread at study entry					
No	34/78	24.6 (19.2-NE)	23/45	20.4 (15.4-25.0)	0.64 (0.38-1.10)
Yes	146/258	17.1 (14.6-20.6)	77/120	11.7 (7.4-13.4)	0.64 (0.49-0.85)
Etiology					
Hepatitis B	86/164	19.0 (16.1-NE)	46/76	12.4 (6.7-16.9)	0.58 (0.40-0.83)
Hepatitis C	31/72	24.6 (19.8-NE)	24/36	12.6 (7.4-18.4)	0.43 (0.25-0.73)
Non-viral	63/100	17.0 (11.7-22.8)	30/53	18.1 (11.7-26.3)	1.05 (0.68-1.63)
PD-L1 status					
TC or IC ≥1%	44/86	22.8 (17.0-NE)	24/36	12.6 (7.4-17.1)	0.52 (0.32-0.87)
TC and IC <1%	27/49	19.9 (13.9-NE)	17/28	15.4 (11.4-26.3)	0.81 (0.44-1.49)
Unknown	109/201	18.0 (16.1-24.0)	59/101	13.4 (9.7-18.6)	0.69 (0.50-0.94)
Prior local therapy					
No	95/175	19.4 (16.7-23.7)	52/80	13.1 (7.4-16.1)	0.61 (0.44-0.86)
Yes	85/161	19.0 (16.1-24.9)	48/85	14.4 (10.2-20.8)	0.71 (0.50-1.02)
High risk*					
Yes	44/64	7.6 (6.6-12.8)	29/37	5.5 (4.1-6.7)	0.62 (0.39-1.00)
No	136/272	22.8 (19.1-24.9)	71/128	15.7 (13.2-19.0)	0.68 (0.51-0.91)

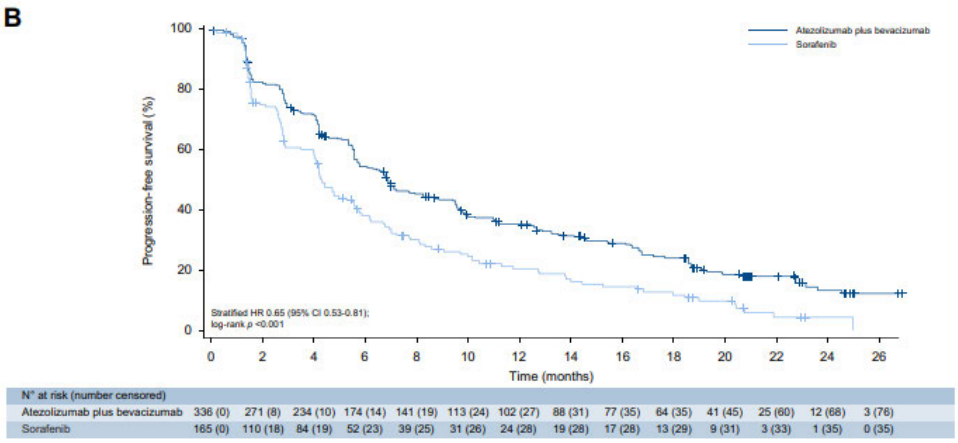
Source: Cheng, et al. (2022) (1)

6.1.5.2 Progression free survival

For independently assessed PFS the latest published DCO was August 2020: Median follow up was median 15.6 months. The median PFS per independently assessed RECIST 1.1 was 6.9 months (95% CI 5.7-8.6) with atezo-bev compared with 4.3 months (95% CI 4.0-5.6) with sorafenib (stratified HR for progression or death 0.65; 95% CI 0.53-0.81; descriptive p <0.001) (1).

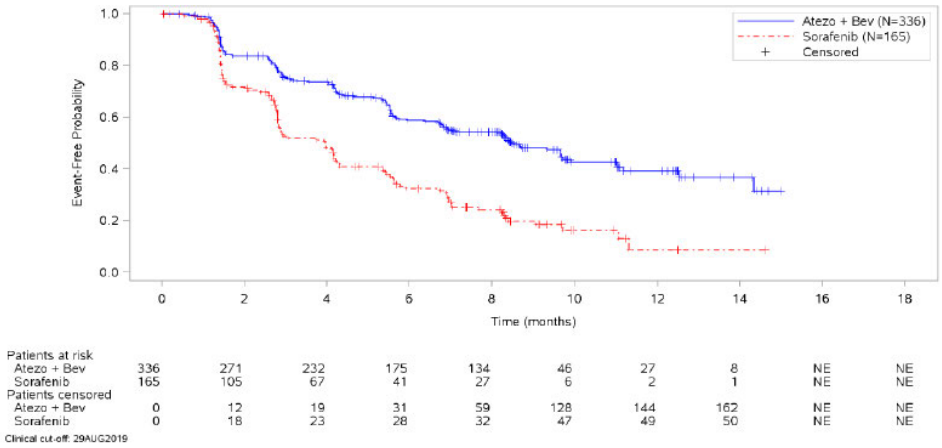
The median PFS per investigator assessed RECIST 1.1 was 7.1 months (95% CI 5.7-8.4) with atezo-bev compared with 2.9 months (95% CI 2.8-4.2) with sorafenib (stratified HR for progression or death 0.45; 95% CI 0.3.6-0.57; descriptive p <0.001) with DCO August 2019, see Figure 12(1).

Figure 11. Independently assessed PFS Kaplan-Meier data from the IMBrave-150 study, dco August 2019



Source: Cheng, A.-L., et al.. J. Hepatol., 76(4), 862–873.

Figure 12. Investigator assessed PFS Kaplan-Meier data from the IMBrave-150 study



Source: GBA – Module 4 – IMBrave150. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/613/

7. Comparative analyses of efficacy

STRIDE and Atezo+Bev was compared using an indirect treatment comparison which is presented in the following sections. Additional details are provided in Appendix C.

7.1.1 Differences in definitions of outcomes between studies

There are no relevant differences in how the outcomes are defined in the studies. However, it should be noted that there is no long-term follow-up from IMbrave150 beyond two years. It is, difficult to know if there is a tail in the IMbrave150 study as in

HIMALAYA, as there is a clear difference between the mechanism of action between tremelimumab (CTLA-4 inhibitor, immunotherapy) and bevacizumab (VEGF inhibitor, anti-angiogenic therapy).

7.1.2 Method of synthesis

Overall survival

For both STRIDE and atezo-bev proportional hazard (PH) is assumed. Given the imbalance between trials regarding some key potential prognostic factors (PFs) and treatment effect modifiers (TEMs) such as etiology, macrovascular invasion or region and given the fact that both trials include sorafenib as a common comparator an anchored Matching-Adjusted Indirect Comparison (MAIC) was identified to be the most relevant approach to adjust for imbalance in PFs and TEMs. The potential drawback of such approach is that it considers less data and uncertainty might increase. Results from a MAIC based on the proportional hazards assumption (PHA) and with a piecewise approach as well as unadjusted results from a Buchers ITC are presented.

Progression free survival

Investigator assessed PFS was reported for HIMALAYA. As PFS may differ if assessed by the investigator or by independent reviewers (BICR), the investigator assessed was also chosen for IMbrave150 when comparing PFS in the ITC. Investigator assessed PFS have only been reported at the primary DCO in August 2019 for IMbrave150, after a median follow up of 8.6 months. Median PFS at this time point was 7.1 months for atezo-bev. With the limited follow up time for atezo-bev, a piecewise approach was not feasible. Results from a MAIC where median investigator assessed PFS are compared are thus presented, these results must, however, be interpreted with caution as the PHA tests returned ambiguous results. Furthermore, results from an unadjusted Buchers ITC are presented below.

MAIC methodology

The following preliminary steps were taken in performing the MAIC:

- Use of the individual patient data (IPD) from HIMALAYA to keep only patients eligible to the competitor's trial.
    - This was done through the comparison of the eligibility criteria and the application of the exclusion criteria of the competitor's trial should the eligibility criteria be more restrictive than the ones from HIMALAYA.
    - Assessed the number of patients from the HIMALAYA trial who would have been eligible for the competitor's trial and therefore kept conducting the MAICs.
- Generation of baseline descriptive statistics on the restricted HIMALAYA trial (i.e. after application of the exclusion criteria from the competitor's trial when required) and comparison with competitor's baseline characteristics to assess imbalances between trials.

- A specific focus was made on the characteristics known to be potential PFs and TEMs.

After restriction of the HIMALAYA population, anchored MAICs were implemented through the following steps:

- Weights associated with each HIMALAYA patient were estimated through the generation of a logistic regression model based on a similar approach to propensity score weighting:

$$log(w_i) = \alpha_0 + \alpha_1 X_i$$

where X_i is the covariate vector for the i-th patient in the HIMALAYA trial and w_i is the weight attributed to the i-th patient treated with STRIDE or sorafenib.

  - All factors identified as being TEMs and available in the HIMALAYA IPD and reported for the comparator's trial were included in the adjustment model, as recommended by the NICE DSU (72).
  - As recommended by the NICE DSU (72) the method of moments was used to estimate these parameters so that the reweighted mean characteristics of the HIMALAYA trial matched the competitor's trial. This meant minimising $\sum_i \exp(\alpha_i^T X_i)$ when the vector of TEMs is null in the competitor's trial, i.e., $\overline{X_{competitor's\ trial}} = 0$.

- Indirect comparison using the Bucher approach was then conducted on the weighted data from HIMALAYA and the published results from the competitor's trial:

$$\mathrm{d}_{\mathrm{STRIDE\ vs\ A+B}} = \mathrm{d}_{\mathrm{STRIDE\ vs\ sorafenib}} - \mathrm{d}_{\mathrm{A+B\ vs\ sorafenib}}$$

where $\mathrm{d}_{\mathrm{STRIDE\ vs\ sorafenib}}$ corresponds to the reweighted relative treatment effect of STRIDE vs sorafenib.

  - The Bucher formulae was applied to estimate the HR for time-to-event outcomes between the log HR obtained through the MAIC steps for HIMALAYA and the log HR of the competitor's trial.

Finally, different steps were conducted for each MAIC to assess the validity of the analysis:

- The distribution of weights was analyzed to detect any overly influential individual and to study the populations' overlap. The rescaled weight is also calculated to examine the distribution of the weights as the rescaled weights are relative to the original unit weights of each individual. The rescaled weight is calculated as

$$\widetilde{w}_i = \frac{\widehat{w}_i}{\sum_i \widehat{w}_i} * N$$

- The effective sample size (ESS) was estimated to assess the quality of the matching as it can detect extreme situations where few individuals have important weights driving the results. ESS was obtained by:

$$\frac{\sum_i (\widehat{w}_i)^2}{\sum_i \widehat{w}_i^{\,2}}$$

- Descriptive statistics were generated between the competitor's trial baseline characteristics and the reweighted HIMALAYA characteristics to assess whether imbalances previously observed between populations have been reduced through the weighting process.

Restricting the HIMALAYA population

The comparison of the eligibility criteria of HIMALAYA and IMbrave 150 led to the identification of the following differences:

- BCLC stage: No restriction in IMbrave 150 and few stage A included vs HIMALAYA restricted to stages B and C
- Ascites: Exclusion of moderate or severe ascites in IMbrave 150 vs exclusion of clinically meaningful ascites in HIMALAYA
- Bleeding events: Exclusion of prior bleeding event in prior 6 months in IMbrave 150 vs exclusion of active or prior GI bleeding in prior 12 months in HIMALAYA
- Countries: No patients coming from China mainland in HIMALAYA, while 15.6% in IMbrave 150.
- Some patients from HIMALAYA presented a Child Pugh of B at baseline whereas for both trials inclusion was restricted to A
- Some patients from HIMALAYA presented an ECOG PS of 2 at baseline whereas for both trials inclusion was restricted to 0 or 1

Therefore, HIMALAYA was restricted to patients with Child Pugh A and ECOG PS of 0 or 1. After restriction, 1,145 out of 1,171 patients were kept for HIMALAYA for the analyses based on the intention-to-treat (ITT) population.

Adjustment

After restriction of HIMALAYA to patients eligible to IMbrave 150, each remaining patient was reweighted to obtain overall population characteristics similar to IMbrave 150.

The treatment effect modifier (TEM) adjusted for in the MAIC are listed in Table 17 below. For IMBRAVE 150, the distribution of the ALBI was only reported in an abstract[36], and related to a cohort that was not the ITT population. Therefore, the reported ALBI score was not used in the weighting process of MAIC given the absence of comparable data. However, ALBI score distributions were calculated for IMbrave 150 and HIMALAYA populations for reference.

Table 16. IMbrave 150 sample size comparison.

Cohort	Population	All	Atezolizumab + bevacizumab	Sorafenib
Global + expanded	N	**558**	375	**183**
Global	N	**501**	336	**163**
ALBI score reported population	N	**530**	335	**195**
	ALBI grade 1, n	278	**191**	87
	mALBI grade 2a, n	109	72	37
	mALBI grade 2b, n	143	72	71

The weighting model was based on ten factors, their estimated weights are detailed in Table 17. Those values highlighted that five factors seemed to have a stronger impact on the weight distribution, with having hepatitis B, MVI or EHS increasing the weight while being from Asia or having BCLC stage C decreased the weight.

Table 17. Complete list of factors and their estimated weights used for the weighting process of the MAIC of HIMALAYA vs IMbrave 150 compared to the list of TEMs identified.

Variable identified as TEM	Adjustment made on		Weights of each covariate
Age	% ≥ 65 years old		0.2371
Gender	% males		-0.3078
Region	% from Asia excluding Japan		-0.6965
MVI	% of MVI		0.9401
EHS	% of EHS		0.5784
AFP	% Serum AFP ≥ 400 ng/mL		-0.0549
Etiology	% HBV	1.3132	
	% HCV	0.1584	
ECOG	% ECOG 0		-0.1365
BCLC	% BCLC C		-0.7179

An effective sample size (ESS) of 760.2 (64.9% of initial sample size) was obtained after weighting. As shown in Figure 13 and Table 18 below, no extreme individual was identified based on the weights. Though four patients have a rescaled weight higher than 5, their non-rescaled weight was lower than 5 (out of 760.2).

Figure 13. Distribution of rescaled weights of HIMALAYA vs IMbrave 150 intention-to-treat population.

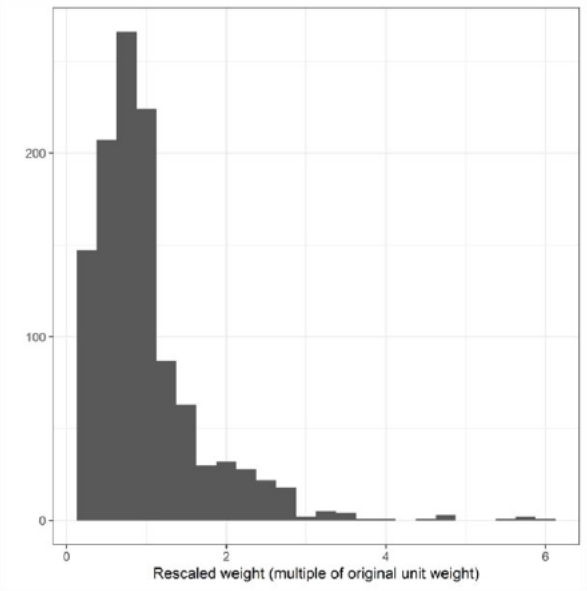


Table 18. Distribution of weights of HIMALAYA vs Imbrave 150 efficacy MAIC

	Rescaled weights	Non-rescaled weights
Min	0.1437	0.1175
Q1	0.5702	0.4661
Median	0.8309	0.6792
Mean	1.0000	0.8174
Q3	1.2076	0.9871
Max	6.2042	5.0713

Abbreviations: MAIC, Matching-Adjusted Indirect Comparison; Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile

Baseline characteristics of patients in IMbrave150 and HIMALAYA before and after adjustments in order to match the comparator population for the ITC are provided in Table 19.

Table 19. Baseline characteristics of IMbrave150, HIMALAYA, restricted HIMALAYA and reweighted HIMALAYA population

TRIAL	Imbrave 150	HIMALAYA – Original		HIMALAYA – Restricted		HIMALAYA – Reweighted	
ARM	Global	Sorafenib	STRIDE	Sorafenib	STRIDE	Sorafenib	STRIDE
N / ESS	501	389	393	379	387	243.4	270.5
Age ≥ 65 y.o. (%)	50.3	49.9	50.4	49.3	50.9	50.1	53.8
Male (%)	82.3	86.6	83.2	86.3	83.2	84.4	80.7
Asia excluding Japan (%)	40.3	40.1	39.7	40.9	40.1	39.4	39.7
MVI (%)	39.6	25.7	26.2	25.9	25.3	42.0	38.8
EHS (%)	60.7	52.2	53.2	52.5	53.5	62.5	58.3
AFP ≥ 400 (%)	37.7	31.9	36.9	31.9	37.0	33.8	39.1
Hepatitis B (%)	48.0	30.6	31.0	30.9	31.5	46.9	47.7
Hepatitis C (%)	21.3	26.7	28.0	26.4	27.6	20.6	22.7
ECOG 0 (%)	62.0	62.0	62.1	62.8	62.5	60.4	63.4
ECOG 1 (%)	38.0	37.8	37.7	37.2	37.5	39.6	36.6
ECOG 2 (%)	0.0	0.3	0.3	0.0	0.0	0.0	0.0
Child Pugh A (%)	100.0	97.4	98.5	100.0	100.0	100.0	100.0
BCLC B (%)	15.3	17.0	19.6	17.2	19.9	15.1	19.4
BCLC C (%)	81.7	83.0	80.4	82.8	80.1	84.9	80.6
ALBI grade 1 (%)	*NR*	52.2	55.2	53.6	56.1	52.8	53.4
ALBI grade 2 (%)	*NR*	47.6	44.3	46.4	43.7	47.2	46.6
ALBI grade 3 (%)	*NR*	0.3	0.3	0.0	0.0	0.0	0.0

7.1.3 Results from the comparative analysis

In the HIMALAYA trial, a statistically significant and clinically meaningful improvement of overall survival was shown in the STRIDE-arm compared to the sorafenib-arm (HR 0.78; 95%CI 0.67-0.92). Most importantly, a long-term benefit was seen in the landmark analyses as a higher proportion of patients alive at 18 months (48.7% vs 41.5%), 24 months (40.5% vs 32.6%), 36 months (30.7% vs 19.8%) and 48 months (25.2% vs 15.1%) with

STRIDE compared to sorafenib. Based on the indirect treatment comparisons, STRIDE can be considered, on a statistical level, to have a comparable efficacy for OS compared to atezo-bev (MAIC HR 1.09; 95%CI 0.80-1.48) (Buchers ITC HR: 1.18 95%CI 0.88-1.59) (63). However, it is important to consider that while 4-year data from the HIMALAYA trial shows a durable OS-effect, the long-term efficacy (one of the most important components in evaluating IO treatments) of atezo-bev is unknown as updated follow up results for IMbrave150 have not been published, and OS data is not available beyond 18 months. The durability of the OS effect of atezo-bev in uHCC beyond 18 months, therefore, remains uncertain.

Table 20. Results from the comparative analysis of STRIDE vs. atezo-bev for ITT population

Outcome measure	HIMALAYA original – STRIDE vs sorafenib	HIMALAYA MAIC* – STRIDE vs sorafenib	Imbrave 150 – atezobev vs sorafenib	Result – STRIDE vs atezobev unadjusted Buchers ITC	Result – STRIDE vs atezobev MAIC
PFS DCO3	0.89 [0.77, 1.03]	0.78 [0.65, 0.93]	0.45 [0.36, 0.57]	1.98 [1.50, 2.61]	1.73 [1.30, 2.32]
OS, DCO3	0.78 [0.67, 0.92]	0.72 [0.60, 0.87]	0.66 [0.52, 0.85]	1.18 [0.88, 1.59]	1.09 [0.80, 1.48]

*HIMALAYA MAIC refers to the restricted and reweighted sample.

7.1.4 Efficacy – results per OS

According to the indirect comparisons, STRIDE can be considered, on a statistical level, to have a comparable efficacy for median OS compared to atezo-bev (MAIC HR 1.09; 95% CI 0.80-1.48) (Buchers ITC HR: 1.18 95%CI 0.88-1.59). See section 7.1.3.

7.1.5 Efficacy – results per PFS

According to the indirect comparisons, STRIDE can be considered, on a statistical level, to have a lower efficacy for median PFS compared to atezo-bev (MAIC HR 1.73; 95% CI 1.30-2.32) (Buchers ITC HR: 1.98 95% CI 1.50-2.61). See section 7.1.3. However, as mentioned elsewhere in the document, long-term data for PFS in IMbrave150 have not been published (see section 6.1.5).

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model.

The economic model evaluates the costs of STRIDE vs atezo-bev using a three-state partitioned-survival structure based on survival curves extrapolated from observed time

to event outcomes in the Himalaya clinical trial and hazard ratios from the MAIC. Extrapolations were carried out for OS, PFS, and TTD. Given that patient-level data is available from the Himalaya trial, independently fitted survival models for all time to event outcomes were used for STRIDE, while survival curves for atezo-bev are assumed to be the same as for STRIDE given the assumption of equal efficacy. Extrapolations for PFS and TTD are based on the primary data cut-off of the Himalaya trial dates 27 August 2021 (DCO3) after a median follow-up of 33.18 months for STRIDE. Extrapolations for OS are based on the updated data with DCO 23 January 2023 after a median follow-up of 49.12 months for STRIDE.

8.1.1 Extrapolation of efficacy data

To select among the different extrapolated curves the following process was adopted:

Parametric survival models using standard distributions (exponential, Weibull, Gompertz, gamma, lognormal, loglogistic, and generalized gamma) were fitted to the individual arms of the trial. In addition, piecewise survival modelling, a technique that involves fitting independent parametric functions to different periods (or pieces) of survival follow-up, was included in the model alongside the standard functions listed above. This is more commonly referred to as spline-based modelling, or splines and knots. Spline and knots survival functions include 1 knot, 2 knots, and 3 knots, with scales equal to normal, odds, and hazard for each number of knots. Eventually, the best fitting curves were evaluated on the basis of statistical fit to the trial data (using the Akaike's Information Criterion [AIC] and Bayesian Information Criterion [BIC]), visual fit of the extrapolated curve to the trial Kaplan-Meier curve, and external clinical experts on the plausibility of long-term survival. Following this process, a preferred extrapolated curve was selected for each endpoint to be applied in the base case. In the eventuality where the choice was subject to some uncertainty with a consequent meaningful impact on results, alternative distributions were explored in scenario analyses.

8.1.1.1 Extrapolation of overall survival

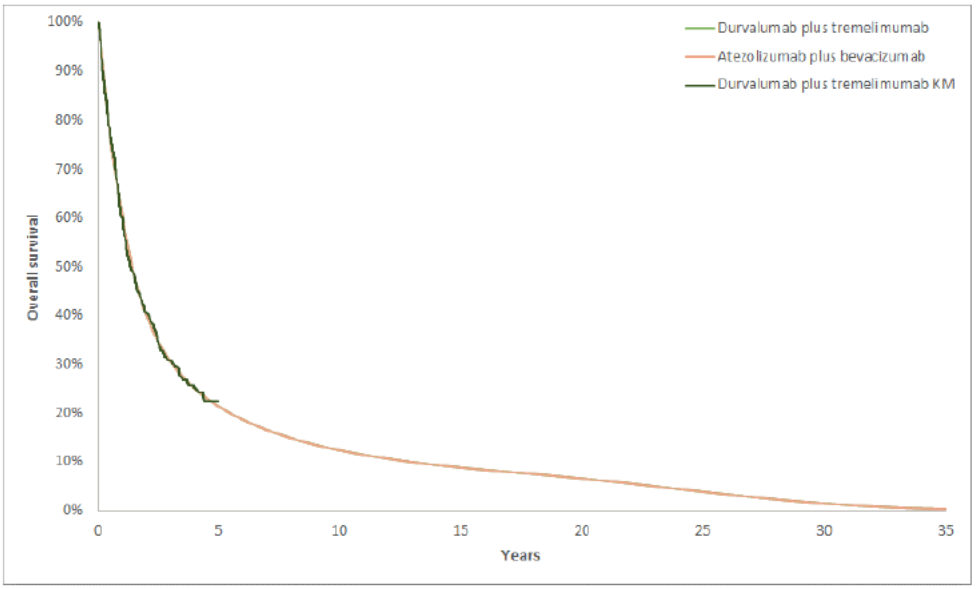
Table 21. Summary of assumptions associated with extrapolation of overall survival.

Method/approach	Description/assumption
Data input	Himalaya clinical trial
Model	Full parametrization models: - Exponential - Weibull - Log-normal - Log-logistic - Gompertz - Generalized gamma - Gamma Piecewise models (splines and knots): - Hazard, 1 knot - Hazard, 2 knots - Hazard, 3 knots - Odds, 1 knot

Method/approach	Description/assumption
	- Odds, 2 knots - Odds, 3 knots - Normal, 1 knot - Normal, 2 knots - Normal, 3 knots
Assumption of proportional hazards between intervention and comparator	Yes. The proportional hazard assumption (PHA) was tested through Schoenfeld's residuals and log-cumulative hazard plots.
Function with best AIC fit	**Intervention**: log-normal **Comparator**: assumed the same
Function with best BIC fit	**Intervention**: log-normal **Comparator**: assumed the same
Function with best visual fit	**Intervention**: odds, 3 knots **Comparator**: assumed the same
Function with the best fit according to external evidence	**Intervention**: odds, 3 knots **Comparator**: assumed the same
Function with best fit according to evaluation of smoothed hazard assumptions	**Intervention**: N/A **Comparator**: N/A
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not necessary as subsequent treatment costs are considered in the model
Assumptions of waning effect	No
Assumptions of cure point	No
Selected parametric function in base case analysis	Intervention: odds, 3 knots Comparator: assumed the same
Validation of selected extrapolated curves	RWE and clinical experts' opinions on clinical plausibility

Figure 14 presents OS Kaplan-Meier data and applied extrapolation function for STRIDE. The STRIDE arm also reflects atezo-bev given the comparable efficacy.

Figure 14. OS Kaplan-Meier data and applied extrapolations



8.1.1.2 Extrapolation of progression-free survival

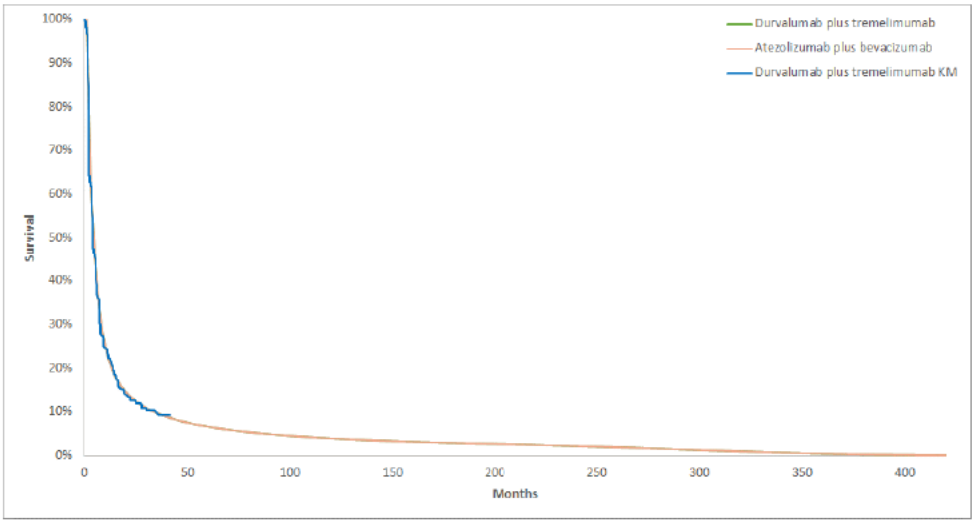
Table 22. Summary of assumptions associated with extrapolation of progression-free survival

Method/approach	Description/assumption
Data input	Himalaya clinical trial
Model	Full parametrization models: - Exponential - Weibull - Log-normal - Log-logistic - Gompertz - Generalized gamma - Gamma Piecewise models (splines and knots): - Hazard, 1 knot - Hazard, 2 knots - Hazard, 3 knots - Odds, 1 knot - Odds, 2 knots - Odds, 3 knots - Normal, 2 knots

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	The proportional hazard assumption (PHA) was tested through Schoenfeld's residuals and log-cumulative hazard plots.
Function with best AIC fit	Intervention: hazard, 3 knots Comparator: assumed the same
Function with best BIC fit	Intervention: hazard, 3 knots Comparator: assumed the same
Function with best visual fit	Intervention: odds, 3 knots Comparator: assumed the same
Function with the best fit according to external evidence	Intervention: odds, 3 knots Comparator: assumed the same
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: N/A Comparator: N/A
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not necessary as subsequent treatment costs are considered in the model
Assumptions of waning effect	No
Assumptions of cure point	No
Selected parametric function in base case analysis	Intervention: odds, 3 knots Comparator: assumed the same
Validation of selected extrapolated curves	N/A

Figure 15 presents PFS Kaplan-Meier data and applied extrapolation functions for both intervention and comparator over the entire time horizon of the model. The STRIDE arm also reflects atezo-bev given the comparable efficacy.

Figure 15: PFS Kaplan-Meier data and applied extrapolations.



8.1.1.3 Extrapolation of time to treatment discontinuation

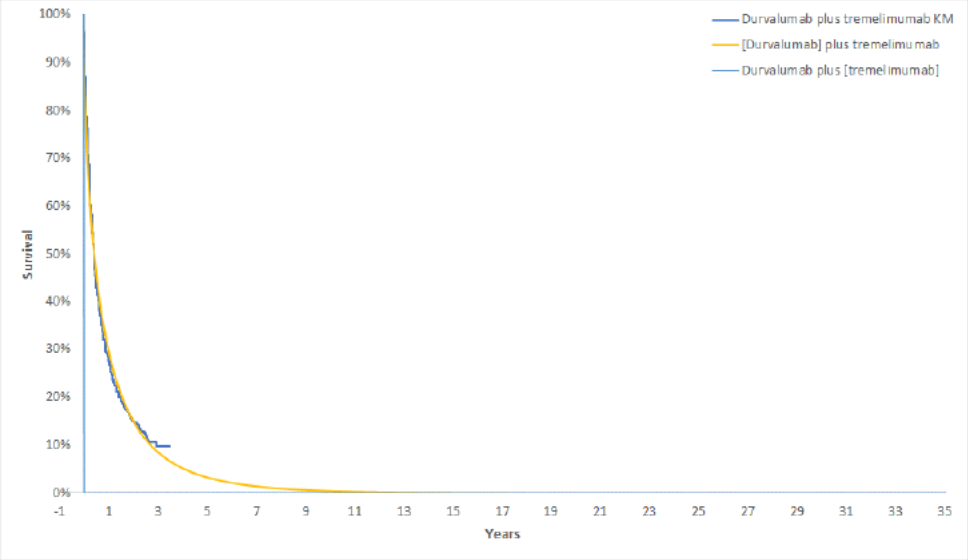
Table 23: Summary of assumptions associated with extrapolation of time to treatment discontinuation.

Method/approach	Description/assumption
Data input	Himalaya clinical trial
Model	Full parametrization models: - Exponential - Weibull - Log-normal - Log-logistic - Gompertz - Generalized gamma - Gamma Piecewise models (splines and knots): - Hazard, 1 knot - Hazard, 2 knots - Hazard, 3 knots - Odds, 1 knot - Odds, 2 knots - Odds, 3 knots - Normal, 1 knot - Normal, 2 knots
Assumption of proportional hazards between intervention and comparator	The proportional hazard assumption (PHA) was tested through Schoenfeld's residuals and log-cumulative hazard plots.
Function with best AIC fit	Intervention: normal, 1 knot Comparator: assumed the same

Method/approach	Description/assumption
Function with best BIC fit	Intervention: normal, 1 knot Comparator: assumed the same
Function with best visual fit	Intervention: Weibull Comparator: assumed the same
Function with the best fit according to external evidence	Intervention: Weibull Comparator: assumed the same
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: N/A Comparator: N/A
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not necessary as subsequent treatment costs are considered in the model
Assumptions of waning effect	No
Assumptions of cure point	No
Selected parametric function in base case analysis	Intervention: Weibull Comparator: assumed the same
Validation of selected extrapolated curves	N/A

Figure 16 presents TTD Kaplan-Meier data and applied extrapolation functions for the intervention over the entire time horizon of the model. In the base case PFS is used to estimate treatment duration rather than using the TTD data. The indication for both is treatment to progression.

Figure 16: TTD Kaplan-Meier data and applied extrapolations.



8.1.2 Calculation of transition probabilities

N/A (partitioned survival model used).

Table 24. Transition in health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	N.A.	N.A
	Death	N.A.	N.A
Recurrence	Death	N.A	N.A
Health state/Transition	N.A.	N.A.	N.A.

8.2 Presentation of efficacy data from additional documentation

N/A

8.3 Modelling effects of subsequent treatments

The calculations consider subsequent treatment costs, but with no separate modelling of the effect of subsequent treatments.

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

Table 25. Estimates in the model

	Modelled average TTD	Modelled median TTD	Observed median from relevant study
STRIDE	19.2 months Sheet TTD cell M49	4.4 months Sheet TTD cell E72	5.5 months
Atezo-bev	19.2 months Sheet TTD cell AK49	4.4 months Sheet TTD cell E72	N/A

Note that PFS was used as proxy for TTD.

Table 26. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length	Pre-progression on treatment	Pre-progression off treatment	Progressed on treatment	Progressed off treatment
STRIDE	19.2 m	19.2 m	0 m	0 m	32.1 m
Atezo-bev	Assumed the same due to equal efficacy assumption				

9. Safety

9.1 Safety data from the clinical documentation

9.1.1 Adverse events

Table 27 summarizes adverse events in both the HIMALAYA study as well as in the IMBrave150 study.(1, 5) In both studies most patients in the treatment arms experienced one or more AEs, regardless of causality. However, the nature and frequency of these events was consistent with that expected for the selected study population and the known safety profile of the study treatments. Quantitative comparisons of grade 3 and 4 AEs, and serious AEs, do not show any significant differences for STRIDE vs. atezo-bev. Sorafenib has also been included, as it was the comparator in both trials.

Table 27. Overview of safety events in A) HIMALAYA study data cut of Aug 27 2021 at final analysis DCO3, in the Safety Analysis Population or B) IMBrave 150 at DCO: August 31, 2020, 12 months after primary analysis in the safety-evaluable population.

	HIMALAYA(5)			IMBrave150(1)		
	STRIDE (N=388)	Sorafenib (N=374)	Difference, % (95 % CI)	Atezo/bev (N=329)	Sorafenib (N=156)	Difference, % (95 % CI)
Number of adverse events, n	NA	NA	NA	3058	1299	RR = 1.1694
Number and proportion of patients with ≥1 adverse events, n (%)	378 (97.4)	357 (95.5)	1.9% (-0.7%;4.6%)	322 (97.9)	154(99.7)	0.8% (-3.2%;1.5%)
Number of serious adverse events*, n	NA	NA	NA	221	83	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	157 (40.5)	111 (29.7)	10.8% (4.1%;17.5%)	160 (48.6)	51 (32.7)	15.9% (6.8%;25.1%)
Number of CTCAE grade ≥ 3 events, n	NA	NA	NA	NA	NA	NA
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	196 (50.5)	196 (52.4)	1.9% (-9.0%;5.2%)	207 (62.9)	89 (57.1)	5.9% (-3.5%;15.2%)
Number of adverse reactions, n	NA	NA	NA	NA	NA	NA

Number and proportion of patients with ≥ 1 adverse reactions, n (%)	294 (75.8)	317 (84.8)	9.0% (-14.6%;-3.4%)	284 (86.3)	148 (94.9)	8.6% (-13.6%;-3.5%)
Number and proportion of patients who had a dose reduction, n (%)	0**	183 (48.9)	48.9% (-54.0%;-43.9%)	0	58 (37.2)	37.2% (-44.8%;-29.6%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	345 (88.9)	353 (94.3)	5.5% (-9.4%;-1.6%)	200 (60.8)	122 (78.2)	17.4% (-25.8%;-9.1%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	53 (13.7)	63 (16.8)	3.2% (-8.3%;1.9%)	34 (10.3)	18 (11.5)	1.2% (-7.2%;4.8%)

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect. § CTCAE v. 5.0 must be used if available.** Dose reductions were only permitted for the STRIDE regimen (durvalumab and tremelimumab) if a patient's weight decreased to ≤30 kg. As no patients had a reduction in weight to ≤30 kg, there were no durvalumab or tremelimumab dose reductions. #relative risk applied without CI 95%.

Table 28. Serious treatment-emergent adverse events, grade 3 or 4, that occurred in 2% or more of patients in any treatment arm in A) HIMALAYA study data cut of Aug 27 2021 at final analysis DCO3, in the Safety Analysis Population or B) IMBrave 150 at data cut-off: August 31, 2020, 12 months after primary analysis in the safety-evaluable population.**

HIMALAYA					IMBrave150	
Adverse events	STRIDE (N=388)		Sorafenib (N=374)		Atezo/bev (N=329)	Sorafenib (N=156)
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of patients with adverse events
Adverse event, n (%)						
Aspartate aminotransferase increased	20 (5.2)	NA	12 (3.2)	NA	17 (5)	5 (3)
Lipase increased	24 (6.2)	NA	11 (2.9)	NA	N/A	N/A
Hypertension	7 (1.8)	NA	23 (6.1)	NA	39 (12)	14 (9)

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect. ** For HIMALAYA the data are for Grade 3 or more TEAEs that occurred in 2% or more of patients. For IMbrave data is for Grade 3 or more event that occurred in 10% or more patients. ***Sorafinib is included in the table as it is the comparator in both HIMALAYA and IMBrave150

Table 29. Adverse events used in the health economic model

Adverse events	STRIDE	Atezo-bev		
	Frequency used in economic model for STRIDE (n=388)	Frequency used in economic model for atezo+bev (n=329)	Source	Justification
Aspartate aminotransferase increased	20 5.2%	23 7.0%	HIMALAYA trial (Abou-Alfa 2022) & IMbrave150 (Finn 2020)	CTCAE Grade 3+ adverse events, 5% cut-off in either treatment arm of the HIMALAYA clinical trial.
Hypertension	7 1.8%	50 15.2%	HIMALAYA trial (Abou-Alfa 2022) & IMbrave150 (Finn 2020)	CTCAE Grade 3+ adverse events, 5% cut-off in either treatment arm of the HIMALAYA clinical trial.
Lipase increased	24 6.2%	0 0%	HIMALAYA trial (Abou-Alfa 2022) & IMbrave150 (Finn 2020)	CTCAE Grade 3+ adverse events, 5% cut-off in either treatment arm of the HIMALAYA clinical trial.

9.2 Safety data from external literature applied in the health economic model.

See above in Section 9.1. A cost-minimization analysis is presented versus atezo-bev where no AEs are taken into consideration.

Table 30. Adverse events that appear in more than X % of patients.

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N.A	N.A.	N.A	N.A.	N.A.	N.A.	N.A.	N.A.

10. Documentation of HRQoL

An assessment of EORTC QLQ-C30 data from HIMALAYA and Imbrave150 is conducted for comparative purposes. As mentioned above, HRQoL data is not relevant for model due to the cost-minimization approach.

Table 31. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	HIMALAYA IMBrave150	Comparative analysis

10.1 Presentation of health-related quality of life – EORTC QLQ-C30

10.1.1 Study design and measuring instrument

Assessment of time to treatment deterioration with EORTC QLQ-C30 were a secondary efficacy objective of HIMALAYA and IMBrave150. PROs were assessed using the European Organization for Research and Treatment of Cancer (EORTC) 30-item Quality of Life Questionnaire (QLQ-C30). Data on time to deterioration (TTD) for GHS/QoL, and

functioning domains will be presented for the HRQoL comparison between HIMALAYA and IMBrave150.

10.1.1.1 HIMALAYA

PRO analyses were conducted in participants in the full analysis set with an evaluable baseline assessment and ≥one evaluable postbaseline assessment. At each postbaseline assessment, the change in score from baseline was categorized as improvement, no change, or deterioration. A clinically meaningful change (deterioration or improvement) was defined as an absolute change ≥10 points from baseline.

The time to deterioration was analyzed in participants in the FAS with baseline scores ≥10 for GHS/QoL and functioning domains. Time to deterioration was defined as time from random assignment until first clinically meaningful deterioration that was confirmed at a subsequent visit (unless observed at last available assessment) or death (any cause) in the absence of clinically meaningful deterioration.

Time to deterioration was analyzed using a stratified log-rank test. HRs and 95% CIs were calculated for STRIDE versus sorafenib and durvalumab versus sorafenib using a Cox proportional hazards model adjusted for treatment, etiology, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and macrovascular invasion.

10.1.1.2 Imbrave-150

The time-to-confirmed-deterioration analyses for PROs were done in the intention-to-treat population, defined as all patients who were randomly assigned to a study treatment, regardless of treatment received. The remaining analyzes of PROs were done in the PRO evaluable population, defined as all randomly assigned patients who had a baseline PRO assessment and at least one PRO assessment after baseline.

The time to deterioration of quality of life, physical functioning, and role functioning, as reported by the patient, with deterioration defined as a decrease from baseline of 10 points or more on the EORTC QLQ–C30 maintained for two consecutive assessments or a decrease of 10 points or more in one assessment followed by death from any cause within 3 weeks.

Kaplan–Meier analysis was applied to the time to deterioration for EORTC QLQ-C30. A stratified two-sided log-rank test was used to analyze the time to deterioration.

10.1.2 Date collection

10.1.2.1 HIMALAYA

Questionnaires were administered via an electronic tablet PRO device and were completed by participants at the study site before any other procedures or meetings with the study nurse or physician to discuss cancer-related issues or health status. Questionnaires were completed on day 1 of treatment and then every 8 weeks (±7 days relative to the first dose of treatment) for the first 48 weeks and then every 12 weeks ± 7

days thereafter, until treatment discontinuation. Participants who discontinued treatment also completed the questionnaires as described above until disease progression and up to 3 months after treatment discontinuation, if participants had disease progression at treatment discontinuation.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted] N (%)
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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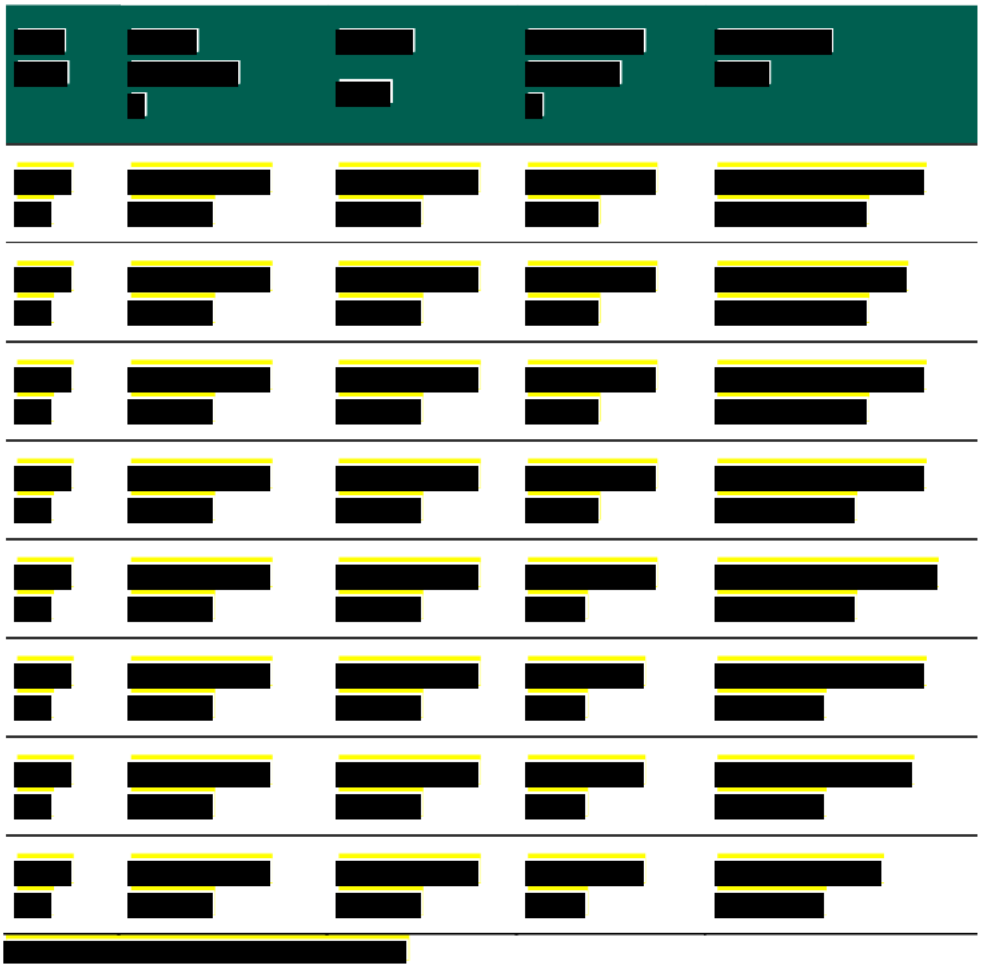
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



10.1.2.2 IMbrave150

Patients completed officially translated and validated versions of the two questionnaires on paper at the clinic site on day 1 of treatment cycle one (i.e, baseline) and on day 1 of every cycle thereafter, up to and including the treatment discontinuation visit. Questionnaires had to be completed during a clinic visit before discussion of the patient's health state, laboratory results, or health record, before administration of study treatment, and before any other study assessments. After treatment discontinuation or disease progression, whichever came first, questionnaires were completed on paper or via telephone every 3 months for 1 year unless the patient withdrew consent.

Table 33. Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Treatment cycle	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of	Number of patients who completed (% of patients expected to complete)
1 (baseline)	A+B: n=336 S: n=165	A+B: n=24 S: n=17	A+B: n=336 S: n=165	A+B: n=312 (92.9%) S: n=148 (89.7%)
2	A+B: n=336 S: n=165	A+B: n=41 S: n=35	A+B: n=313 S: n=139	A+B: n=295 (94.2%) S: n=130 (93.5%)
3	A+B: n=336 S: n=165	A+B: n=59 S: n=67	A+B: n=289 S: n=102	A+B: n=277 (95.8%) S: n=98 (96.1%)
4	A+B: n=336 S: n=165	A+B: n=71 S: n=79	A+B: n=279 S: n=90	A+B: n=265 (95.0%) S: n=86 (95.6%)
5	A+B: n=336 S: n=165	A+B: n=84 S: n=95	A+B: n=266 S: n=75	A+B: n=252 (94.7%) S: n=70 (93.3%)
6	A+B: n=336 S: n=165	A+B: n=91 S: n=102	A+B: n=255 S: n=67	A+B: n=245 (96.1%) S: n=63 (94.0%)
7	A+B: n=336 S: n=165	A+B: n=111 S: n=113	A+B: n=240 S: n=55	A+B: n=225 (93.8%) S: n=52 (94.5%)
8	A+B: n=336 S: n=165	A+B: n=124 S: n=116	A+B: n=223 S: n=51	A+B: n=212 (95.1%) S: n=49 (96.1%)
9	A+B: n=336 S: n=165	A+B: n=136 S: n=125	A+B: n=214 S: n=44	A+B: n=200 (93.5%) S: n=40 (90.9%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
10	A+B: n=336 S: n=165	A+B: n=146 S: n=124	A+B: n=197 S: n=43	A+B: n=190 (96.4%) S: n=41 (95.3%)
11	A+B: n=336 S: n=165	A+B: n=157 S: n=134	A+B: n=180 S: n=32	A+B: n=179 (99.4%) S: n=31 (96.9%)
12	A+B: n=336 S: n=165	A+B: n=186 S: n=139	A+B: n=157 S: n=28	A+B: n=150 (95.5%) S: n=26 (92.9%)
13	A+B: n=336 S: n=165	A+B: n=205 S: n=142	A+B: n=133 S: n=24	A+B: n=131 (98.5%) S: n=23 (95.8%)
14	A+B: n=336 S: n=165	A+B: n=226 S: n=149	A+B: n=112 S: n=16	A+B: n=110 (98.2%) S: n=16 (100.0%)
15	A+B: n=336 S: n=165	A+B: n=252 S: n=154	A+B: n=87 S: n=11	A+B: n=84 (96.6%) S: n=11 (100.0%)
16	A+B: n=336 S: n=165	A+B: n=274 S: n=158	A+B: n=65 S: n=7	A+B: n=62 (95.4%) S: n=7 (100.0%)
17	A+B: n=336 S: n=165	A+B: n=287 S: n=161	A+B: n=51 S: n=5	A+B: n=49 (96.1%) S: n=4 (80.0%)
18	A+B: n=336 S: n=165	A+B: n=296 S: n=161	A+B: n=40 S: n=4	A+B: n=40 (100.0%) S: n=4 (100.0%)
19	A+B: n=336 S: n=165	A+B: n=308 S: n=163	A+B: n=28 S: n=2	A+B: n=28 (100.0%) S: n=2 (100.0%)
20	A+B: n=336 S: n=165	A+B: n=317 S: n=163	A+B: n=20 S: n=2	A+B: n=19 (95.0%) S: n=2 (100.0%)
21	A+B: n=336 S: n=165	A+B: n=322 S: n=163	A+B: n=14 S: n=2	A+B: n=14 (100.0%) S: n=2 (100.0%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
22	A+B: n=336 S: n=165	A+B: n=329 S: n=164	A+B: n=8 S: n=1	A+B: n=7 (87.5%) S: n=1 (100.0%)
23	A+B: n=336 S: n=165	A+B: n=331 S: n=164	A+B: n=5 S: n=1	A+B: n=5 (100.0%) S: n=1 (100.0%)
24	A+B: n=336 S: n=165	A+B: n=334 S: n=164	A+B: n=2 S: n=1	A+B: n=2 (100.0%) S: n=1 (100.0%)

Source (73): **Legend**: A+B, Atezo+bev; S, sorefenib

10.1.3 HRQoL results

10.1.3.1 HIMALAYA

Median time to deterioration was prolonged with STRIDE compared to sorafenib for EORTC QLQ-C30 in HIMALAYA across the domains, QHS/QoL, Physical Functioning and Role Functioning. Please refer to Table 34 for summary table on median time to deterioration and HR between the two arms.

Table 34. Time to deterioration on EORTC QLQ-C30 in HIMALAYA, summary table

	STRIDE	Sorafenib	Intervention vs. comparator
	Median TTD (95% CI)	**Median TTD (95% CI)**	**HR (95% CI)**
GHS/QoL	7.5 (5.8 – 10.8) months	5.7 (4.8 – 7.4) months	0.76 (0.61 - 0.96)
Physical Functioning	12.9 (9.2 – 16.8) months	7.4 (5.7 – 10.4) months	0.68 (0.53 - 0.87)
Role Functioning	9.3 (7.4 – 13.9) months	7.1 (5.6 – 9.2) months	0.70 (0.55 – 0.88)

Source: HIMALAYA CSR + HIMALAYA PRO publication(74)

10.1.3.2 IMbrave-150

Median time to deterioration was prolonged with atezo-bev compared to sorafenib for EORTC QLQ-C30 in IMbrave150 across the domains, QHS/QoL, Physical Functioning and

Role Functioning. Please refer to Table 35 for summary table on median time to deterioration and HR between the two arms.

Table 35. Time to deterioration on EORTC QLQ-C30 in IMBrave150, summary table

	Atezo+Bev	Sorafenib	Intervention vs. comparator
	Median TTD (95% CI)	Median TTD (95% CI)	HR (95% CI)
GHS/QoL	11.2 (6.0 – NE) months	3.6 (3.0 – 7.0) months	0.63 (0.46 - 0.85)
Physical Functioning	13.1 (9.7 – NE) months	4.9 (3.5 – 6.2) months	0.53 (0.39 - 0.73)
Role Functioning	9.1 (6.5 – NE) months	3.6 (2.2 – 6.0) months	0.62 (0.46 – 0.84)

Source: Primairy Imbrave pulication

10.1.4 Descriptive comparison of quality of life

Results on time to deterioration measured with EORTC QLQ-C30 are consistent across HIMALAYA and IMBrave150 for STRIDE and atezo+Bev. Based on a descriptive comparison of the results presented in Table 34 and Table 35, STRIDE can be considered to have similar efficacy in prolonging the time to deterioration of quality of life compared to atezo+Bev.

10.2 EQ-5D-5L and EQ-VAS - HIMALAYA

10.2.1 Study design and measurement.

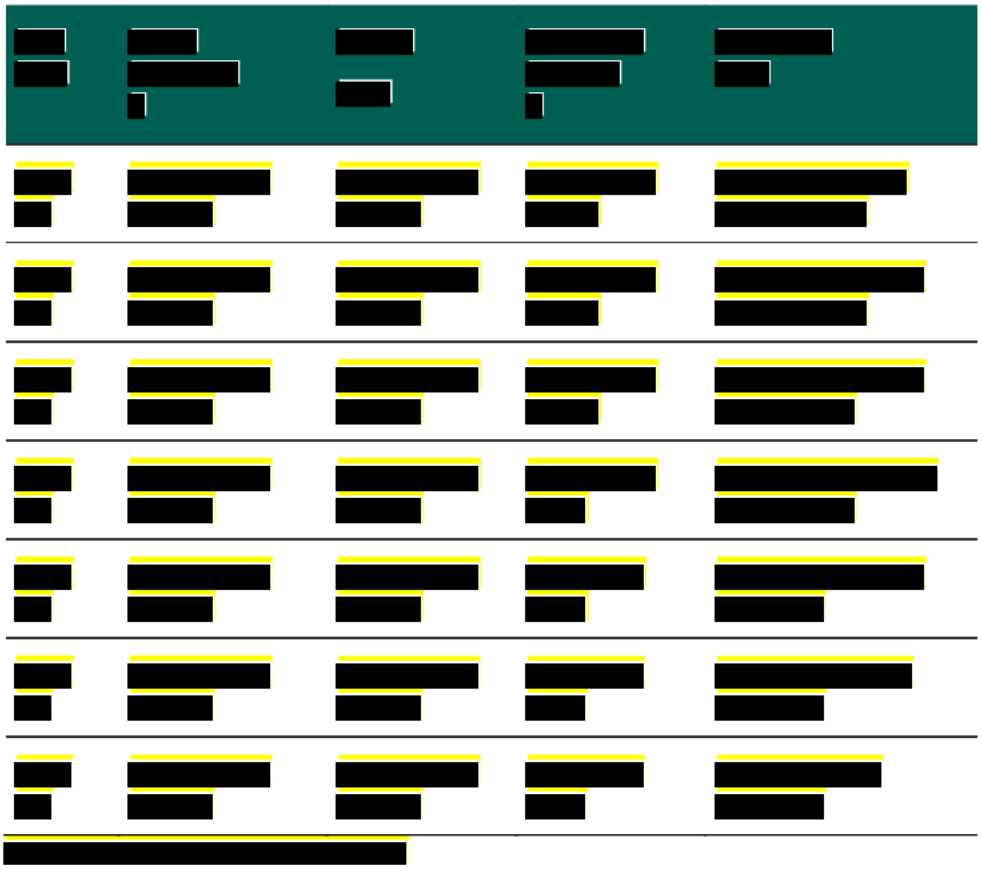
The EuroQoL 5 Dimensions 5 levels (EQ-5D-5L) and EuroQoL visual analogue scale (EQ-VAS) measurements were also collected in HIMALAYA at the same time points as EORTC QLQ-C30.

10.2.2 Data collection

Compliance rates for EQ-5D-5L at baseline were ≥ 77% and generally similar across treatment arms for the first 48 weeks (≥ 65% majority of timepoints) (Table 36). In general, the compliance rate was acceptable to good (> 60%) for the T300+D and the D arms at most timepoints of the study and for the S arm up to Week 48. The EQ-5D-5L index and VAS measurements were similar across treatment arms. Both the EQ-5D-5L index and VAS scores for the T300+D and D arms were mostly stable with a trend towards improvement over time. Therefore, slightly higher mean scores over time were observed in patients who received T300+D and D compared to S.

Compliance a summary of completed questionnaires are show in Table 36.

[redacted]



10.2.3 HRQoL results

Both scales showed similar results across treatment arms. Both the EQ-5D-5L and EQ-VAS scores for the STRIDE treatment arm were mostly stable with a trend towards improvement over time. Therefore, slightly higher mean scores over time were observed in patients who received STRIDE compared with sorafenib. Post-hoc analyses of the HIMALAYA EQ-5D data were conducted to determine treatment specific health state utility values by applying country specific value sets to the EQ-5D data from HIMALAYA [redacted] with a VAS summary of mean EQ-5D-5L scores presented in Figure 18. In an analysis it was found that treatment status (whether a patient is on/off treatment) was the strongest predictor of health state utility value, and was associated with a higher impact on patient utility than type of treatment, progression status, or baseline Child-Pugh score.

10.3 Health state utility values (HSUV) used in the health economic model

N.A.

10.3.1 HSUV calculation

N.A.

10.3.1.1 Mapping

N.A.

10.3.2 Disutility calculation

N.A.

10.3.3 HSUV results

N.A.

Table 37. Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N.A.	N.A.	N.A.	N.A.
HSUV B	N.A.	N.A.L	N.A.	N.A.
[Disutilities]	N.A.	N.A.	N.A.	N.A.

10.4 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N.A.

10.4.1 Study design

N.A.

10.4.2 Data collection

N.A.

10.4.3 HRQoL results

N.A.

10.4.4 HSUV and disutility results

N.A.

Table 38. Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N.A.	N.A.	N.A.	N.A.
HSUV B	N.A.	N.A.L	N.A.	N.A.
[Disutilities]	N.A.	N.A.	N.A.	N.A.

Table 39. Overview of literature -based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	N.A.	N.A.	N.A.	N.A.
HSUV B		N.A.		
[Disutility A]		N.A.		

11. Resource use and associated costs

The spectrum of costs for managing patients with uHCC are described below. Included costs are reported in 2024 Danish kroner (DKK). Costs from previous years were inflated using the subgroup of the consumer price index from Statistics Denmark (2024). The model includes the following costs, which are discussed in detail below:

- Pharmaceutical costs
- Administration costs
- Disease management costs
- Adverse events related costs
- Subsequent treatments costs

- Patient costs
- Other costs (e.g. end of life care)

11.1 Medicine costs (intervention and comparator)

The medicine costs for first line and subsequent treatments are outlined in Table 40 and **Error! Reference source not found.**, respectively, and they were based on prices from m edicinpriser.dk (AIP). For treatments with multiple pack options, the pack with the lowest cost per mg was used. Prices are updated in May 2024. The model also allows specification of simple percentages discounts for each drug. Drug acquisition costs are applied in line with the dosing schedules for each treatment detailed in Table 40.

When vial sharing is allowed (wastage is excluded), the cost per mg of a treatment is multiplied by the dose in a cycle to derive acquisition costs. This assumes vial sharing is possible between patients. When vial sharing is not allowed (base case; wastage is included), doses are rounded up to the full vial to account for the lost drug. For weight-dosed treatments, the mean patient weight has been used to estimated drug costs. It is assumed there are no wastage costs associated with treatments that are administered orally. The estimated acquisition cost per dose is shown in Table 41. The relative dose intensity (RDI) for STRIDE was obtained from HIMALYA and the RDIs for other treatments were assumed to be 100% in the absence of more precise information.

Table 40. Medicine costs used in the model – first line

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Durvalumab	50 mg/ml	2.4 ml (vial)	4 278.60 kr
	50 mg/ml	10 ml (vial)	17 672.28 kr
Tremelimumab	20 mg/ml	15 ml (vial)	162 357.23 kr
Atezolizumab	60 mg/ml	20 ml (vial)	28 952.64 kr
Bevacizumab	25 mg/ml	4 ml (vial)	1 895.27 kr
	25 mg/ml	16 ml (vial)	6 986.84 kr

Table 41. Dosing schedules

Regimen	Treatment	Prescribed dose	Dose per admin.	Frequency	Admin. method
Primary treatment					
Treatment 1					
STRIDE	Durvalumab	1500 mg	1500 mg	Q4W	IV
Atezo-bev	Atezolizumab	1200 mg	1200 mg	Q3W	IV
Treatment 2					
STRIDE	Tremelimumab	300 mg	300 mg	1 dose only	IV
Atezo-bev	Bevacizumab	15 mg/kg	1050 mg	Q3W	IV

Table 42. Acquisition cost per dose (DKK)

Regimen	RDI	Treatment	No vial sharing	Vial sharing
Primary treatment				
Treatment 1				
STRIDE	97.7%	Durvalumab		53 016.84
Atezo-bev	100%	Atezolizumab		28 952.64
Treatment 2				
STRIDE	100%	Tremelimumab		162 357.23
Atezo-bev	100%	Bevacizumab	19 659.49	18 576.26

11.2 Medicine costs – co-administration

N.A.

11.3 Administration costs

Administration unit costs are presented in Table 43. Oral administration costs are assumed to be negligible. For combination therapies (e.g. STRIDE) in which drugs are administered during the same visit, the cost for the administration of the second drug is assumed to be included in the cost of administration of the first drug. Dosing schedules are detailed in Table 41 above.

Table 43. Administration costs used in the model

Administration type	Unit cost [DKK]	DRG code	Reference
Oral	0 kr	NA	Assumption
IV	1 947.00 kr	07MA98[§]	DRG 2024
IV subsequent*	0 kr	NA	Assumption

Administration type	Unit cost [DKK]	DRG code	Reference

§ DRG code: 07MA98, MDC07 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC229, Kræft i leveren UNS - Treatment code: BWAA6, Medicingivning intravenøst* Used for combination therapies administered during the same visit

11.4 Disease management costs

Resource use and monitoring costs are applied to the progression-free and progressed health states. An end-of-life cost is applied to the death health state, see section 11.8.

A modelling approach based on itemized costs was adopted. Itemized costs apply a cost to each individual resource use a patient may receive (Table 44). Treatment-specific resource use costs are applied to each treatment arm. The frequency of itemized resource use per week for STRIDE was estimated based on feedback from a Danish clinical expert. Following an expert interview, these frequencies were in line with clinical practice in Denmark. For atezo+bev, frequencies have been sourced from the DMC evaluation of atezo+bev in HCC(40). Patients usually experience many side effects that leads to further consultations with the oncologist. Additionally, there is the need for frequent dose reductions and adaptions that create extra burden on the health care resources. The itemized resource use frequency and costs per week for STRIDE and atezo-bev are presented separately in Table 45 and Table 46.

Table 44. Disease management costs used in the model

Activity	Unit cost [DKK]	DRG code	Reference
Appointment with oncologist	1 947.00 kr	2024 DRG code: 07MA98, MDC07 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC229, Kræft i leveren UNS	
Appointment within clinician nurse specialist	0 kr		
Appointment with palliative care physician/nurse	0 kr		Assumed to be included within DRG tariff for oncologist visit
Lab cost	0 kr.		
Endoscopy	5 581.00 kr	2024 DRG code: 06PR04, Endoskopi el. intubation i øvre mavetarmreg. - Diagnosis code: DC229, Kræft i leveren UNS - Treatment code: KUJD02, Gastroskopi	
Abdominal CT	2 585.00 kr	2024 DRG code: 30PR06, MR-scanning, kompliceret - Diagnosis code: DC229, Kræft i leveren UNS, - Treatment code: UXCD40, CT-skanning af lever	

Activity	Unit cost [DKK]	DRG code	Reference
Abdominal MRI	2 511.00 kr	2024 DRG code: 30PR02, MR-scanning, kompliceret - Diagnosis code: DC229, Kræft i leveren UNS, - Treatment code: UXMD40, MR-skanning af lever	
Hospitalization	43 630.00 kr	2024 DRG code: 07MA08, Ondartede sygdomme i lever, galdeveje og bugspytkirtel, pat. mindst 18 år - Diagnosis code: DC229, Kræft i leveren UNS - Duration: >=12 timer (lang)	
GP Visit	160.72 kr	1st April 2024 'Honorartabel': 0101, Konsultation	

Table 45. STRIDE – resource use frequency

Resource use	Frequency per week			Costs per week		
	Progression-free (cycle 1)	Progression-free (subsequent cycles)	Disease progression	Progression-free (cycle 1)	Progression-free (subsequent cycles)	Disease progression
Appointment with oncologist	0.231 (~4 weeks)	0.231 (~4 weeks)	0.231 (~4 weeks)	449.31 kr	449.31 kr	449.31 kr
Appointment with hepatologist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Appointment with Gastroenterologist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Appointment with Radiologist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Appointment within clinician nurse specialist	0.231 (~4 weeks)	0.231 (~4 weeks)	0.231 (~4 weeks)	0.00 kr	0.00 kr	0.00 kr
Appointment with palliative care physician/nurse	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
AFP test	0.231 (~4 weeks)	0.231 (~4 weeks)	0.231 (~4 weeks)	0.00 kr	0.00 kr	0.00 kr
Liver function test*	0,231 (~4 weeks)	0,231 (~4 weeks)	0,231 (~4 weeks)	0.00 kr	0.00 kr	0.00 kr
INR	0.231 (~4 weeks)	0.231 (~4 weeks)	0.231 (~4 weeks)	0.00 kr	0.00 kr	0.00 kr
Complete blood count	0.231 (~4 weeks)	0.231 (~4 weeks)	0.231 (~4 weeks)	0.00 kr	0.00 kr	0.00 kr
Biochemestry	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Endoscopy	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Abdominal CT	0.077 (~12 weeks)	0.077 (~12 weeks)	0.077 (~12 weeks)	198.85 kr	198.85 kr	198.85 kr
Abdominal MRI	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Hospitalization	0.010 (~100 weeks)	0.010 (~100 weeks)	0.010 (~100 weeks)	419.52 kr	419.52 kr	419.52 kr
Hospital follow-up: Specialist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Hospital follow-up: GP	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Hospital follow-up: Nurse	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr

Table 46. Atezolizumab plus bevacizumab – resource use frequency

Resource use	Frequency per week			Costs per week		
	Progression-free (cycle 1)	Progression-free (subsequent cycles)	Disease progression	Progression-free (cycle 1)	Progression-free (subsequent cycles)	Disease progression
Appointment with oncologist	0.333	0.333	0.250	649.00 kr	649.00 kr	486.75 kr
Appointment with hepatologist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Appointment with Gastroenterologist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Appointment with Radiologist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Appointment within clinician nurse specialist	0.333	0.333	0.250	0.00 kr	0.00 kr	0.00 kr
Appointment with palliative care physician/nurse	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
AFP test	0.231	0.231	0.231	0.00 kr	0.00 kr	0.00 kr
Liver function test*	0.231	0.231	0.231	0.00 kr	0.00 kr	0.00 kr
INR	0.231	0.231	0.231	0.00 kr	0.00 kr	0.00 kr
Complete blood count	0.333	0.333	0.231	0.00 kr	0.00 kr	0.00 kr
Biochemistry	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Endoscopy	1.000	0.000	0.000	5,581.00 kr	0.00 kr	0.00 kr
Abdominal CT	0.083	0.083	0.083	215.42 kr	215.42 kr	215.42 kr
Abdominal MRI	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Hospitalization	0.010	0.010	0.010	419.52 kr	419.52 kr	419.52 kr
Hospital follow-up: Specialist	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Hospital follow-up: GP	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr
Hospital follow-up: Nurse	0.000	0.000	0.000	0.00 kr	0.00 kr	0.00 kr

11.5 Costs associated with management of adverse events

The costs of managing adverse events were primarily based on input from a clinical expert interview. The model accounts for grade 3+ AEs that occurred with a frequency of at least 5% in either arm (Table 47). The cost of managing aspartate aminotransferase increased, increased amounts to 4 visits with the oncologist plus 4 blood counts. Hypertension is dealt with by the family doctor and therefore it was assumed to be equivalent to one extra GP visit. According to the consulted Danish clinical expert, lipase levels are not checked within the standard routine of diseases management for this indication and therefore no extra cost was added.

Patient AE costs were calculated by the frequency of AEs listed in HIMALAYA. The frequency of AEs not included in HIMALAYA were sourced from the relevant literature and NICE technology appraisals. The rate of AEs is calculated at the frequency of AEs multiplied by the number of patients within the clinical trial, and then divided by the total patient years (total number of patients in the clinical trial multiplied by the duration of the clinical trial). The rate of AEs multiplied by the AE costs is used to give the patient AE costs, per treatment, and applied to the life years per cycle within the 'Engine' sheets.

Table 47. Cost associated with management of adverse events

	DRG code	Unit cost
Aspartate aminotransferase increased	4 oncologist visit (see DRG in Table 44)	7 788.00 kr
Hypertension	1 GP visit (see tariff in Table 44)	160.72 kr
Lipase increased	Not used as routine	0.00 kr

11.6 Subsequent treatment costs

The subsequent treatments were based on Danish clinical expert input. Sorafenib would be used as the first subsequent treatment by a majority of the patients (70-80%) treated with immunotherapy as first-line treatment in the advanced setting and regorafenib would be used as the second subsequent treatment (30-40% out of those who go on to second subsequent therapy). Patients who do not receive these treatments will receive best supportive care. The subsequent treatment lines are not modelled separately. Instead we assumed a treatments mix of 75% sorafenib and 25% regorafenib modelled as a lumpsum cost based on doses from the Summary of Product Characteristics for each product and treatment durations based on data on subsequent therapies from HIMALAYA (Table 48, Table 49). The subsequent therapy costs are then estimated by multiplying the daily dose with the cost per mg and the treatment duration.

Table 48. Medicine costs of subsequent treatments from clinical expert feedback

Medicine	Strength	Package size	Pharmacy purchase price per pack [DKK]	Relative dose intensity	Average duration of treatment [days]
Sorafenib	200 mg	112 (tablet)	17 438.48 kr	78.3%*	242.6
Regorafenib	160 mg	84 x 40 mg (tablet)	19 218.06 kr	100%**	167.8

*RDI based on HIMALAYA, **RDI assumed to be 100% in the absence of more precise information

Table 49. Distribution of subsequent treatments applied in the model according to Danish clinical expert

Subsequent treatment	Primary treatment (%) after STRIDE
Regorafenib	25%
Sorafenib	75%

11.7 Patient costs

Patient costs in the model were related to the frequency and duration of healthcare visits related to ongoing monitoring of HCC, given that initial treatments are all taken orally and therefore patients do not need to have to travel to the hospital for treatment administration. The unit costs of patients time and transport were taken from Medicinrådet's unit costs list (Værdisætning af enhedsomkostninger, section 5: Patient- og pårørenderelaterede omkostninger), assuming 203 DKK/hour for patient time and transportation cost of 140 DKK per. The duration of patient time used for consultation are assumed to be 1 hour, and includes time for tests and nurse consultation as well. The duration of patient time used for hospitalizations is assumed to be 24 hours. Patient time for administration of IV medicine have been based on the infusion time stated in the SmPCs of durvalumab, tremelimumab, atezolizumab and bevacizumab, see

Table 50. A single transportation cost has been included for each administration, regardless of the number of drugs administered during the visit. The base case only includes oral drugs for subsequent treatment, and no patient costs have been assumed for these subsequent therapies. Patient costs per treatment and health state are detailed in Table 51.

Table 50. Patient time in relation to administration

Patient time of administrations		
	First administration	Subsequent administrations
Durvalumab	60 min.	60 min.
Tremelimumab	60 min.	No subsequent administration
Atezolizumab	60 min.	30 min
Bevacizumab	90 min.	30 min.

Table 51. Patient costs per week

Patient time costs			
	Progression-free (cycle 1)	Progression free (Subsequent cycles)	Disease progression
Durvalumab plus tremelimumab	782.72 kr	275.22 kr	173.72 kr
Atezo-bev	1,334.46 kr	353.30 kr	184.13 kr
Patient transport costs			
Durvalumab plus tremelimumab	184.42 kr	79.42 kr	44.42 kr
Atezo-bev	339.68 kr	106.35 kr	48.01 kr

11.8 Other costs: end of life

The economic model includes a one-off cost for the end-of-life care applied at the transition to the death health state to account for the cost of terminal care. The value presented in the model is based on the end-of-life cost presented in Round et al. (2015) (77). The authors' estimation considered health care, social care, charity care, and informal care costs for breast, colorectal, lung, and prostate cancers. Although the model was based on English tariffs, it is expected to reflect an amount representative also for the Danish system. Additionally, the same source was used in previous assessment submitted to DMC and Amgros. Given the uncertainty associated with such an estimate, the sensitivity of the results with respect to this cost was tested and it was found that it has limited significance.

The cost from Round et al. (2015) (77) has been converted in DKK from GBP using the exchange rate yearly average for 2013 from the Danish National Bank (78). It was then adjusted for differences in the price level indexes between the two countries using the price level indexes list from Eurostat (79). Finally, the amount was inflated to 2024 levels using the price index from Statistics Denmark (80) and the resulting 82 193.80 kr cost was applied in the economic model.

12. Results

The results sections include the cost-minimization results versus atezo-bev. Based on the MAIC presented above, in which HIMALAYA population has been adjusted to be comparable to IMbrave 150 population, STRIDE and atezo-bev can be considered, on a statistical level, to have a comparable efficacy for overall survival (HR STRIDE vs atezo-bev= 1.09 [0.80, 1.48]).

For progression free survival a different development over time appears with the effect of STRIDE being delayed compared to atezo-bev. This may be due to CTCL-4 inhibitors (part of STRIDE) and anti-VEGF (part of atezo-bev) different modes of actions. Based on the MAIC, atezo-bev performed better than STRIDE in terms of PFS (HR STRIDE vs atezo-bev=1.73 [1.30, 2.32]). However, this result should be interpreted with caution as IMbrave 150 PFS is captured only for 14 months and because tests for the PHA returned ambiguous results as shown in Appendix C.

In the context of immunotherapies such as the current one, in which OS benefits constitute the most relevant component of the treatment efficacy, it is important noticing that the 4 year data update from the HIMALAYA trial shows a durable OS effect. At the same time, long-term follow-up data for IMbrave150 have not been published, and OS effect beyond 18 months is unknown.

12.1 Base Case overview

The basic assumptions from the base case analysis are summarized in Table 52.

Table 52. Base case overview

Model features	Description	Justification
Comparator	Atezolizumab 1200 mg + bevacizumab 15 mg/kg every three weeks	Danish treatment guidelines
Type of model	Partitioned survival model	Builds on survival curves from the HIMALAYA study. Atezo-bev included through indirect treatment comparison, assuming equal efficacy in the base case
Time horizon	Lifetime (35 years)	To capture the totality of costs associated with the treatments. Different horizons are considered in scenario analysis
Treatment line	1st line (subsequent therapy costs are included as lump-sum costs, but not modelled explicitly)	As per indication
Measurement and valuation of health effects	Health effects assumed equal and not included in the model	Cost-minimization approach used. The indirect treatment comparison indicates no significant difference

Model features	Description	Justification
		in OS between STRIDE and atezo-bev. Atezo-bev has numerically better OS HR, but STRIDE has long-term data with clear tail development over time.
Included costs	• Pharmaceutical costs • Administration costs • Monitoring costs • Adverse event costs • Patient and transport costs • Subsequent therapy costs	Standard cost items
Dosage of medicine	Tremelimumab 300 mg for one single dose + durvalumab 1500 mg Q4W Atezolizumab 1200 mg + 15 mg/kg of bevacizumab Q3W	According to the HIMALAYA study dosing and the SmPC (EPAR) According to national treatment guideline and the IMPower150 study. Validated by Danish clinical expert
Subsequent therapies included	Yes, but only included as lump-sum costs	Based on expert elicitation on Danish clinical practice
Time on treatment	Based on extrapolated PFS KM data from HIMALAYA for time on treatment to make the data comparable between STRIDE and atezo-bev	Need to extrapolate as KM data does not cover the relevant time horizon (treatment to disease progression or unacceptable toxicity)
Average time on treatment	STRIDE: 19.2 months Atezo-bev: 19.2 months	
Parametric function for PFS	STRIDE: Spline 3 odds Atezo-bev: Same as for STRIDE based on assumption of equal efficacy (HR=1)	Based on visual fit and clinical plausibility
Parametric function for OS	STRIDE: Spline 3 odds Atezo-bev: Same as for STRIDE based on assumption of equal efficacy (HR=1)	Based on visual fit and clinical plausibility
Inclusion of waste	Yes	No vial sharing assumed.
Average time in model health state • **Progression free (PF)** • **Post progression (PP)** • **Overall survival (OS)**	STRIDE PF: 19.2 months Atezo-bev PF: 19.2 months STRIDE PF: 32.1 months Atezo-bev PF: 32.1 months STRIDE OS: 51.2 months Atezo-bev OS: 51.2 months	

12.1.1 Base case results

Following these considerations, the two treatments were compared in a cost minimization analysis in which the full set of costs presented above in section 11 was considered. The base case considered a discount rate of 3.5% and a time horizon of 35 years (adopting, for STRIDE, the same extrapolation curves described in section 8). Given the assumption of comparable efficacy, the hazard ratio between STRIDE and atezo-bev was set to 1 for both OS and PFS. TTD curves were set equal to PFS for both treatments. Given the requirement for an endoscopy before starting administration of the atezo-bev regimen, treatment-specific disease management costs have been applied (see section 11.4).

Table 53. Base case results, discounted estimates (DKK)

Cost items	Durvalumab plus tremelimumab	Atezolizumab plus bevacizumab	Incremental
Drug acquisition costs	1 074 845	1 133 267	-58 423
Drug administration costs	34 299	45 389	-11 090
Adverse event costs	401	1 219	-818
Monitoring costs	190 491	216 896	-26 404
End-of-life cost	73 785	73 785	0
Subsequent treatment	137 384	137 384	0
Patient time and transport costs	48 944	58 318	-9 374
Total costs	**1 560 150**	**1 666 259**	**-106 109**

When STRIDE is compared with atezo-bev at list prices, STRIDE is cost saving with 106 109 DKK. The impact on the results of several aspects considered in the base case has been explored in deterministic scenario analyses and probabilistic sensitivity analyses.

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The results obtained from deterministic one-way sensitivity analyses are presented in Table 54.

Table 54. One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)
Base case			-106 109 DKK
Time horizon	20 yrs	Different time horizons were explored to consider costs differences in the short term	-94 032 DKK
	10 yrs		-57 521 DKK
	4 yrs		-5 869 DKK
Discount rate	0%	To explore methodological uncertainty given changing inflation rates and investments in the healthcare sector	-161 859 DKK
	5%		-89 595 DKK
Disease management costs	Equal for both treatments (except endoscopy requirement for Atezo-bev)	To consider same health care resources consumption between the two treatments	-79 651 DKK
TTD	Stopping rule at 5 years for both treatments	To evaluate the case in which no patients are undergoing treatment after a certain point in time	-174 912 DKK
PFS extrapolation	Generalized gamma	Parametric PFS distribution with lowest AIC/BIC values	-64 371 DKK
OS extrapolation	Lognormal	Parametric PFS distribution with lowest AIC/BIC values	-104 725 DKK

Table 54 reports results in terms of incremental cost for STRIDE vs Atezo-bev in a variety of scenarios in which changes to time horizon, discount rate, and other inputs are explored. It is notable that STRIDE is associated with negative incremental costs across all analyzed settings.

12.2.2 Probabilistic sensitivity analyses

Robustness of results is further investigated in the probabilistic sensitivity analysis below. The distribution of probabilistic results over the run iterations are displayed in Figure 19 (incremental cost for STRIDE vs atezo-bev) and Figure 20 (total costs of STRIDE and atezo-bev). After 1000 iterations, the probabilistic total costs are 2 092 606 DKK for atezo-bev and 1 896 277 DKK for STRIDE, corresponding to an incremental cost is -196 329 DKK (Table 55).

Table 55. Probabilistic vs. base case results, total and incremental costs

	STRIDE total cost (DKK)	Atezo-bev total cost (DKK)	Incremental cost (DKK)
Base case results	1 560 150 kr	1 665 943 kr	-105 793 kr
PSA results	1 896 277 kr	2 092 606 kr	-196 329 kr

Figure 19. Incremental costs distribution STRIDE vs Atezo-bev

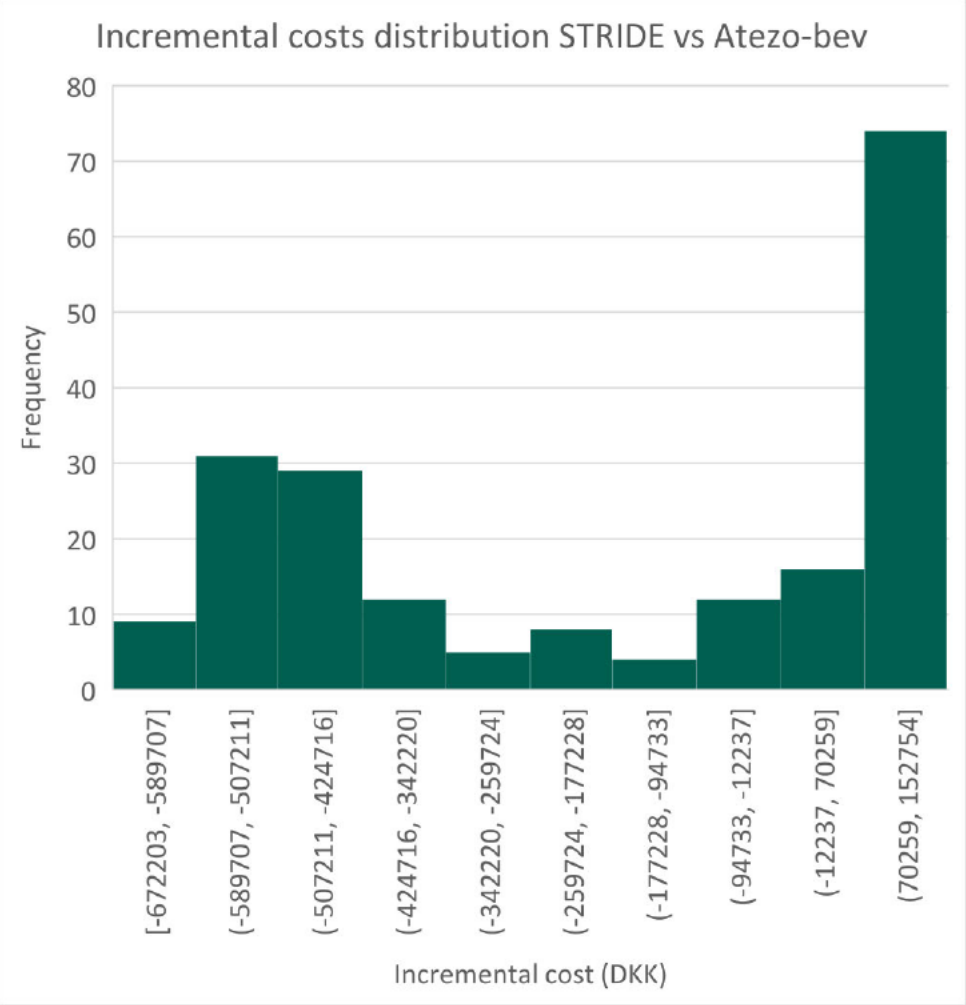
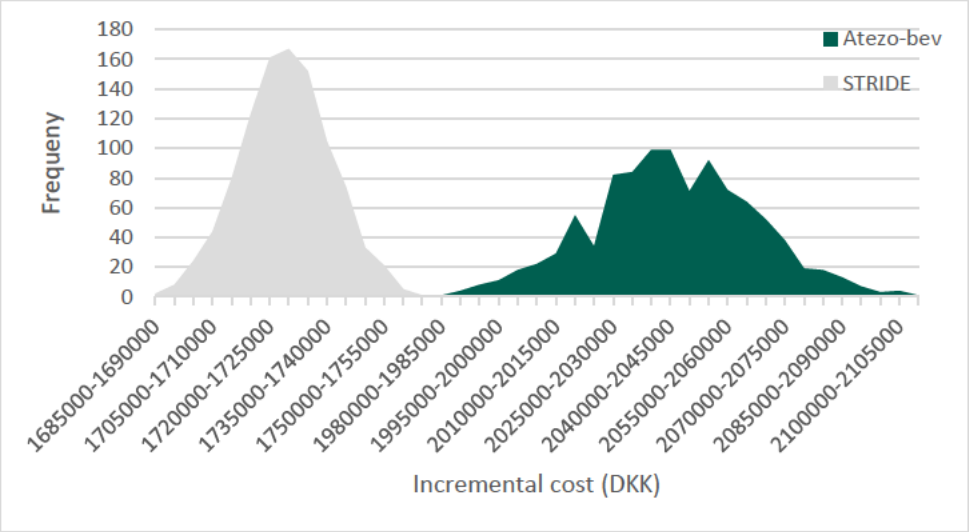
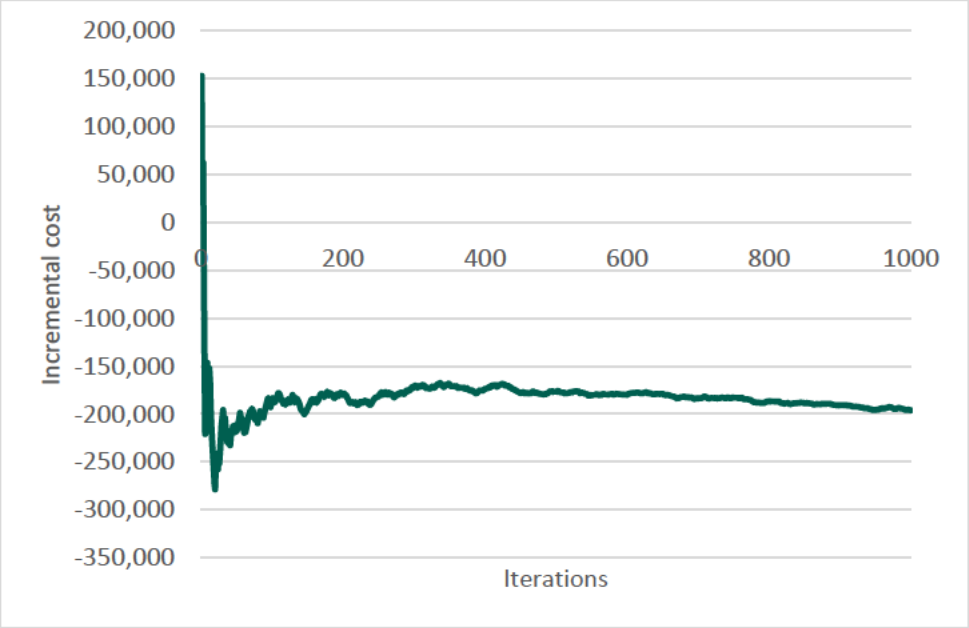


Figure 20. Total costs distribution for STRIDE and Atezo-bev



The stability of the results over iterations is shown in Figure 21.

Figure 21. Accumulated average for the incremental cost (DKK) - stability over PSA iterations



13. Budget impact analysis

13.1 Number of patients (including assumptions of market share)

The expected number of patients assumed in the budget impact analysis follow the same reasoning described in section 3.2 with the only additional assumption that the number of patients who are not eligible for treatment with dual immunotherapy or atezo-bev are excluded. Approximately 80% of those eligible for systemic treatment (68 patients in the first year increasing to 70 in year 5) are considered (Table 56). The market shares of STRIDE are assumed to increase gradually from 30% in the first year to around 50% in year 5.

Table 56. Number of new patients expected to be treated over the next five-year period if the pharmaceutical is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
STRIDE	20	24	28	31	35
Atezo-bev	48	45	41	38	35
			Non-recommendation		
STRIDE	0	0	0	0	0
Atezo-bev	68	69	69	69	70

Assuming 0.5% population growth and otherwise stable incidence

13.2 Budget impact

The budget impact is obtained by multiplying the patient numbers in Table 56 with the cost per patient. The budget impact decreases from around DKK 1 427 427 in year 1 to a budget impact of DKK 185 669 in year 5 (Table 57).

Table 57. Expected budget impact of recommending the pharmaceutical for the indication (undiscounted)

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	45 152 385 kr	58 937 865 kr	67 834 544 kr	74 266 143 kr	80 225 470 kr
The pharmaceutical under consideration is NOT recommended	43 724 958 kr	57 842 635 kr	67 092 119 kr	73 846 544 kr	80 039 801 kr
Budget impact of the recommendation	1 427 427 kr	1 095 230 kr	742 425 kr	419 599 kr	185 669 kr

14. List of experts

We have consulted the Danish [redacted] for the development of the economic model.

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Appendix A. Main characteristics of studies included.

Table 58: Main characteristic of the HIMALAYA study

Trial name: HIMALAYA	NCT number: NCT03298451
Objective	This is a randomized, open-label, multi-center, global, Phase III study to assess the efficacy and safety of durvalumab plus tremelimumab combination therapy and durvalumab monotherapy versus sorafenib in the treatment of patients with no prior systemic therapy for unresectable HCC. The patients cannot be eligible for locoregional therapy.
Publications – title, author, journal, year	Ghassan K. Abou-Alfa, George Lau, Masatoshi Kudo, Stephen L. Chan, et Al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. N Engl J Med Evid 2022;1 (5)
Study type and design	Randomized, open label, sponsor blind, multicenter, global, phase III study of Durvalumab and Tremelimumab as first line treatment in patients with unresectable Hepatocellular carcinoma. Patients in HIMALAYA were randomly assigned using an Interactive Web Response System (IWRS) in a 1:1:1 ratio to receive STRIDE, durvalumab, or sorafenib. Randomization was stratified according to macrovascular invasion (yes or no), etiology of liver disease (hepatitis B or C virus [but not both] or other/nonviral), and ECOG performance status 0 (fully active, able to carry on all predisease performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work). The study is ongoing, Estimated completion 2024-08-27.
Sample size (n)	Intervention: STRIDE 393 and comparator: Sorafenib 389
Main inclusion criteria	HCC based on histopathological confirmation No prior systemic therapy for HCC Barcelona Clinic Liver Cancer (BCLC) stage B (that is not eligible for locoregional therapy) or stage C Child-Pugh Score class A ECOG performance status of 0 or 1 at enrollment https://clinicaltrials.gov/study/NCT03298451

Trial name: HIMALAYA	NCT number: NCT03298451
Main exclusion criteria	Hepatic encephalopathy within past 12 months or requirement for medication to prevent or control encephalopathy Clinically meaningful ascites Main portal vein tumor thrombosis Active or prior documented GI bleeding (eg, esophageal varices or ulcer bleeding) within 12 months HBV and HVC co-infection, or HBV and Hep D co-infection https://clinicaltrials.gov/study/NCT03298451
Intervention	Durvalumab 1500 mg plus tremelimumab 300 mg 1 dose at Week 0, followed by durvalumab 1500 mg monotherapy starting 4 weeks after the first and final infusion of the combination therapy until confirmed PD, unacceptable toxicity, or any discontinuation criteria are met.
Comparator(s)	Sorafenib 400 mg (oral) twice daily until confirmed PD at the Investigator's discretion, unacceptable toxicity, or any discontinuation criteria are met.
Follow-up time	At data cutoff (DCO3: 27th August 2021), the median (range) follow-up durations were 33.18 (31.74 to 34.53) months, and 32.23 (30.42 to 33.71) months for STRIDE and sorafenib, respectively. The median follow-up time was 33.18 (CI 31.75-34.53) months in STRIDE-arm and 32.23 (30.42-33.71) months in sorafenib-arm (5) Updated analysis: The updated analysis was performed after 912 OS events in all arms (DCO4: 23rd Jan, 2023). The median follow-up time was 49.12 (CI 46.95-50.17) months in STRIDE-arm and 47.31 (45.08-49.15) months in sorafenib-arm (63)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint** : - To evaluate OS of patients receiving STRIDE compared with patients receiving sorafenib **Secondary objectives relating to the STRIDE regimen**: - To evaluate OS at 18, 24, and 36 months for patients receiving STRIDE compared with patients receiving sorafenib - To evaluate PFS, TTP, ORR, DCR, and DoR for patients receiving STRIDE compared with patients receiving sorafenib - To evaluate HRQoL via TTD in EORTC-QLQ-C30 and EORTC-QLQ-HCC18

Trial name: HIMALAYA	NCT number: NCT03298451
	- To investigate the immunogenicity of durvalumab and tremelimumab by measuring for presence of ADAs - To evaluate the pharmacokinetics and pharmacodynamics of durvalumab and tremelimumab **Exploratory endpoint:** - Viral aetiology subgroup analysis (65) - Liver function subgroup analysis (81) - Outcomes in the Asian subgroup (82) - Temporal patterns of immune-mediated adverse events (83) - Outcomes by occurrence of immune-mediated adverse events (83) - Adverse event profiles and time to onset and resolution (84) **Endpoints included in this application:** - OS - PFS (investigator assessed) - HRQoL
Method of analysis	All efficacy analyses were intention-to-treat analyses. Efficacy endpoint was analyzed using a stratified log-rank test adjusting for etiology of liver disease (HBV versus HCV versus others), ECOG (0 versus 1), and macro-vascular invasion (yes versus no). The effect of STRIDE versus sorafenib was estimated using a stratified Cox proportional hazards model, adjusting for the stratification factors, with a corresponding confidence interval (CI) and P value.
Subgroup analyses	Prespecified subgroup analysis for OS (5) • Sex (male versus female) • Age at randomization (<65 versus ≥65 years of age) • PD-L1 expression (positive versus negative) • Etiology of liver disease (HBV versus HCV versus others) • ECOG (0 versus 1) • Macro-vascular invasion (yes versus no) • Extrahepatic spread (yes versus no) • Region (Asia excluding Japan versus Japan versus rest of the world) • Alpha-fetoprotein (AFP) (<400 versus ≥400)

Trial name: HIMALAYA	NCT number: NCT03298451
	Other baseline variables may also be assessed if there is clinical justification, or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the 536 consistency of treatment effect across expected prognostic and/or predictive factors. Forest plots will be performed. No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of OS. Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. A model will be constructed containing treatment and the stratification factors to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test. Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon (85). Additionally, for each subgroup, the HR (durvalumab 1500 mg plus tremelimumab 300 mg × 1 dose combination versus sorafenib 400 mg BID) and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a forest plot including the HR and 95% CI. If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and OS will not be formally analyzed. In this case, only descriptive summaries will be provided.
Other relevant information	NA

Table 59: Main characteristic of the IMBrave150 study

Trial name: IMBrave150	NCT number: NCT03434379
Objective	This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab compared with sorafenib in participants with locally advanced or metastatic Hepatocellular Carcinoma (HCC) who have received no prior systemic treatment.
Publications – title, author, journal, year	Kaseb AO, Guan Y, Gok Yavuz B, Abbas AR, Lu S, Hasanov E, Toh HC, Verret W, Wang Y. Serum IGF-1 Scores and Clinical Outcomes in the Phase III IMbrave150 Study of Atezolizumab Plus Bevacizumab versus Sorafenib in Patients with Unresectable Hepatocellular Carcinoma. J Hepatocell Carcinoma. 2022 Oct 11;9:1065-1079. doi: 10.2147/JHC.S369951. eCollection 2022. Li Y, Liang X, Li H, Chen X. Atezolizumab plus bevacizumab versus nivolumab as first-line treatment for advanced or unresectable hepatocellular carcinoma: A cost-effectiveness analysis. Cancer. 2022 Nov 15;128(22):3995-4003. doi: 10.1002/cncr.34457. Epub 2022 Sep 16.

Trial name: IMBrave150	NCT number: NCT03434379
	Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Lim HY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Ma N, Nicholas A, Wang Y, Li L, Zhu AX, Finn RS. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022 Apr;76(4):862-873. doi: 10.1016/j.jhep.2021.11.030. Epub 2021 Dec 11. Salem R, Li D, Sommer N, Hernandez S, Verret W, Ding B, Lencioni R. Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: Results from the IMbrave150 trial. Cancer Med. 2021 Aug;10(16):5437-5447. doi: 10.1002/cam4.4090. Epub 2021 Jun 29. Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, Kudo M, Breder V, Merle P, Kaseb A, Li D, Mulla S, Verret W, Xu DZ, Hernandez S, Ding B, Liu J, Huang C, Lim HY, Cheng AL, Ducreux M. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021 Jul;22(7):991-1001. doi: 10.1016/S1470-2045(21)00151-0. Epub 2021 May 27.,Wen F, Zheng H, Zhang P, Liao W, Zhou K, Li Q. Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. Liver Int. 2021 May;41(5):1097-1104. doi: 10.1111/liv.14795. Epub 2021 Feb 8.,Wen F, Zheng H, Zhang P, Liao W, Zhou K, Li Q. Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. Liver Int. 2021 May;41(5):1097-1104. doi: 10.1111/liv.14795. Epub 2021 Feb 8. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745
Study type and design (1)	This is a Phase III, randomized, multicenter, open-label, two-arm study designed to evaluate the efficacy and safety of atezolizumab and bevacizumab versus sorafenib in patients with locally advanced or metastatic HCC who have received no prior systemic treatment. Patients will be randomized in a 2:1 ratio to one of two treatment arms: Arm A (experimental arm): Atezolizumab 1200 mg IV infusions Q3W (dosed in 3-week cycles) and bevacizumab 15 mg/kg Q3W (dosed in 3-week cycles) or Arm B (control arm): Sorafenib 400 mg by mouth (PO), twice per day (BID), continuously. Randomization will be stratified according to the following stratification factors: Geographic region (Asia excluding Japan vs. rest of world) Macrovascular invasion and/or extrahepatic spread (presence vs. absence)

Trial name: IMBrave150	NCT number: NCT03434379
	Baseline AFP (< 400 vs. ≥ 400 ng/mL) ECOG performance status (0 vs. 1) The trial is completed.
Sample size (n)	336 patients received atezolizumab in combination with bevacizumab and 165 patients received sorafenib.(1)
Main inclusion criteria	**Inclusion Criteria:** - Locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) - No prior systemic therapy for HCC. Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization. - At least one measurable untreated lesion - ECOG Performance Status of 0 or 1 - Adequate hematologic and end-organ function - For women of childbearing potential: agreement to remain abstinent - For men: agreement to remain abstinent - Child-Pugh class A https://clinicaltrials.gov/study/NCT03434379
Main exclusion criteria	**Exclusion Criteria:** - History of leptomeningeal disease - Active or history of autoimmune disease or immune deficiency - History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan - Known active tuberculosis - 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 - Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within at least 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 1 month after the last dose of sorafenib

Trial name: IMBrave150	NCT number: NCT03434379
	- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC - Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high-risk for bleeding - A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment. - Moderate or severe ascites - History of hepatic encephalopathy - Co-infection of HBV and HCV - Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases - Uncontrolled tumor-related pain - Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures - Uncontrolled or symptomatic hypercalcemia - Treatment with systemic immunostimulatory agents - Inadequately controlled arterial hypertension - Prior history of hypertensive crisis or hypertensive encephalopathy - Evidence of bleeding diathesis or significant coagulopathy - History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction including sub-occlusive disease related to the underlying disease or requirement for routine parenteral hydration - Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture - Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses - Local therapy to liver within 28 days prior to initiation of study treatment or non-recovery from side effects of any such procedure - Chronic daily treatment with a non-steroidal anti-inflammatory drug (NSAID) https://clinicaltrials.gov/study/NCT03434379
Intervention	Atezolizumab in combination with Bevacizumab: Atezolizumab will be administered by IV, 1200 mg on day 1 of each 21 day cycle. Bevacizumab will be administered by IV, 15 mg/kg on day 1 of each 21

Trial name: IMBrave150	NCT number: NCT03434379
	day cycle. 336 patients received atezolizumab in combination with bevacizumab. (1)
Comparator(s)	Sorafenib will be administered by mouth, 400 mg twice per day, on days 1-21 of each 21-day cycle. 165 patients received sorafenib (1).
Follow-up time	As of the date of clinical data cutoff (August 29, 2019), the median duration of follow-up was 8.6 months (8.9 months in the atezolizumab–bevacizumab group and 8.1 months in the sorafenib group) (36). On August 31,2020, median followup was 15.6 (range,0-28.6) months (1).
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Primary endpoint:** - OS in the Global Population (29Aug2019 (up to approximately 18 months) and 31Aug2020 (up to approximately 30 months) - PFS-IRF (29Aug2019 (up to approximately 18 months) **Secondary endpoint:** - ORR-IRF in the Global Population (29Aug2019 (up to approximately 18 months). - ORR-IRF (***mRECIST) in the Global Population (29Aug2019 (up to approximately 18 months). - ORR-INV in the Global Population (29Aug2019 (up to approximately 18 months). - DOR-IRF in the Global Population (29Aug2019 (up to approximately 18 months)). - DOR-IRF Per HCC mRECIST in the Global Population (29Aug2019 (up to approximately 18 months)). - DOR-INV in the Global Population (29Aug2019 (up to approximately 18 months)). - PFS-IRF Per HCC mRECIST in the Global Population (29Aug2019 (up to approximately 18 months)) - PFS-INV in the Global Population (29Aug2019 (up to approximately 18 months)) - TTP-IRF in the Global Population (29Aug2019 (up to approximately 18 months)) - TTP-IRF Per HCC mRECIST in the Global Population (29Aug2019 (up to approximately 18 months))

- TTP-INV in the Global Population (29Aug2019 (up to approximately 18 months))
- OS by Baseline AFP in the Global Population (29Aug2019 (up to approximately 18 months))
- PFS-IRF by Baseline AFP in the Global Population (29Aug2019 (up to approximately 18 months))
- PFS-INV by Baseline AFP in the Global Population (29Aug2019 (up to approximately 18 months))
- TTD in the Global Population (29Aug2019 (up to approximately 18 months))
- Percentage of Participants With Adverse Events (AEs) in the Global Population (Up to end of study (up to approximately 40 months))
- Maximum Serum Concentration (Cmax) of Atezolizumab at Cycle 1 in the Global Population (Post-dose on Day 1 of Cycle 1 (cycle length = 21 days))
- Trough Serum Concentration (Cmin) of Atezolizumab in the Global Population (Pre-dose on Day 1 of Cycles 2, 3, 4, 8, 12 and 16 (cycle length = 21 days))
- Percentage of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab in the Global Population (Baseline and post-baseline on Day 1 (pre-dose) of Cycles 2, 3, 4, 8, 12, 16 (cycle length = 21 days) and treatment discontinuation visit (up to approximately 30 months)) (86)

Exploratory analysis:(1)

- Objective response as determined by the investigator according to imRECIST
- PFS as determined by the investigator according to imRECIST
- TTP as determined by the investigator according to imRECIST
- DOR as determined by the investigator according to imRECIST

Endpoints included in this application:

- OS
- PFS (investigator assessed)
- HRQoL

Method of analysis	The analyses of PFS, TTP, and OS will be performed on the basis of all randomized patients (the ITT population), with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study drug. ORR will be analyzed on the basis of all randomized patients who have measurable disease at baseline. DOR will be assessed only in patients who have an objective response. TTD analyses will be conducted on basis of all patients with a

non-missing baseline PRO assessment. Change-from-baseline analysis of PROs will be performed using patients who have both a non-missing baseline assessment and at least one post-baseline assessment, with patients grouped according to the treatment assigned at randomization.

Safety analyses will be performed on the basis of all randomized patients who received any amount of study drug (the safety population), with patients grouped according to the treatment the patient actually received.

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab in combination with bevacizumab compared with sorafenib on the basis of the co-primary efficacy endpoints of OS and objective response as assessed by the investigator according to RECIST v1.1.

OS and ORR will be tested in parallel with the overall type I error controlled at a two-sided significance level of 0.05, where initially OS will be tested at a two-sided significance level of 0.048 and ORR will be tested at a two-sided significance level of 0.002, applying a group sequential weighted Holm procedure to recycle α from the rejected hypothesis to the not-rejected one.

The stratified two-sided log-rank test will be used as the primary analysis to compare OS between the two treatment arms. The results from the unstratified log-rank test and the stratified and unstratified Wilcoxon test will also be provided. The Kaplan-Meier method will be used to estimate median OS for each treatment arm. Brookmeyer-Crowley methodology will be used to calculate the 95% CI for the median OS for

each treatment arm. Stratified Cox proportional-hazards models will be used to estimate the

HR and its 95% CIs. The unstratified HR will also be provided.

Subgroup analyses

Pre specified subgroup analysis for:

age, sex, race, geographic region, macrovascular, invasion and/or extrahepatic spread, macrovascular invasion, extrahepatic spread, ECOG performance status, HCC etiology, BCLC staging at the time of study entry and baseline PD-L1 expression in tumor tissue for patients with baseline tumor samples.

In order to assess the consistency of treatment effect with respect to the co-primary efficacy endpoints of PFS-IRF according to RECIST v 1.1 and OS across important subgroups, forest plots (including estimated HRs) will be provided, including, but not limited to the above listed factors. Unstratified analysis results will be presented for subgroup analyses due to the potentially limited number of patients in each subgroup. (1)

Trial name: IMBrave150	NCT number: NCT03434379
Other relevant information	NA

Appendix B. Efficacy results per study

Results per study

Table 60: Results per study

Results of HIMALAYA NCT03298451											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median overall survival (time point)	STRIDE	393	16.4 (14.2–19.6)	2.6	1.79–8.01	0.002	HR: 0.78	0.67–0.92	0.0037	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm. Median follow-up: 49.12 (46.95–50.17) and 47.31 (45.08–49.15). DCO 23rd January 2023	Abou-Alfa et al. (2022b)
	Sorafenib	389	13.8 (12.3–16.1)								
4-year overall survival	STRIDE	393	25,2% (20.8–29.7)	10.1%	2.39–19.01	0.01	HR: 0.78	0.67–0.92	0.0037	The survival rates are based on the Kaplan–Meier estimator. The HR is based	Abou-Alfa et al. (2022b)

Results of HIMALAYA NCT03298451											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										on a Cox proportional hazards model with adjustment for stratification, and study arm. DCO 23rd January 2023	Sangro et al. 2024
	Sorafenib	389	15.1% (11.5–19.2)								
Median PFS Progres-sion free in blue	STRIDE	393	3.78 (3.68–5.32) 12.5%	0.29 7.6%	NA	NA	HR=0.90	0.77–1.05	0.1625	Progression-free survival was assessed according to the RECIST 1.1 criteria, and since PFS was not included in multiple testing procedure (MTP), it is not controlled for multiplicity and statistical testing was performed at a nominal 5% significance level. DCO: 27th August 2021	Abou-Alfa et al. (2022)
	Sorafenib	389	4.07 (3.75–5.49) 4.9 %								
Median TTP	STRIDE	393	5.42 (3.81-5.62)	0.13	NA	p=0.3439	NA	NA	NA	Time to progression was determined by investigator assessment based on the RECIST 1.1 guidelines. DCO: 27th August 2021	Abou-Alfa et al. (2022)
	Sorafenib	389	5.55 (5.13-5.75)								

Results of HIMALAYA NCT03298451											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR	STRIDE	393	20.1%(NA)	15.0%	10.5%-19.6%	NA	OR: 4.69	2.85–8.04	p<0.0001	Confidence intervals calculated according to the recommended method by Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49)	Abou-Alfa et al. (2022)
	Sorafenib	389	5.1%(NA)								
DoR	STRIDE	393	22.3 m(8.54–NR)	3.9 m	NA	NA	NA	NA	NA		Abou-Alfa et al. (2022)
	Sorafenib	389	18.4 m(6.51–25.99)								
OS HBV	STRIDE	122	18.7 m	6.4 m	NA	NA	HR=0.64	0.48-0.86	NA	The HR and 95% CI are estimated from an unstratified Cox proportional hazards model using the Efron method to control for ties. DCO: 27th August 2021	Abou-Alfa et al. (2022)
	Sorafenib	119	12.3 m								

Results of HIMALAYA NCT03298451											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS HCV	STRIDE	110	15.4 m	2.3 m			HR=1.06	0.76-1.49		The HR and 95% CI are estimated from an unstratified Cox proportional hazards model using the Efron method to control for ties. DCO: 27th August 2021	Abou-Alfa et al. (2022)
	Sorafenib	104	17.1 m								
OS Nonviral	STRIDE	161	16.4 m	3.0 m			HR=0.74	0.57-0.95		The HR and 95% CI are estimated from an unstratified Cox proportional hazards model using the Efron method to control for ties. DCO: 27th August 2021	Abou-Alfa et al. (2022)
	Sorafenib	166	13.4 m								
Any AE	STRIDE	388	378 (97.4%)	0.01968	-0.006667 , 0.04603	NA	RR=1.021	0.993-1.049	P=0.1444	Confidence intervals calculated according to the recommended method by Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49)	Abou-Alfa et al. (2022)
	Sorafenib	374	357 (95.5%)								

Results of HIMALAYA NCT03298451											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Any grade 3 or 4	STRIDE	388	196 (50.5)	-0.01891	-0.08988 , 0.05206	NA	RR=0.97	0.84-1.11	P = 0.711	Confidence intervals calculated according to the recommended method by Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49)	Abou-Alfa et al. (2022)
	Sorafenib	374	196 (52.4)								
TRAEs	STRIDE	388	294 (75.8)	-0.08986	-0.1459 , -0.03379	NA	RR=0.89	0.83-0.95	P = 0.0019	Confidence intervals calculated according to the recommended method by Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49)	Abou-Alfa et al. (2022)
	Sorafenib	374	317 (84.8)								
Discontinuations	STRIDE	388	53 (13.7)	3.19 %	-1.9-8.3	NA	RR=0.81	0.58-1.14	P = 0.222	Confidence intervals calculated according to the recommended	Abou-Alfa et al. (2022)

Results of HIMALAYA NCT03298451											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
due to AE	Sorafenib	374	63 (16.8)							method by Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49)	

Table 61: Results per study

Results of IMBRAVE150 NCT03434379.											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	Atezo-bev	336	19.2 (17.0-23.7)	5.8	N/A	N/A	HR: 0,66	(0,52-0,85)	0.005	**The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.** Data cut-off of August 31, 2020, after a median (range) follow-up of 15.6 (0-28.6) months overall: 17.6 (0.1-28.6) months in the atezolizumab plus bevacizumab arm and 10.4 (0-27.9) months in the sorafenib arm.	Cheng, A.-L., Quin (2022). Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J. Hepatol., 76(4), 862–873.
	Sorafenib	165	13.4 (11.4-16.9)								
	Sorafenib	165	40%								
Median PFS	Atezo-bev	336	6.9 (5.7-8.6)	2.6	N/A	N/A	HR: 0,65	0,52-0,85	0.005	**The absolute difference in effect is estimated using a two-sided t-test.** Data cut-off of August 31, 2020	Cheng, A.-L., (2022).
	Sorafenib	161	4.3 (4.0 – 5.6)								

Results of **IMBRAVE150** NCT03434379.											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ORR	Atezo-bev	326	97 (30%) (25-35)	19 %	11- 26	<0.001			NA	The percentage of patients with a confirmed complete or partial response. Data cut-off of August 31, 2020	Cheng, A.-L., (2022).
	Sorafenib	159	18 (11%) (7-17)								
Treatment-related adverse events	Atezo-bev	329	284 (86)	9%	3.3%-13.8%	0.0032	RR=0.91	0.86 0.96	P = 0.0010	Data cut-off of August 31, 2020 Confidence intervals calculated according to the recommended method by Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49)	Cheng, A.-L., (2022).
	Sorafenib	156	148 (95)								
Treatment-related grade 3/4	Atezo-bev	329	143 (43%)	3%	-6.3% to 12.4%	0.5345	RR=0.94	0.76-1.16	P = 0.57	Confidence intervals calculated according to the recommended method by Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with	Cheng, A.-L., (2022).
	Sorafenib	156	72 (46%)								

Results of **IMBRAVE150** NCT03434379.											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
adverse events										confidence, 2nd ed. BMJ Books. (p. 49)	
OS HBV	Atezo-bev	164	19.0 (16.1-NE)	6.4 m		NA	HR=0.58	(0.40-0.83)		Hazard ratios for patient subgroups are from unstratified analyses using the Cox proportional-hazards model. Confidence intervals for subgroup analyses are not adjusted for multiple comparisonsData cut-off of August 31, 2020	Cheng, A.-L., (2022).
	Sorafenib	79	12.4 (6.7-16.9)								
OS HCV	Atezo-bev	72	24.6 (19.8-NE)	12 m		NA	HR=0.43	(0.25-0.73)		Hazard ratios for patient subgroups are from unstratified analyses using the Cox proportional-hazards model. Confidence intervals for subgroup analyses are not adjusted for multiple comparisons. Data cut-off of August 31, 2020	Cheng, A.-L., (2022).
	Sorafenib	36	12.6 (7.4-18.4)								

Results of IMBRAVE150 NCT03434379.											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS Nonviral	Atezo-bev	100	17.0 (11.7-22.8)	1.1 m		NA	HR=1.05	(0.68-1.63)		Hazard ratios for patient subgroups are from unstratified analyses using the Cox proportional-hazards model. Confidence intervals for subgroup analyses are not adjusted for multiple comparisons Data cut-off of August 31, 2020	Cheng, A.-L., (2022).
	Sorafenib	53	18.1 (11.7-26.3)								

Appendix C. Comparative analysis of efficacy

Table 62 Comparative analysis of studies comparing durvalumap plus tremelimumab to atezo-bev for patients with HCC

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
PFS (Adjusted MAIC)	HIMALAYA HR=0.78(0.65-0.93) and IMbrave 150 HR=0.45(0.36-0.57)	NA	NA	NA	HR: 1.73	1.30–2.23	NA	MAIC based on DCO3	No, cost minimization analysis conducted.
PFS (unadjusted)	HIMALAYA HR=0.89 (0.77 – 1.03) and IMbrave150 HR=0.45(0.36-0.57)	NA	NA	NA	HR: 1.98	1.50 – 2.61	p < 0.001	Buchers ITC based on DCO3	No, cost minimization analysis conducted.
PFS (unadjusted – BICR)	HIMALAYA HR=0.96 (0.77-1.19) and IMbrave150 HR=0.65 (0.53 – 0.81)	NA	NA	NA	HR: 1.48	1.08 – 2.01	p = 0.0132	Buchers ITC based on BICR PFS analysis from HIMALAYA (FAS-32w subset) and independently assessed PFS from Imbrave150	No, cost minimization analysis conducted.

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
OS	HIMALAYA HR=0.72(0.66-0.92) and IMbrave 150 HR=0.66(0.52-0.85)	NA	NA	NA	HR=1.09	(0.80-1.48)	NA	MAIC DCO 3. 4 year OS from HIMALAYA	No, cost minimization analysis conducted.
OS (unadjusted)	HIMALAYA HR=0.78 (0.67 – 0.92) and IMbrave 150 HR=0.66(0.52-0.85)	NA	NA	NA	HR=1.18	0.88-1.59	p=0.2735	Buchers ITC based on 4-year overall survival (HIMALAYA)	No, cost minimization analysis conducted.

This appendix reports additional details related to the MAIC of STRIDE and atezolizumab plus bevacizumab that are not described in the sections above.

Proportional hazard assumption IMbrave150

Figure 22: Original OS Kaplan-Meier curve for Imbrave150

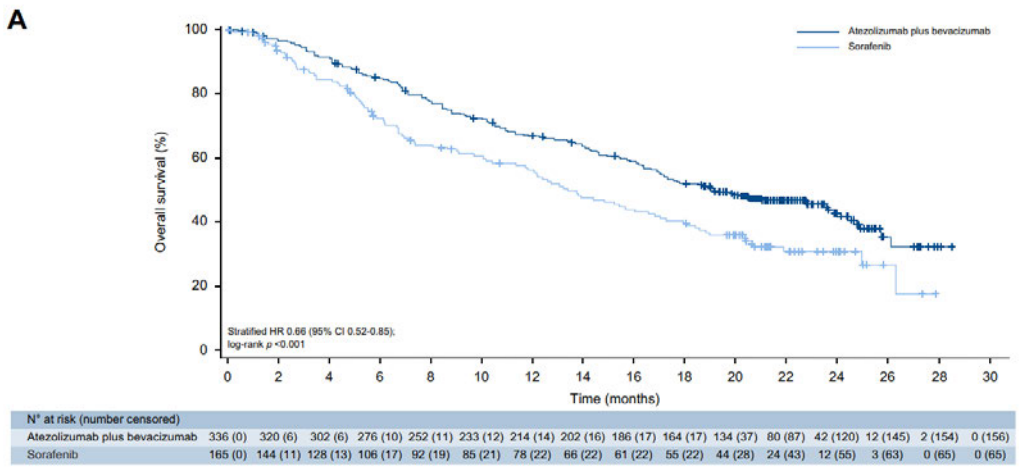
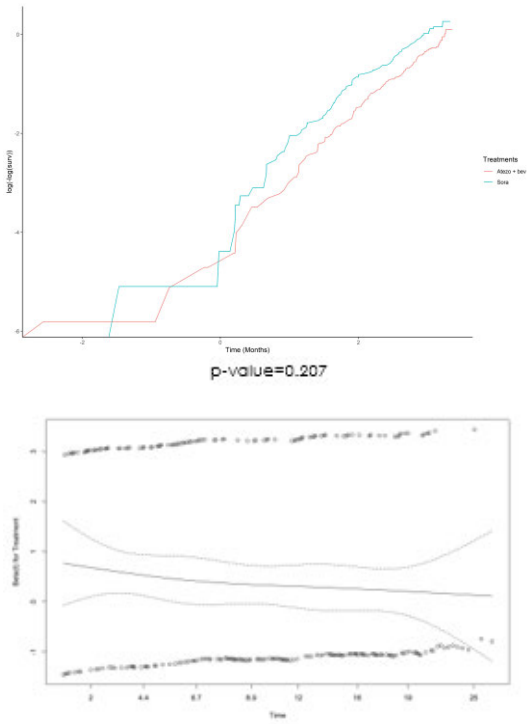


Figure 23: OS log-log plot and Schoenfeld residuals for IMbrave150



The following results were observed:

- The Kaplan-Meier curves do not cross each other, the effect of each treatment is fairly similar across time
- The log-log curves cross and then seem parallel
- The p-value of the Schoenfeld test is higher than 0.05

- A minor trend over time seems to exist on the Schoenfeld residuals plot

Based on the KM curves, the log-log plot and the Schoenfeld plot, the proportional hazard assumption was not rejected.

Figure 24: Original PFS Kaplan-Meier curve for Imbrave 150

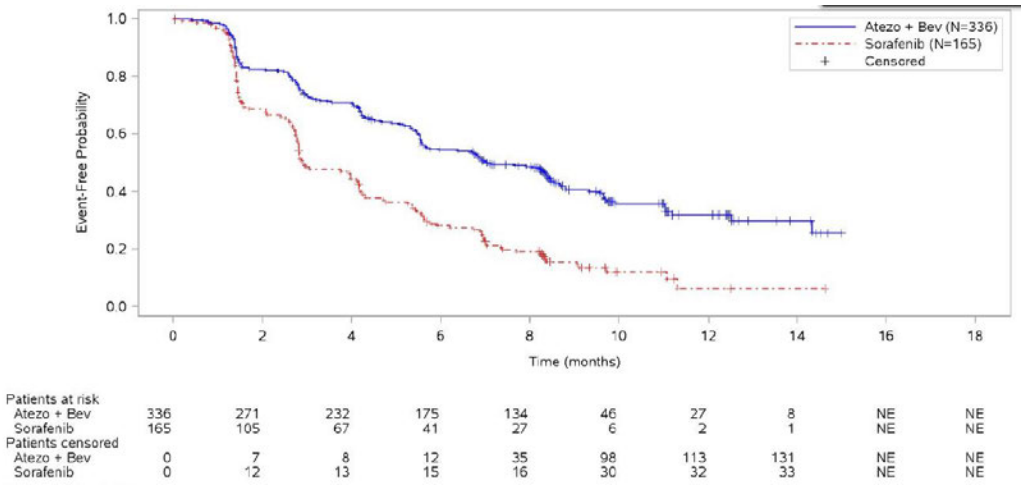
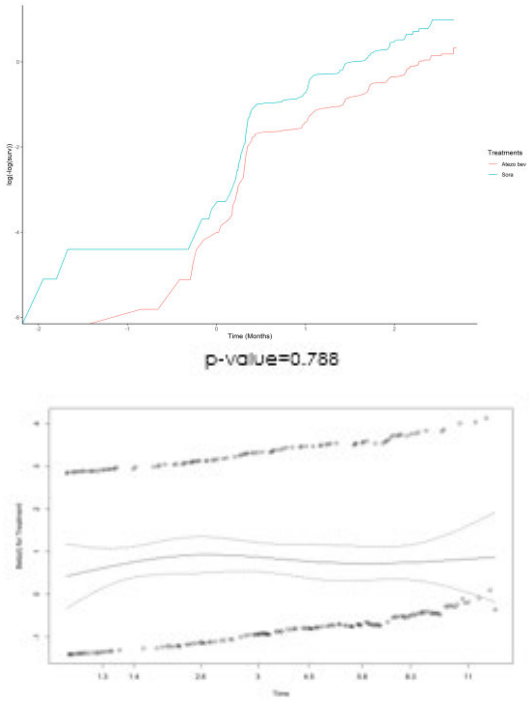


Figure 25: PFS log-log plot and Schoenfeld residuals for IMbrave 150



The following results were observed:

- The Kaplan-Meier curves do not cross each other, the effect of each treatment is similar across time
- The log-log curves do not cross each other

- The p-value of the Schoenfeld test is higher than 0.05
- No trend over time exists on the Schoenfeld residuals plot

Based on the KM curves, the log-log plot and the Schoenfeld plot, the proportional hazard assumption was not rejected.

Proportional hazard assumption HIMALAYA

Figure 26: OS Kaplan-Meier curves of STRIDE vs. sorafenib

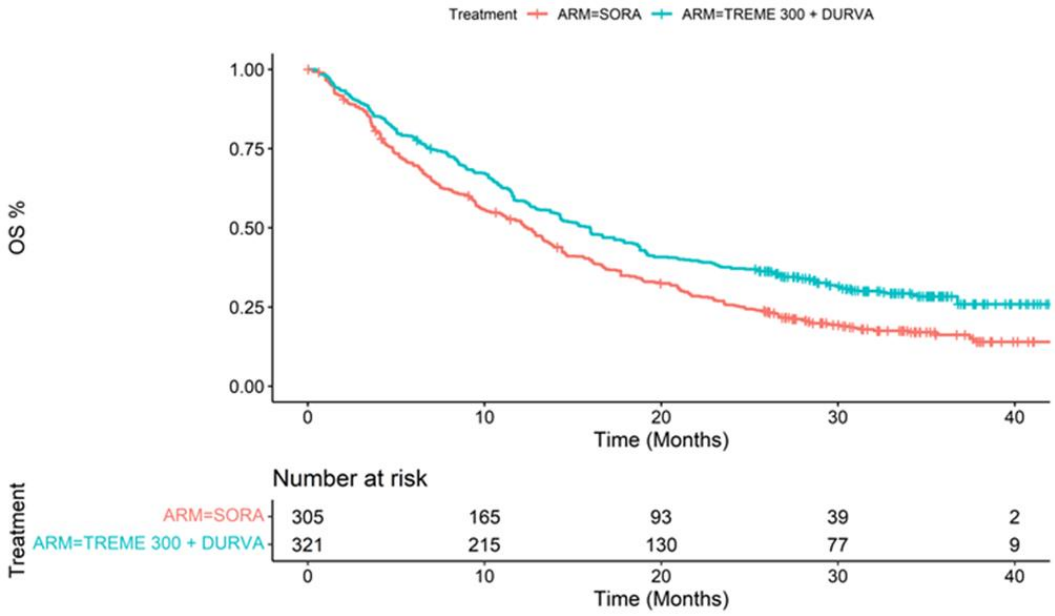
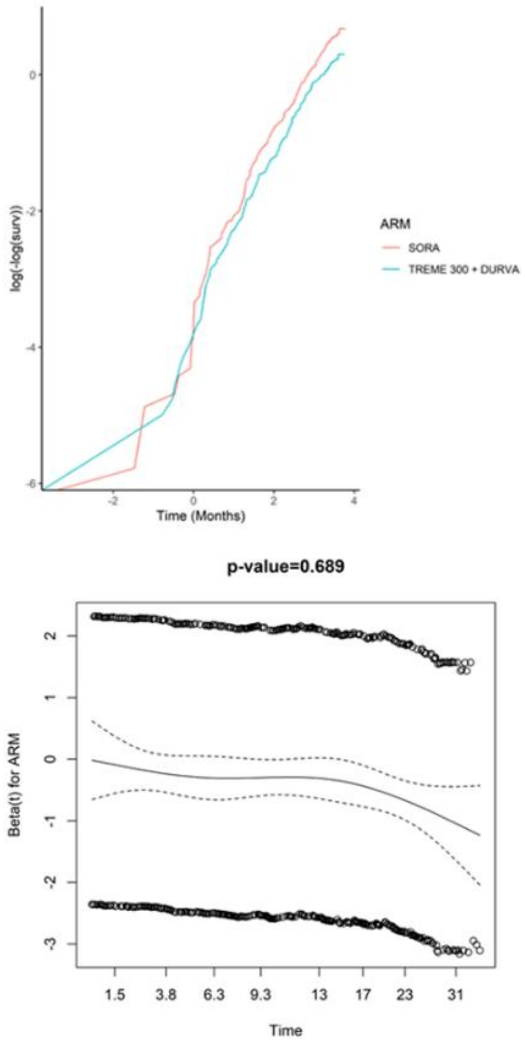


Figure 27: OS log-log plot and Schoenfeld residuals of STRIDE vs. sorafenib



The following results were observed:

- The Kaplan-Meier are similar over the first few months and then seem proportional
- The curves on the log-log plot are crossing before being parallel
- The p-value of the Schoenfeld test is higher than 0.05
- No specific trend over time observed on the Schoenfeld residuals plot

Therefore, the PHA was not rejected for OS based on the Kaplan-Meier curves, log-log plot and Schoenfeld residuals.

Figure 28: PFS Kaplan-Meier curves of STRIDE vs. sorafenib

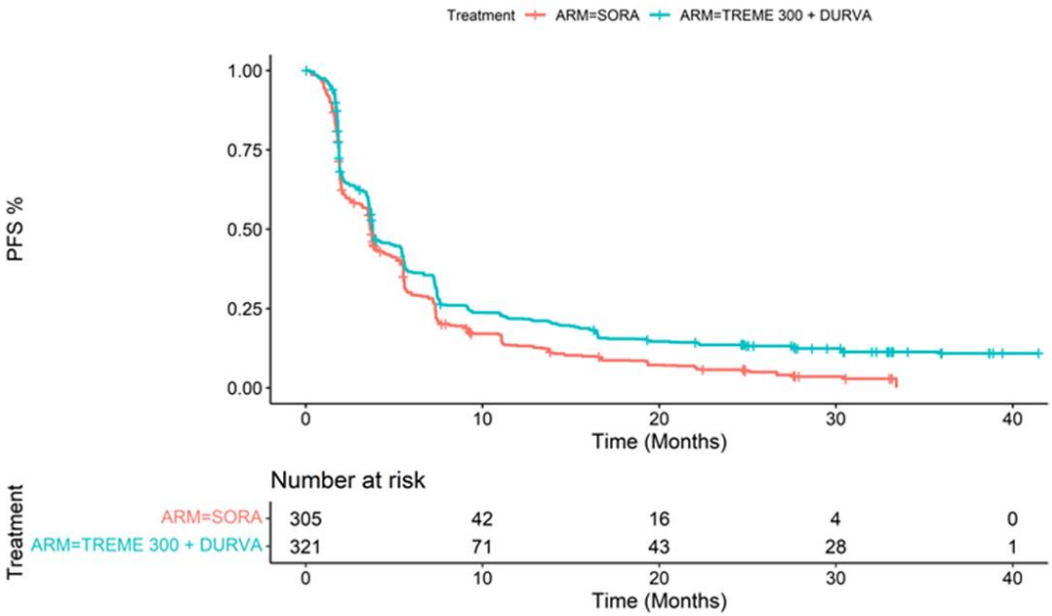
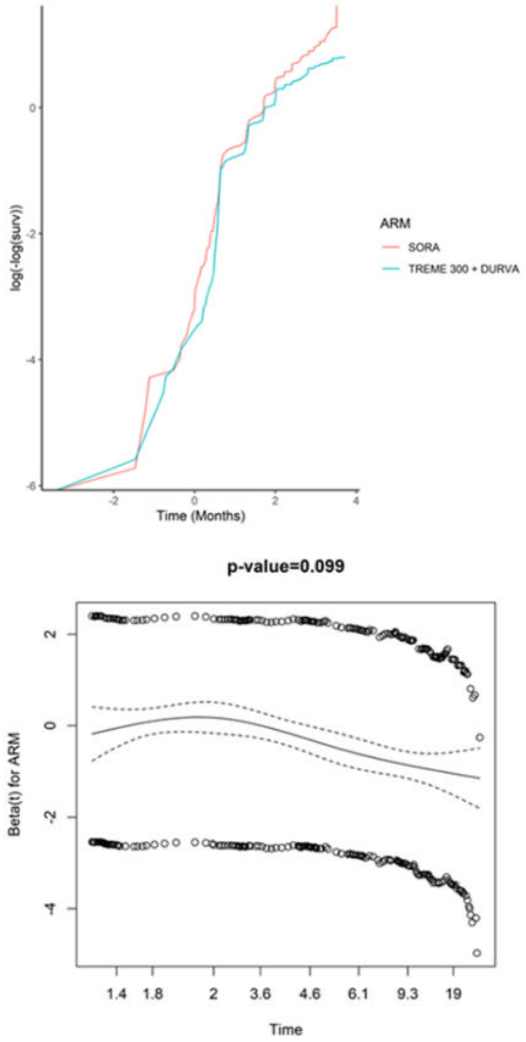


Figure 29: PFS log-log plot and Schoenfeld residuals of STRIDE vs. sorafenib



The following results were observed:

- The Kaplan-Meier are similar up to 5 months and then seem proportional
- The curves on the log-log plot are crossing and are similar, which was expected given the Kaplan-Meier
- The p-value of the Schoenfeld test is higher than 0.05 but still significant at the 10% level
- A slight trend over time observed on the Schoenfeld residuals plot

Therefore, the PHA tests for PFS returned somewhat ambiduous results.

Detailed efficacy MAIC results

The comparison of the eligibility criteria of HIMALAYA and IMbrave 150 led to the identification of the following differences:

- BCLC stage: No restriction in IMbrave 150 and few stage A included vs HIMALAYA restricted to stages B and C
- Ascites: Exclusion of moderate or severe ascites in IMbrave 150 vs exclusion of clinically meaningful ascites in HIMALAYA

- Bleeding events: Exclusion of prior bleeding event in prior 6 months in IMbrave 150 vs exclusion of active or prior GI bleeding in prior 12 months in HIMALAYA
- Countries: No patients coming from China mainland in HIMALAYA, while 15.6% in IMbrave 150.
- Some patients from HIMALAYA presented a Child Pugh of B at baseline whereas for both trials inclusion was restricted to A
- Some patients from HIMALAYA presented an ECOG PS of 2 at baseline whereas for both trials inclusion was restricted to 0 or 1

Therefore, HIMALAYA was restricted to patients with Child Pugh A and ECOG PS of 0 or 1. After restriction, 1,145 out of 1,171 patients were kept for HIMALAYA for the analyses based on the intention-to-treat (ITT) population.

After restriction of HIMALAYA to patients eligible to IMbrave 150, each remaining patient was reweighted to obtain overall population characteristics similar to IMbrave 150.
The weighting model was based on ten factors, their estimated weights are detailed in Table 63. Those values highlighted that five factors seemed to have a stronger impact on the weight distribution, with having hepatitis B, MVI or EHS increasing the weight while being from Asia or having BCLC stage C decreased the weight.

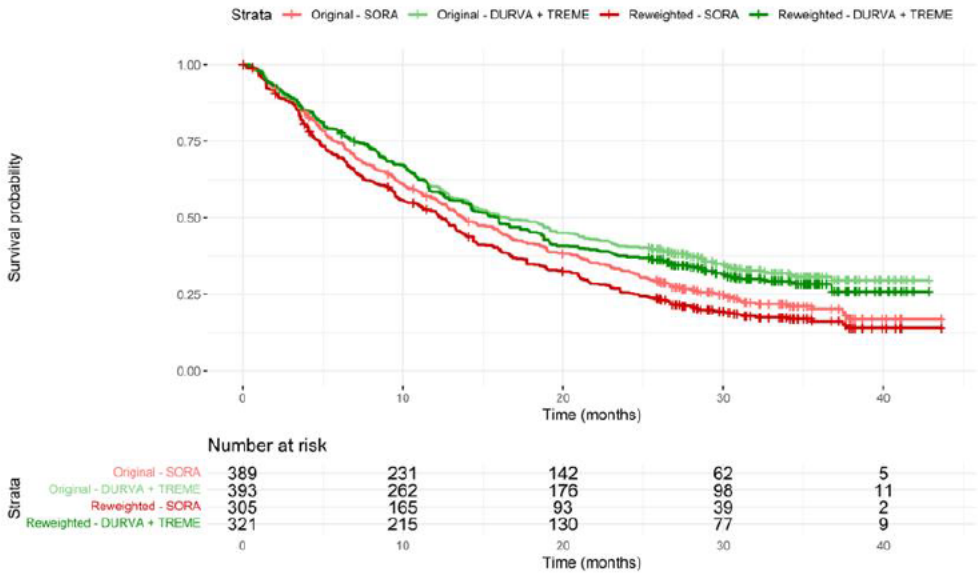
Table 63: Complete list of factors and their estimated weights used for the weighting process of the MAIC of HIMALAYA vs IMbrave 150 compared to the list of TEMs identified

Variable identified as TEM	Adjustment made on	Weights of each covariate
Age	% ≥ 65 years old	0.2371
Gender	% males	-0.3078
Region	% from Asia excluding Japan	-0.6965
MVI	% of MVI	0.9401
EHS	% of EHS	0.5784
AFP	% Serum AFP ≥ 400 ng/mL	-0.0549
ECOG	% ECOG 0	-0.1365
BCLC	% BCLC C	-0.7179
Etiology	% HBV	1.3132
	% HCV	0.1584

An effective sample size (ESS) of 760.2 (64.9% of initial sample size) was obtained after weighting. No extreme individual was identified based on the weights. Though four patients have a rescaled weight higher than 5, their non-rescaled weight was lower than 5 (out of 760.2).
After reweighting, populations from IMbrave 150 and reweighted HIMALAYA were balanced as shown in Table 19 above. ALBI grade 1 remained around 52% in HIMALAYA after restriction and reweighting. This proportion was close to the reported proportion of grade 1 patients in Imbrave150 (52%, 278/530).
It has to be noted that the reweighted HIMALAYA population differed from the original HIMALAYA population. The reweighted population had higher proportion of MVI, EHS, and hepatitis B as well as a lower proportion of hepatitis C.

The restriction and weighting process of the MAIC decreased the survival in patients in all treatment arms (Figure 30).

Figure 30: OS of reweighted vs. original HIMALAYA, and comparison with sorafenib arm in IMbrave 150.



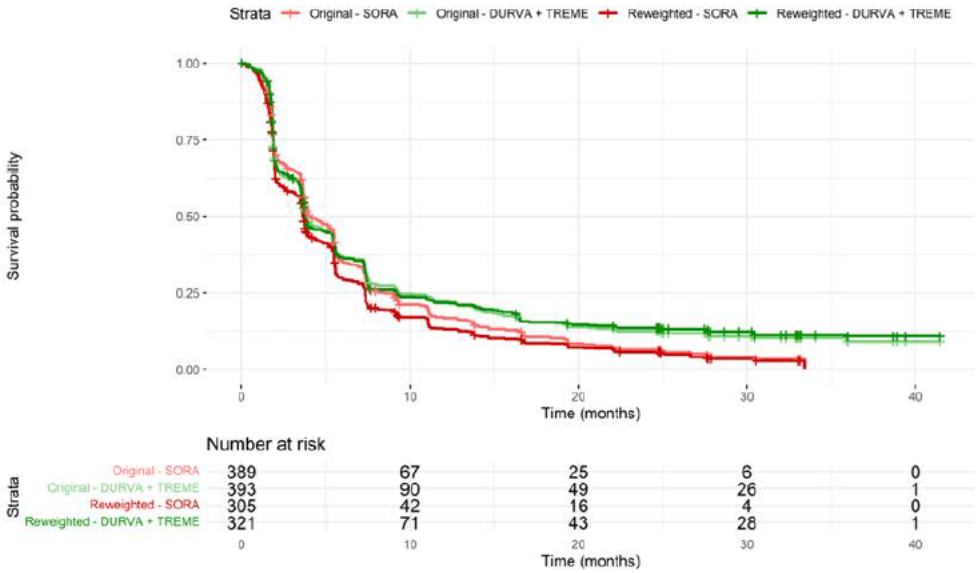
After restriction and reweighting, the OS HR of STRIDE vs sorafenib decreased and became closer to the HR of atezolizumab + bevacizumab vs sorafenib as shown in Table 64. The results obtained from the MAIC of HIMALAYA vs IMbrave 150 for OS are reported in Table 64. There was no significant difference between STRIDE and atezolizumab + bevacizumab in terms of OS.

Table 64: HIMALAYA vs. IMbrave 150 MAIC OS results

Comparison	Cohort	HR [95% CI]
STRIDE vs sorafenib	HIMALAYA original	0.78 [0.67, 0.92]
	HIMALAYA from MAIC	0.72 [0.60, 0.87]
Atezolizumab + bevacizumab vs sorafenib	IMbrave 150	0.66 [0.52, 0.85]
MAIC OS		
STRIDE vs. atezolizumab + bevacizumab		1.09 [0.80, 1.48]

The restriction and weighting process of the MAIC decreased the PFS in patients in all treatment arms (Figure 31)

Figure 31: PFS of reweighted vs original HIMALAYA



After restriction and reweighting, the PFS HR of STRIDE vs sorafenib decreased and became closer to the HR of atezolizumab + bevacizumab vs sorafenib as shown in Table 65. Atezolizumab + bevacizumab performed significantly better than STRIDE in terms of PFS (Table 65).

Table 65: HIMALAYA vs IMbrave 150 MAIC PFS results

Comparison	Cohort	HR [95% CI]
STRIDE vs sorafenib	HIMALAYA original	0.89 [0.77, 1.03]
	HIMALAYA from MAIC	0.78 [0.65, 0.93]
Atezolizumab + bevacizumab vs sorafenib	IMbrave 150	0.45 [0.36, 0.57]
MAIC PFS		
STRIDE vs. atezolizumab + bevacizumab		1.73 [1.30, 2.32]

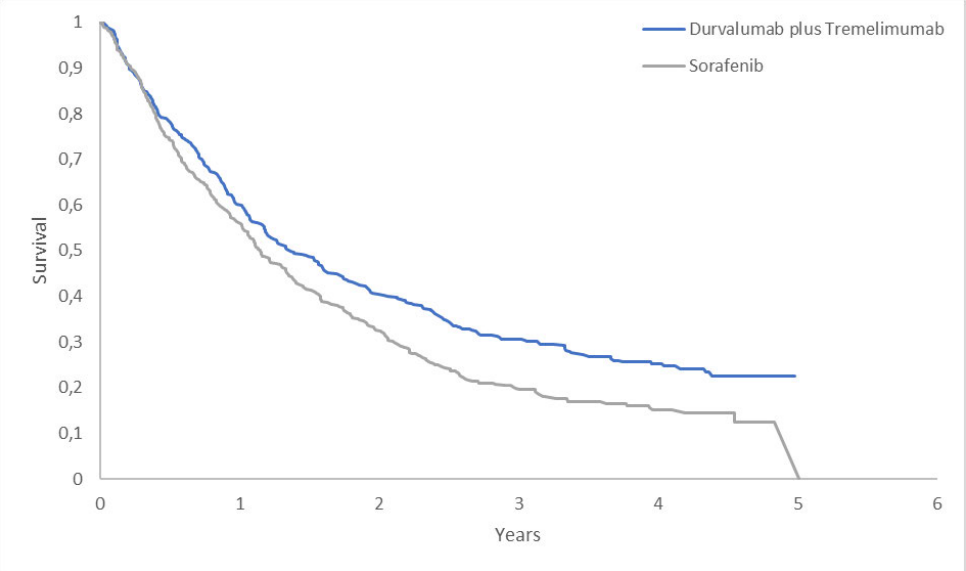
Appendix D. Extrapolation

D.1 Extrapolation of overall survival

D.1.1 Data input

Kaplan–Meier (KM) plots for treatments included in HIMALAYA are presented in Figure 32. Independently fitted survival curves are used as base case to allow for more flexibility in the survival estimates. Please note that sorafenib is included in some of the graphs below, although it is not used as a comparator in this health economic analysis. While we are not it in the cost-minimization analysis, it is used as an anchor in the indirect treatment comparison with atezo-bev and is therefore relevant to cover as well.

Figure 32: Kaplan–Meier data, overall survival



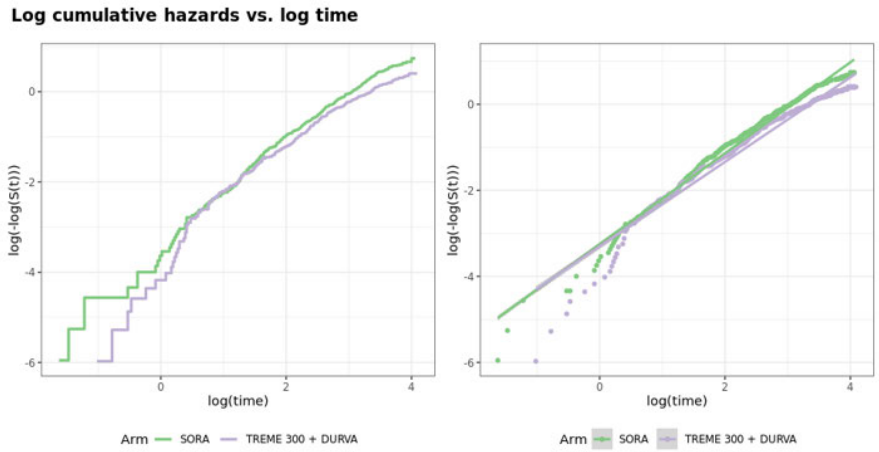
D.1.2 Model

Both standard parametric survival models (one-piece extrapolation models) and spline and knots models were explored. The spline and knots models can be especially relevant for immunotherapy, as these may potentially capture the tail development better than standard parametric models

D.1.3 Proportional hazards

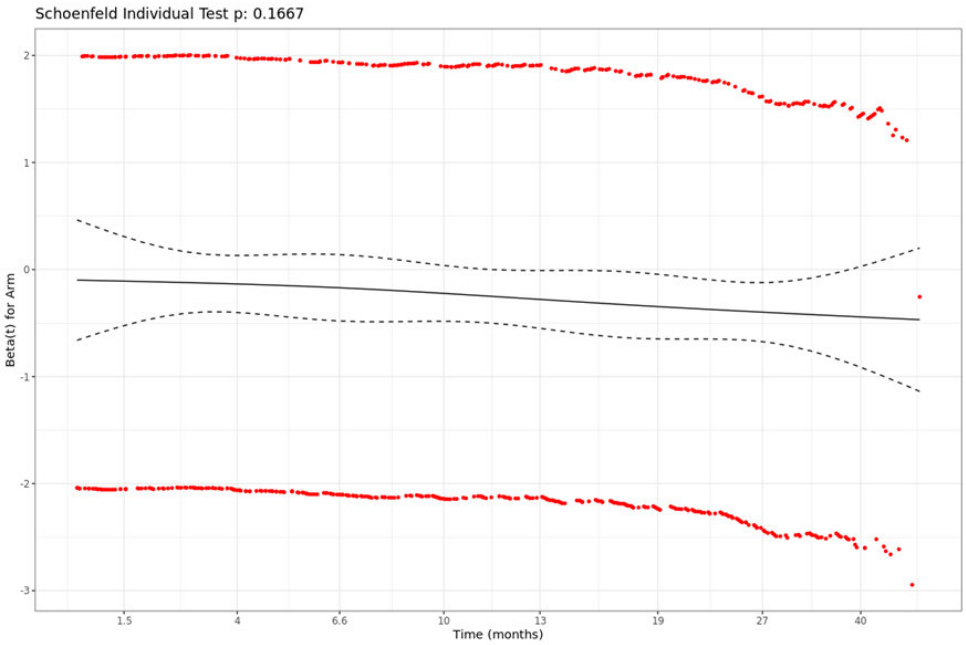
Figure 33 gives the cumulative hazard diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. Parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival.

Figure 33: Cumulative hazard plots – OS



The Schoenfeld residuals can be used to test the proportional hazard assumption. If PH, the plot of the residuals against time should show a linear trend with slope equal to 0. The visual inspection of this plot is as important as the test, however, a p-value is also output as the result of a test of non-negative slope (Therneau and Grambsch). Figure 34 describes the Schoenfeld residuals, which have been calculated using the km transform.

Figure 34: Schoenfeld residual plots - OS



D.1.4 Evaluation of statistical fit (AIC and BIC)

Table 66 shows the AIC and BIC values for both one-piece and splines models as fitted to STRIDE and sorafenib respectively.

Table 66: Goodness of fit statistics to overall survival for STRIDE (green cells highlight the lowest value; yellow cell highlight the model chosen for the base case)

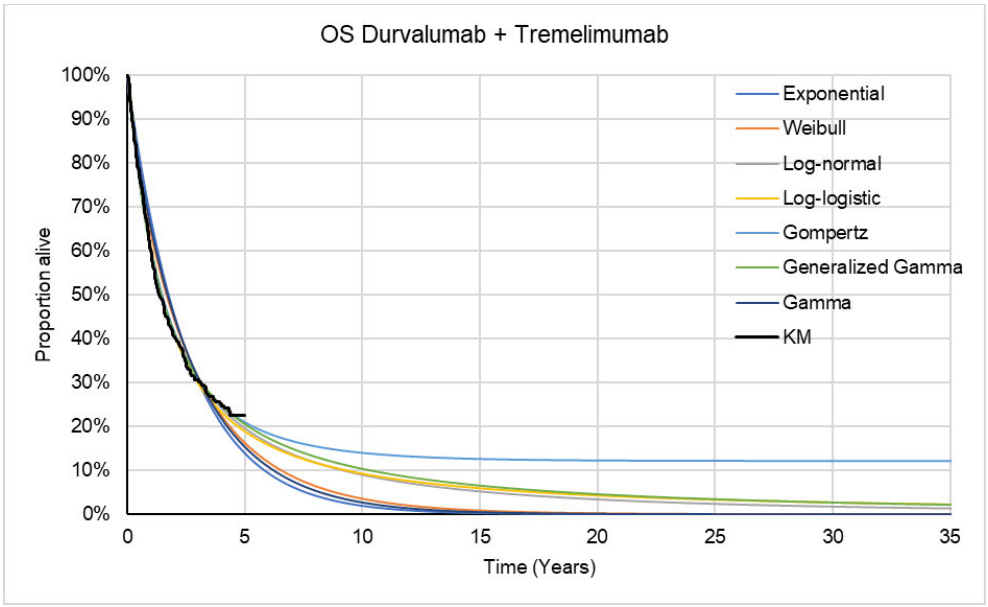
One-piece models			Splines and knots models		
Distribution	AIC	BIC	Distribution	AIC	BIC
Exponential	2571.1	2575.1	Hazard, 1 knot	2541.0	2552.9
Weibull	2565.9	2573.8	Hazard, 2 knots	2542.5	2558.4
Log-normal	2537.1	2545.1	Hazard, 3 knots	2542.2	2562.1
Log-logistic	2543.0	2550.9	Odds, 1 knot	2540.6	2552.5
Gompertz	2548.4	2556.4	Odds, 2 knots	2542.5	2558.4
Generalized gamma	2538.2	2550.2	Odds, 3 knots	2541.6	2561.5
Gamma	2569.6	2577.6	Normal, 1 knot	2538.6	2550.5
			Normal, 2 knots	2540.2	2556.1
			Normal, 3 knots	2540.0	2559.8

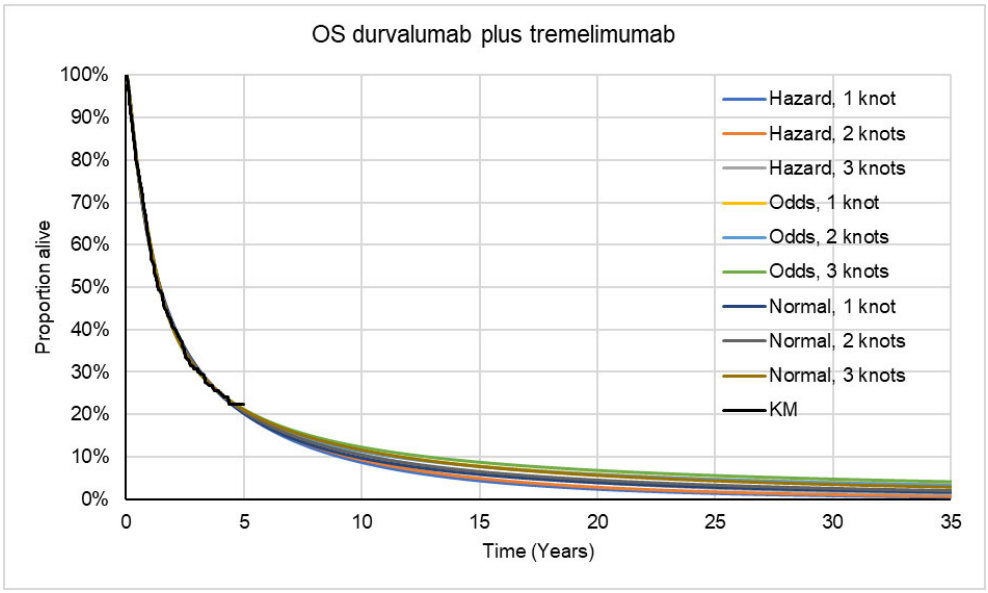
D.1.5 Evaluation of visual fit

One-piece and splines and knots parametric survival plots for STRIDE is given in Figure 35. The models are plotted with the KM data to illustrate how well they capture the trends. The statistically best fitting parametric model, based on AIC and BIC, for the STRIDE arm is the log-normal model.
Also considering clinical plausibility, the curves that provide a visually good fit, as well as a projection as expected by clinicians have been selected for the base case. This is the odds, 3 knots curve for STRIDE.

Spline and knots survivals include 1 knot, 2 knots, and 3 knots, with scales equal to normal, odds, and hazard for each number of knots.

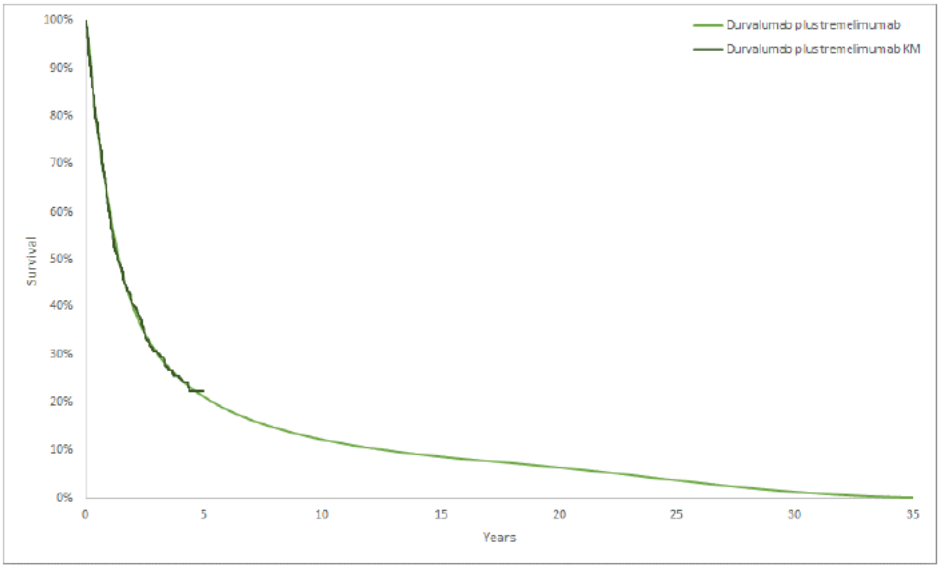
Figure 35: Overall survival STRIDE





The selected curve for included in the base case illustrated in Figure 36.

Figure 36: Summary of preferred OS model



D.1.6 Evaluation of hazard functions

The hazard function shows an increasing trend at the beginning but the hazard then decreases gradually over time [redacted] This indicates that an OS extrapolation that takes the decreasing mortality risk over time into account should be the preferred choice.

[redacted]

D.1.7 Validation and discussion of extrapolated curves

Based on the recent systematic review by Lin et al. (87), 23 randomised controlled phase 3 trials (see Table 1, Lin et al. 2022) comparing immune checkpoint inhibitors treatment versus chemotherapy across three cancer types (non–small cell lung cancer, urothelial carcinoma and melanoma) were selected to inform on long-term (>24 months) survival probabilities from previous IO trials. The Embase database was searched for complementary full-text publications and conference abstracts on the included trials published between 22 May 2022 and 20 February 2023 to ensure the inclusion of latest publicly available data. Overall survival rates at 24, 36, 48 and 60 months from the experimental and control arms were extracted, when available based on length of follow-up. If landmark values for overall survival rates were not provided in text of the publications, the values were estimated by manual inspection of the curves in figures.

The conditional mortality rate was estimated as the difference between landmark OS at time t + 12 month minus OS at time t, divided by OS at time t. For example, the conditional survival for the time period between 24 and 36 months is estimated as:

(landmark OS at 36 months - landmark OS at 24 months)/landmark OS at 24 months.

These values were estimate for each trial and then the average for all included trials was estimated for the time periods 24 – 36 months, 36 – 48 months, and 48 – 60 months. There were too few relevant studies with follow-up longer than 60 months to obtain reliable estimates for the survival development beyond 60 months.

Based on the extracted landmark overall survival rates, the mean conditional survival decreases from 26.3% between 24 and 36 months to 12.1% between 48 and 60 months in the IO arms identified in the systematic review. Comparing this to the OS modelling for the base case, we can see that the modelled results are close to the ones from a relevant selection of previous IO trials with long-term follow up (Table 67). The modelled conditional mortality was 18.0% between 36 and 48 months in the base-case HIMALYA modelling vs 19.4% in previous IO trials, and 14.9% between 48 and 60 months vs 12.1% in previous IO trials.

Table 67: Mean conditional mortality rates in HIMAYA base-case modelling vs previous IO trials with long-term follow-up

Outcome	Time period (months)		
	24-36 m	*36-48 m*	*48-60 m*
Conditional mortality, Previous IO studies*	26.3%	19.4%	12.1%
Conditional mortality, HIMALAYA modelling	23.8%	18.0%	14.9%
Conditional mortality, HIMALAYA trial	24.2%	17.9%	n/a**

Note: *, Based on studies included in systematic review by Lin et al. (2022) (87); **, Too much censoring to give reliable estimate;

To conclude, at least up to 5 years, the relative mortality in the IO arm in the HIMALAYA base-case modelling is well in line with what has been observed in previous IO trials.

The landmark OS data from the studies included in the results for the long-term OS development in Table 67 above are detailed in Table 68, which also clearly highlight the difference in landmark survival between the IO treatment (with a sustained survival in the long term) and the control arms.

Table 68: IO studies and data for analysis of tail development

Study	Arm	OS 24	OS 36	OS 48	OS 60	Reference
NSCLC trials:						
CheckMate 017/057	E	27%	17%	14%	13%	Borghaei et al. 2021 (88)
CheckMate 017/057	C	14%	8%	5%	3%	Borghaei et al. 2021 (88)
OAK	E	30%	21%	16%		Mazieres et al. 2020 (89)
OAK	C	22%	12%	9%		Mazieres et al. 2020 (89)
KEYNOTE-010	E	35%	23%	18%	16%	Herbst et al. 2021 (90)
KEYNOTE-010	C	16%	11%	9%	7%	Herbst et al. 2022 (90)
KEYNOTE-042	E	39%	25%	20%	17%	de Castro et al. 2022 (91)
KEYNOTE-042	C	29%	17%	12%	9%	de Castro et al. 2022 (91)
Impower 110	E	42%	29%	24%		Jassem et al. 2021 (92)
Impower 110	C	31%	26%	22%		Jassem et al. 2021 (92)
CheckMate 227	E	40%	33%	28%	24%	Hellman et al. 2019, Brahmer et al. 2023 (93, 94)
CheckMate 227	C	33%	22%	18%	14%	Hellman et al. 2019, Brahmer et al. 2023 (93, 94)
Impower 132	E	40%	27%			Nishio et al. 2021 (95)
Impower 132	C	35%	26%			Nishio et al. 2021 (95)
KEYNOTE-024	E	51%	44%	36%	32%	Reck et al. 2021 (96)
KEYNOTE-024	C	33%	25%	20%	16%	Reck et al. 2021 (96)
KEYNOTE-189	E	46%	31%	24%	19%	Garassino et al. 2023 (97)
KEYNOTE-189	C	27%	17%	14%	11%	Garassino et al. 2023 (97)
KEYNOTE-407	E	36%	30%	22%	18%	Novello et al. 2023 (98)
KEYNOTE-407	C	31%	19%	12%	10%	Novello et al. 2023 (98)
Impower 130	E	40%				West et al. 2019 (99)
Impower 130	C	30%				West et al. 2019 (99)
Impower 131	E	33%				Jotte et al. 2020 (100)
Impower 131	C	27%				Jotte et al. 2020 (100)
CheckMate 026	*No rates presented*					Carbone et al. 2017 (101)
CheckMate 9LA	E	38%	27%			Paz-Ares et al. 2022 (102)
CheckMate 9LA	C	26%	19%			Paz-Ares et al. 2022 (102)

Study	Arm	OS 24	OS 36	OS 48	OS 60	Reference
EMPOWER-Lung 1	*No rates presented*					Garassino et al. 2023 (103)
NCT01285609	E	24%				Govindan 2017 (104)
NCT01285609	C	18%				Govindan 2017 (104)
Melanoma trials:						
CA184-024	E	29%	21%	19%	18%	Maio et al. 2015 (105)
CA184-024	C	19%	12%	10%	9%	Maio et al. 2015 (105)
CheckMate 066	E	58%	51%	44%	39%	Robert et al. 2020 (106)
CheckMate 066	C	26%	22%	18%	17%	Robert et al. 2020 (106)
CheckMate 037	E	39%				Larkin et al. 2018 (107)
CheckMate 037	C	34%				Larkin et al. 2018 (107)
UC trials:						
KEYNOTE-045	E	27%	21%	17%		Fradet et al., Balar at al. 2022 (108, 109)
KEYNOTE-045	C	14%	11%	10%		Fradet et al., Balar at al. 2022 (108, 109)
Imvigor 211	E	22%				Van der Heijden et al. 2021 (110)
Imvigor 211	C	13%				Van der Heijden et al. 2021 (110)
KEYNOTE-361	E	37%				Powles et al. 2021 (111)
KEYNOTE-361	C	32%				Powles et al. 2021 (111)
Imvigor 130	*Indication withdrawn*					Galsky et al. 2020 (112)

Note: C: Control; E: Experimental; OS24: Landmark OS at 24 months

D.1.8 Adjustment of background mortality

The model adjust for background mortality using the life table from DMC, 'Nøgletalsoplysninger', 14-03-2023.

D.1.9 Adjustment for treatment switching/cross-over

The model includes a detailed consideration of subsequent treatment costs and therefore adjusting for treatment switching/cross-over is not necessary.

D.1.10 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence period. In the base case no treatment waning was applied.

D.1.11 Cure-point

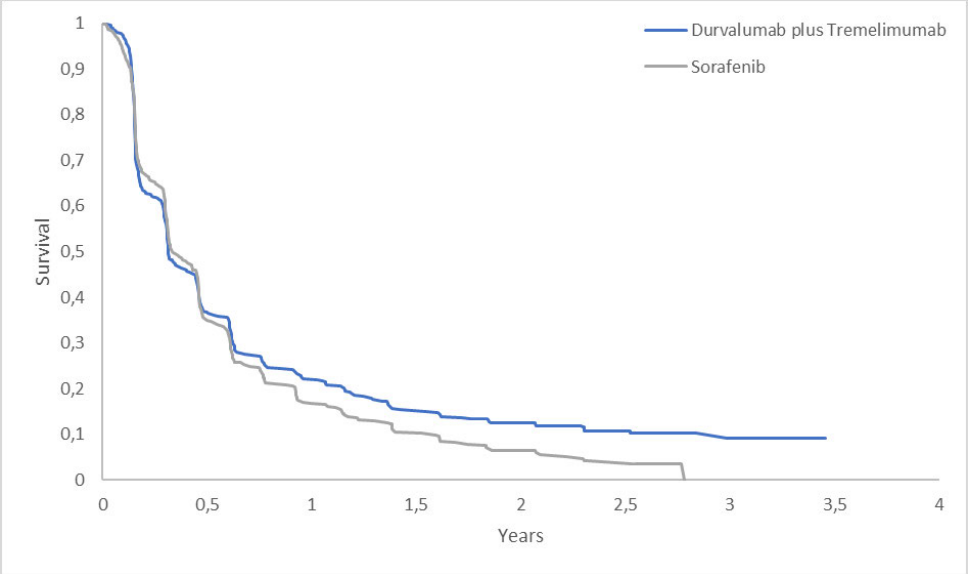
As the OS data are relatively mature, the tail development of STRIDE can be captured with the extrapolation modelling. We have not used any specific cure-point modelling.

D.2 Extrapolation of progression-free survival

D.2.1 Data input

Investigator assessment (INV) is used as the definition of progression to be consistent with the PFS used in the MAIC and provide a longer follow-up, and because PFS INV was a secondary endpoint in the HIMALAY trial. Kaplan–Meier plots for treatments included in HIMALAYA are presented in Figure 38.

Figure 38: Kaplan–Meier data, progression-free survival (full population)



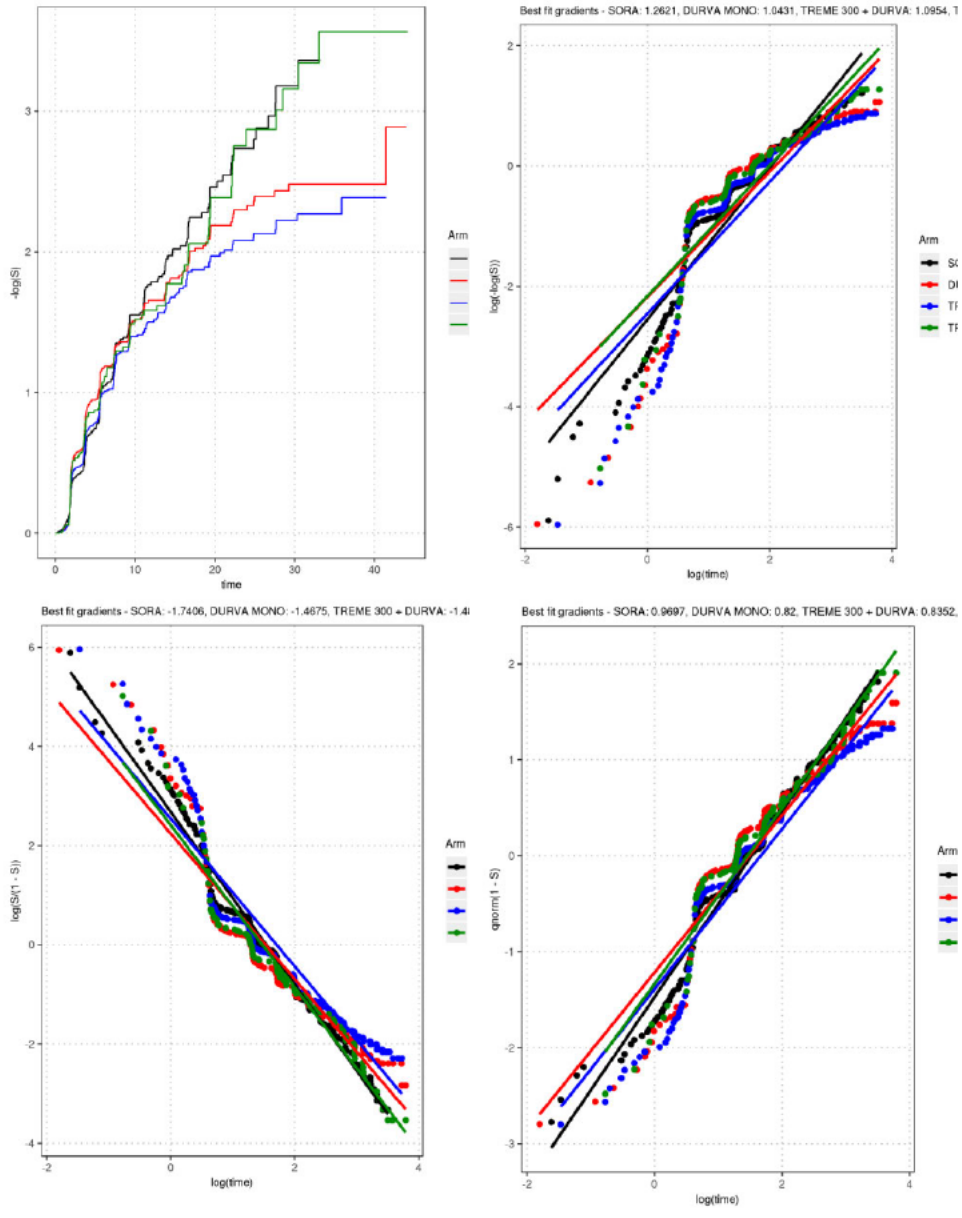
D.2.2 Model

Both standard parametric survival models (one-piece extrapolation models) and spline and knots models were explored. The spline and knots models can be especially relevant for immunotherapy, as these may potentially capture the tail development better than standard parametric models.

D.2.3 Proportional hazards

Figure 39 gives the cumulative hazard diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the exponential diagnostic plot, the gradient corresponds to the hazards and parallel lines indicate proportional hazards. In the Weibull, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the Loglogistic diagnostic plot, parallel lines indicate proportional odds and in the Lognormal diagnostic plot, parallel lines indicate constant acceleration.

Figure 39: Cumulative hazard plots – PFS

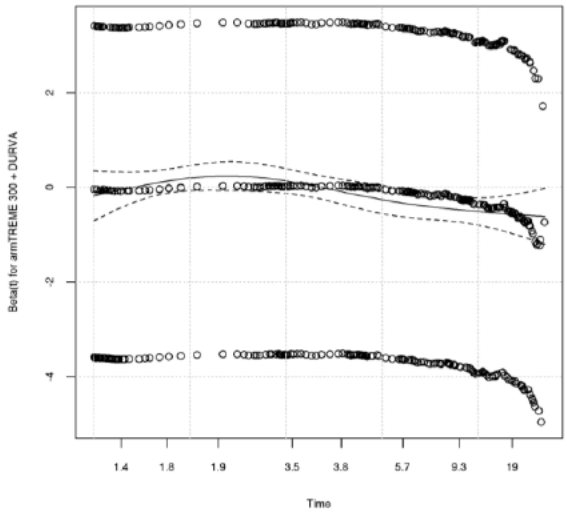


The Schoenfeld residuals can be used to test the proportional hazard assumption. If PH, the plot of the residuals against time should show a linear trend with slope=0. The visual inspection of this plot is as important as the test, however, a p-value is also output as the result of a test of non-negative slope (Therneau and Grambsch). Table 69 and Figure 40 describe the Schoenfeld residuals, which have been calculated using the km transform.

Table 69: Schoenfeld residuals – PFS

	rho	chisq	p
DURVA MONO	-0.097	11.0254782180724	< 0.001
TREME 300 + DURVA	-0.085	8.40726159309864	0.004
Global		13.217115450609	0.004

Figure 40: Schoenfeld residual plots - PFS



D.2.4 Evaluation of statistical fit (AIC and BIC)

Table 70 shows the AIC and BIC values for both one-piece and splines models as fitted to STRIDE.

Table 70: Goodness of fit statistics to progression-free survival for STRIDE (green cells highlight the lowest value; yellow cell highlight the model chosen for the base case)

One-piece models			Splines and knots models		
Distribution	AIC	BIC	Distribution	AIC	BIC
Exponential	2167.51	2171.48	Hazard, 1 knot	1996.5	2008.5
Weibull	2156.63	2164.57	Hazard, 2 knots	1970.1	1986
Log-normal	2047.32	2055.27	Hazard, 3 knots	1959.3	1979.1
Log-logistic	2049.02	2056.97	Odds, 1 knot	1986.6	1998.5
Gompertz	2091.49	2099.44	Odds, 2 knots	1967.2	1983.1
Generalized gamma	1996.3	2008.22	Odds, 3 knots	1961.4	1981.3

Gamma	2167.61	2175.56	Normal, 1 knot	1986.6	1998.5
			Normal, 2 knots	1967.2	1983.1
			Normal, 3 knots	1961.4	1981.3

D.2.5 Evaluation of visual fit

One-piece parametric survival plots and spline and knots for STRIDE are given in Figure 41. The models are plotted with the KM data to illustrate how well they capture the trends. The statistical best fitting parametric model based on AIC and BIC is the Hazard, 3 knots model for STRIDE.

The curves were also assessed visually as well as compared to the base case selection for OS. Based on this, the following curve was selected for the base case: odds, 3 knots curve for STRIDE.

Spline and knots survivals include 1 knot, 2 knots, and 3 knots, with scales equal to normal, odds, and hazard for each number of knots.

Figure 42 illustrates the selected curves for each treatment regimen included in the base case.

Figure 41: Progression-free survival STRIDE

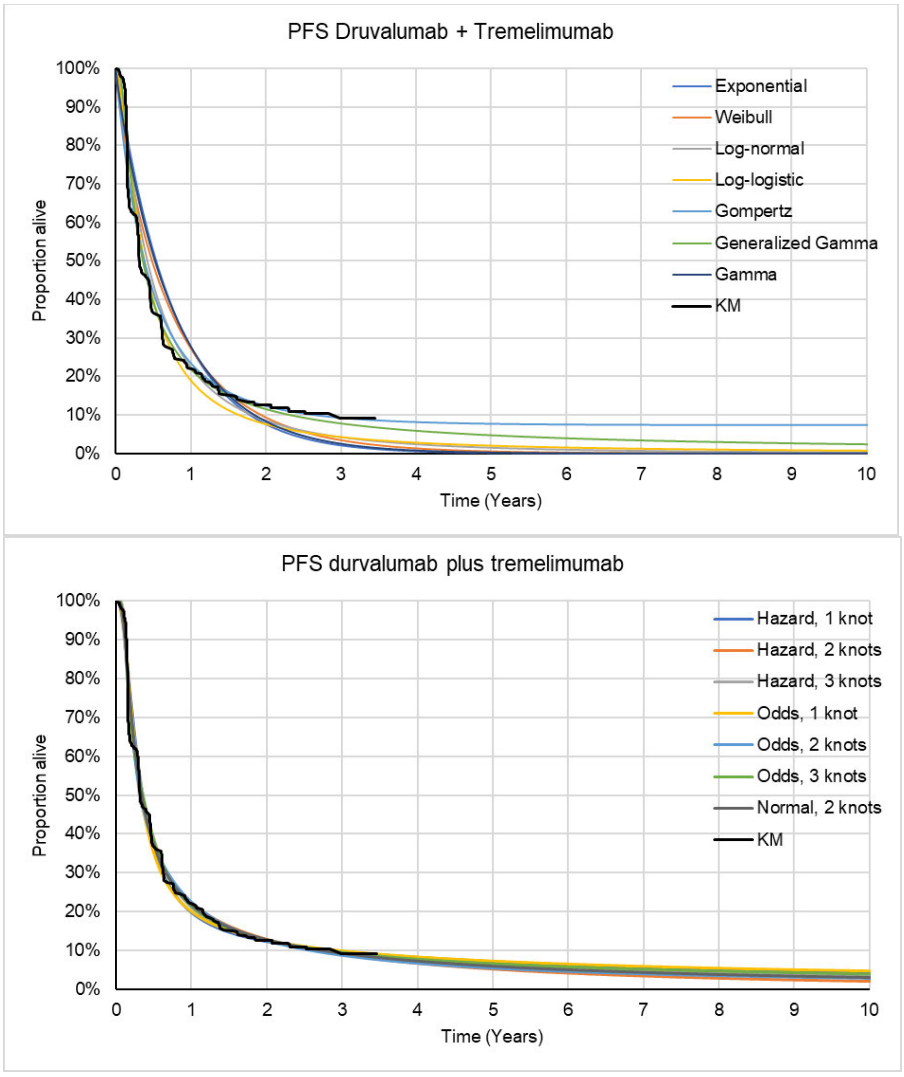
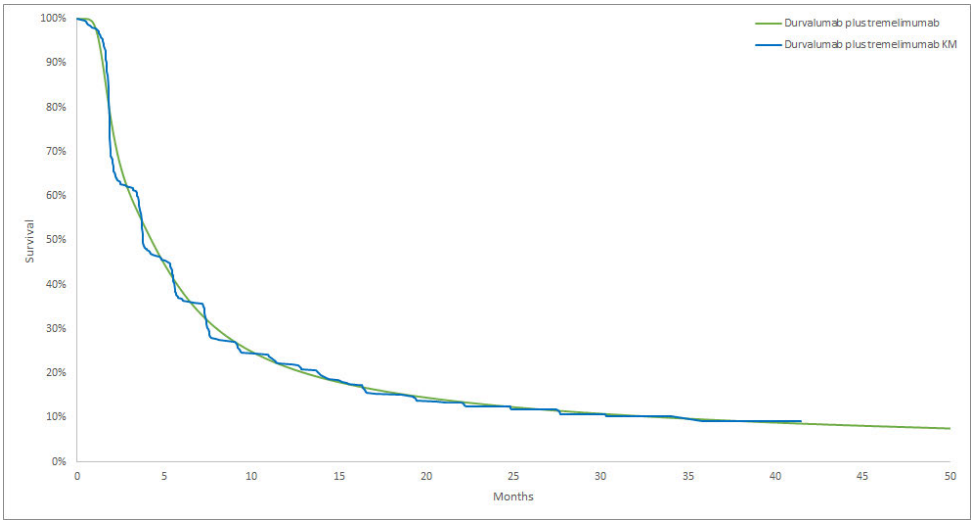


Figure 42: Summary of preferred PFS model



D.2.6 Evaluation of hazard functions

The hazard function shows an increasing trend for the first two months but the hazard then decreases gradually over time [redacted] This indicates that PFS extrapolation that takes the decreasing progression risk over time into account should be the preferred choice.

[redacted]

D.2.7 Validation and discussion of extrapolated curves

PFS data are now relatively mature and the chosen extrapolation has both good statistical and visual fit to the data.

D.2.8 Adjustment of background mortality

Relevant for OS

D.2.9 Adjustment for treatment switching/cross-over

Not relevant for PFS

D.2.10 Waning effect

The base case does not include any treatment effect waning, but the economic model has options allowing the user to specify a time at which treatment effect waning starts and ends (usually in line with a stopping rule), and the proportion of patients to which it applies. This can be implemented separately for OS and PFS.

D.2.11 Cure-point

As the PFS data are mature, the tail development of STRIDE can be captured with the extrapolation modelling. We have not used any specific cure-point modelling.

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

KM plots for treatments included in HIMALAYA are presented in [redacted]

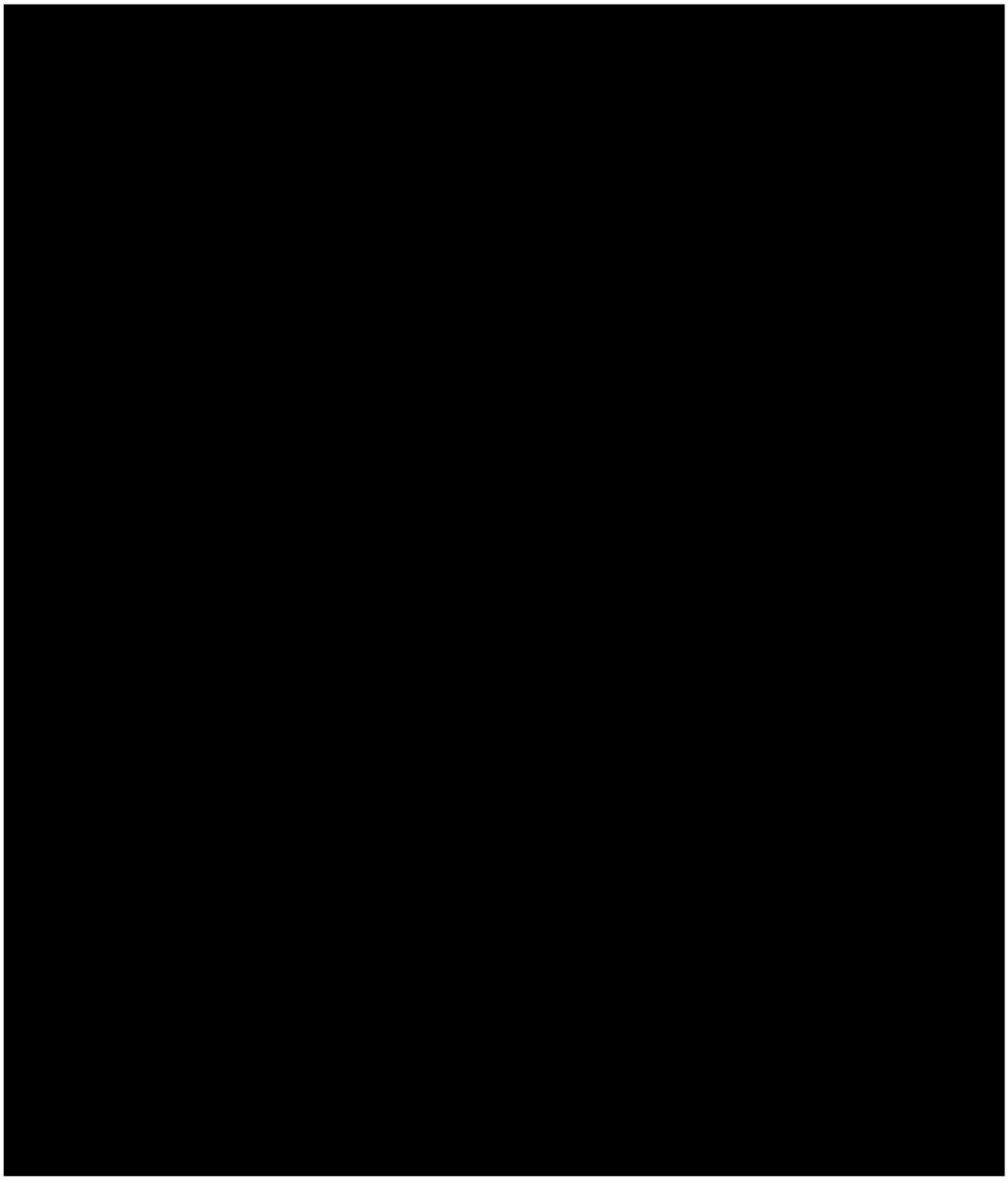
D.3.2 Model

Both standard parametric survival models (one-piece extrapolation models) and spline and knots models were explored. The spline and knots models can be especially relevant for immunotherapy, as these may potentially capture the tail development better than standard parametric models.

D.3.3 Proportional hazards

Figure 45 gives the cumulative hazard diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution In the exponential diagnostic plot, the gradient corresponds to the hazards and parallel lines indicate proportional hazards In the Weibull, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the Loglogistic diagnostic plot, parallel lines indicate proportional odds and in the Lognormal diagnostic plot, parallel lines indicate constant acceleration.

[redacted]

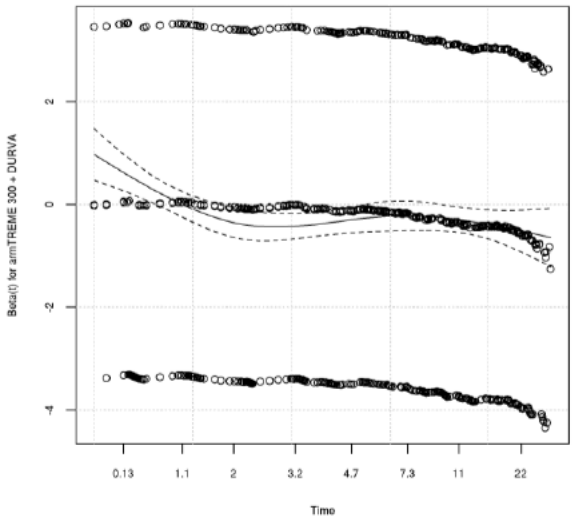


The Schoenfeld residuals can be used to test the proportional hazard assumption. If PH, the plot of the residuals against time should show a linear trend with slope=0. The visual inspection of this plot is as important as the test, however, a p-value is also output as the result of a test of non-negative slope (Therneau and Grambsch). Table 71 and Figure 46 describe the Schoenfeld residuals, which have been calculated using the km transform.

Table 71: Schoenfeld residuals

	rho	chisq	p
DURVA MONO	-0.089	9.54093413097714	0.002
TREME 300 + DURVA	-0.104	12.9377433275177	< 0.001
Global		16.882340597232	< 0.001

Figure 46: Schoenfeld residual plots



D.3.4 Evaluation of statistical fit (AIC and BIC)

Table 72 shows the AIC and BIC values for both one-piece and splines models as fitted to STRIDE.

Table 72: Goodness of fit statistics to time to treatment discontinuation for STRIDE (green cells highlight the lowest value; yellow cell highlight the model chosen for the base case)

One-piece models			Splines and knots models		
Distribution	AIC	BIC	Distribution	AIC	BIC
Exponential	2323.30	2327.27	Hazard, 1 knot	2205.32	2217.24
Weibull	2203.40	2211.35	Hazard, 2 knots	2199.15	2215.05
Log-normal	2231.53	2239.48	Hazard, 3 knots	2200.43	2220.30
Log-logistic	2217.70	2225.65	Odds, 1 knot	2199.15	2211.08
Gompertz	2233.82	2241.77	Odds, 2 knots	2201.26	2217.16
Generalized gamma	2204.70	2216.62	Odds, 3 knots	2199.90	2219.77
Gamma	2211.29	2219.24	Normal, 1 knot	2197.36	2209.28
			Normal, 2 knots	2199.07	2214.97
			Normal, 3 knots	NA	NA

D.3.5 Evaluation of visual fit

One-piece parametric survival plots for STRIDE is shown in [redacted]

The models are plotted with the KM data to illustrate how well they capture the trends. The statistical best-fitting single parametric model based on the lowest AIC and BIC is Normal, 1 knot, and Log-normal for the STRIDE,. The base case model uses the Weibull curve for STRIDE.

Spline and knots survivals include 1 knot, 2 knots, and 3 knots, with scales equal to normal, odds, and hazard for each number of knots. For some survivals the splines did not converge, therefore the values were not available.

Figure 48 illustrates the selected curve included in the base case.

[redacted]

D.3.6 Evaluation of hazard functions

The hazard function is highest at the beginning but is then declining quite rapidly. It is then relatively stable for a while, but after that the hazard decreases gradually over time again (Figure 49).

[redacted]

D.3.7 Validation and discussion of extrapolated curves

TTD data are now relatively mature and the chosen extrapolation has reasonable statistical and visual fit to the data.

D.3.8 Adjustment of background mortality

Relevant for OS but not for TTD.

D.3.9 Adjustment for treatment switching/cross-over

Not relevant for TTD.

D.3.10 Waning effect

Not relevant for TTD.

D.3.11 Cure-point

Not relevant for TTD.

Appendix E. Serious adverse events

E.1 Serious adverse events – HIMALAYA

Most patients in the treatment arms experienced one or more AEs, regardless of causality. However, the nature and frequency of these events was consistent with that expected for the selected study population and the known safety profile of the study treatments. A summary of treatment-related adverse events (TRAEs) experienced by patients in the STRIDE and sorafenib treatment arms of HIMALAYA is presented in Table 73 (5).

Table 73: Summary of AEs experience by patients in HIMALAYA trial (SAS), DCO3

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

Footnotes: *[a]TRAEs leading to death in the STRIDE arm included myasthenia gravis, nervous system disorder, myocarditis, acute respiratory distress syndrome, pneumonitis, hepatic failure, hepatitis (all n51 each), and immune-mediated hepatitis (n=2); [b]TRAEs leading to death in the sorafenib arm included cerebral hematoma, hepatic failure, and haematuria (all n=1 each); [c]TRAEs leading to death in the STRIDE arm included pneumonitis, hepatitis, myocarditis, myasthenia gravis (all n=1 each), and immune-mediated hepatitis (n=2).*
Abbreviations: *AE: adverse event; SAE: serious adverse event; SAS: safety analysis set; SMQ: standardised MedDRA queries; TRAE: treatment-related adverse event; STRIDE: single tremelimumab regular interval durvalumab regime.*
Source: *Abou-Alfa et al (2022);(5) Sangro et al (2022).*

Grade 3 or 4 adverse events occurred in 50.5% and 52.4% of patients treated with STRIDE and sorafenib, respectively, (Table 74). The most common grade 3 or 4 adverse events

with STRIDE were increased lipase (6.2%), and increased aspartate aminotransferase (5.2%). Common grade 3 or 4 with sorafenib were hand-foot syndrome (PPE, 9.1%) and hypertension (6.1%) (48). Treatment emergent adverse events grade 4 or 4 is listed in Table 74.

Table 74: Treatment emergent adverse events grade 3 or 4 in the Safety analysis set (SAS) (DCO3). (5)

	HIMALAYA(5)	
	Number of adverse events	Number of adverse events
Adverse event, n (%)		
Diarrhea	17 (4.4)	16 (4.3)
Abdominal pain	5 (1.3)	12 (3.2)
Pruritus	0	1 (0.3)
Rash	6 (1.5)	4 (1.1)
Palmar-plantar erythrodysesthesia syndrome	0	34 (9.1)
Aspartate aminotransferase increased	20 (5.2)	12 (3.2)
Alanine aminotransferase increased	10 (2.6)	7 (1.9)
Amylase increased	14 (3.6)	4 (1.1)
Blood bilirubin increased	3 (0.8)	8 (2.1)
Gamma-glutamyltransferase increased	8 (2.1)	7 (1.9)
Lipase increased	24 (6.2)	11 (2.9)
Decreased appetite	5 (1.3)	3 (0.8)
Asthenia	7 (1.8)	10 (2.7)
Fatigue	8 (2.1)	11 (2.9)
Pyrexia	1 (0.3)	0
Edema peripheral	2 (0.5)	0
Cough	0	1 (0.3)
Insomnia	1 (0.3)	0

Hypertension	7 (1.8)	23 (6.1)
Anemia	11 (2.8)	12 (3.2)
Hyperkalemia	6 (1.5)	9 (2.4)
Hypokalemia	4 (1.0)	2 (0.5)
Hyponatremia	16 (4.1)	11 (2.9)

E.1.1 Immune-mediated adverse events – HIMALAYA

Analysis of the STRIDE safety analysis set show that immune mediated adverse events, both of any grade and grade 3/4 was twice as common for dual immunotherapy STRIDE compared to durvalumab monotherapy. 36.1% and 13.4% of the STRIDE patients experienced any imAE and grade 3 or 4 AEs respectively, compared to 16.5% and 6.3% of the durvalumab monotherapy patients (Table 75).

Table 75: Immune-mediated adverse events categories reported for > 2% of patients in the HCC pool (safety analysis set) *(48)*

Number (%) of patients		
	HCC T300+D Pool (N = 462)	
imAE category	Any grade	CTCAE Grade 3 or 4
Any imAE	167 (36.1)	62 (13.4)
Hypothyroid events	45 (9.7)	0
Hepatic events	34 (7.4)	23 (5.0)
Diarrhoea/colitis	30 (6.5)	17 (3.7)
Dermatitis/rash	26 (5.6)	9 (1.9)
Hyperthyroid	21 (4.5)	1 (0.2)
Other rare/ miscellaneous	10 (2.2)	2 (0.4)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (20 mg/kg) Q4W; HCC, hepatocellular carcinoma; imAE, immune-mediated adverse event; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W.

E.1.2 Hemorrhagic adverse events

The overall frequency of haemorrhagic TRAEs was very low for both total and Grade ≥3 events (Table 76). Haemorrhagic TRAEs were lower in the STRIDE arm compared with the sorafenib arm, with the frequency of patients reporting any haemorrhagic TRAE more than

twice as high in the sorafenib arm (4.8%) compared with the STRIDE arm (1.8%). No treatment-related deaths due to AEs in the haemorrhage SMQ were reported in the STRIDE arm, whereas in the sorafenib arm, deaths due to one event of cerebral haematoma and one event of haematuria were considered treatment-related (HIMALAYA data on file).

Table 76: Summary of treatment-related hemorrhage adverse events reported by highest grade (≥3) (SAS).

Preferred term[a]	Maximum reported CTCAE grade	STRIDE (n=388), n (%)	Sorafenib (n=374), n (%)
Patients with any haemorrhage SMQ AE	Total	7 (1.8)	18 (4.8)
	Grade ≥3	2 (0.5)	6 (1.6)
Gastrointestinal haemorrhage	Total	0	3 (0.8)
	Grade ≥3	0	1 (0.3)
Intra-abdominal haemorrhage	Total	0	1 (0.3)
	Grade ⩾3	0	1 (0.3)
Oesophageal varices haemorrhage	Total	0	0
	Grade ⩾3	0	0

E.2 Serious adverse events – IMBrave150

Grade 3 or 4 adverse events occurred in 56.5% and 55.1% of patients treated with atezo-bev and sorafenib, respectively (Table 77). The most common grade 3 or 4 adverse events with atezo-bev were hypertension (15.2%) and increased alanine aminotransferase (3.6%). Common grade 3 or 4 with sorafenib were hand-foot syndrome (PPE, 8.3%) and hypertension (12.2%).

Table 77: AE with 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) (35)

	Sorafenib (N=156)		Atezo+Bev (N=329)	
MedDRA System Organ Class MedDRA Preferred Term	Grade 3-4	Grade 5	Grade 3-4	Grade 5
Total number of patients with at least one adverse event	86 (55.1%)	9 (5.8%)	186 (56.5%)	15 (4.6%)
Investigations				
Total number of patients with at least one adverse event	25 (16.0%)	0	61 (18.5%)	0
Blood bilirubin increased	10 (6.4%)	0	8 (2.4%)	0
Alanine aminotransferase increased	2 (1.3%)	0	12 (3.6%)	0
Platelet count decreased	2 (1.3%)	0	11 (3.3%)	0
Gastrointestinal disorders				
Total number of patients with at least one adverse event	27 (17.3%)	1 (0.6%)	48 (14.6%)	5 (1.5%)
Diarrhoea	8 (5.1%)	0	6 (1.8%)	0
Vascular disorders				
Total number of patients with at least one adverse event	21 (13.5%)	0	53 (16.1%)	0
Hypertension	19 (12.2%)	0	50 (15.2%)	0
Metabolism and nutrition disorders				
Total number of patients with at least one adverse event	21 (13.5%)	0	30 (9.1%)	0
Decreased appetite	6 (3.8%)	0	4 (1.2%)	0
Hypophosphataemia	6 (3.8%)	0	2 (0.6%)	0
General disorders and administration site conditions				
Total number of patients with at least one adverse event	12 (7.7%)	3 (1.9%)	14 (4.3%)	1 (0.3%)
Asthenia	4 (2.6%)	0	1 (0.3%)	0
Skin and subcutaneous tissue disorders				
Total number of patients with at least one adverse event	21 (13.5%)	0	2 (0.6%)	0
Palmar-plantar erythrodysaesthesia syndrome	13 (8.3%)	0	0	0
Rash	4 (2.6%)	0	0	0
Renal and urinary disorders				
Total number of patients with at least one adverse event	6 (3.8%)	0	14 (4.3%)	0
Proteinuria	1 (0.6%)	0	10 (3.0%)	0
Injury, poisoning and procedural complications				
Total number of patients with at least one adverse event	2 (1.3%)	0	13 (4.0%)	0
Infusion related reaction	0	0	8 (2.4%)	0

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
To the SOC Overall row counts, a patient contributes once for each grade category for which at least one AE with the corresponding highest grade is reported.

E.2.1 Adverse events of special interest – IMBrave150

The EPAR (35) for atezo-bev describes how immune-mediated and haemorrhagic adverse events are of special interest, listed in Table 78 .

Table 78: Summary of Adverse Events of Special Interest for Atezolizumab (Safety-Evaluable Population) *(35)*

	Patients with Moderate Hepatic Impairment		All Patients Population	
	Sorafenib N=18	**Atezo+Bev N=28**	**Sorafenib N=156**	**Atezo+Bev N=329**
Total number of patients with at least one:				
Atezolizumab AESI				
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	12 (66.7%)	22 (78.6%)	62 (39.7%)	142 (43.2%)
Immune-Mediated Hepatitis (Lab Abnormalities)	11 (61.1%)	18 (64.3%)	54 (34.6%)	126 (38.3%)
Immune-Mediated Hepatitis (Diagnosis)	2 (11.1%)	9 (32.1%)	20 (12.8%)	43 (13.1%)
Immune-Mediated Rash	12 (66.7%)	3 (10.7%)	96 (61.5%)	64 (19.5%)
Immune-Mediated Hypothyroidism	0	4 (14.3%)	4 (2.6%)	36 (10.9%)
Infusion-Related Reactions	0	6 (21.4%)	0	36 (10.9%)
Immune-Mediated Hyperthyroidism	0	1 (3.6%)	0	15 (4.6%)
Immune-Mediated Pancreatitis	0	3 (10.7%)	6 (3.8%)	9 (2.7%)
Immune-Mediated Diabetes Mellitus	0	2 (7.1%)	0	8 (2.4%)
Immune-Mediated Colitis	0	1 (3.6%)	1 (0.6%)	6 (1.8%)
Immune-Mediated Pneumonitis	0	0	0	4 (1.2%)
Immune-Mediated Nephritis	0	0	0	3 (0.9%)
Autoimmune Hemolytic Anemia	0	0	0	1 (0.3%)
Immune-Mediated Adrenal Insufficiency	0	0	0	1 (0.3%)
Immune-Mediated Ocular Inflammatory Toxicity	0	0	0	1 (0.3%)
Immune-Mediated Severe Cutaneous Reactions	1 (5.6%)	0	1 (0.6%)	0
Immune-Mediated Vasculitis	0	1 (3.6%)	0	1 (0.3%)
Systemic Immune Activation	0	0	0	1 (0.3%)
Bevacizumab AESI				
Hypertension	4 (22.2%)	5 (17.9%)	40 (25.6%)	102 (31.0%)
Bleeding / Haemorrhage	3 (16.7%)	7 (25.0%)	27 (17.3%)	83 (25.2%)
Proteinuria	0	7 (25.0%)	13 (8.3%)	70 (21.3%)
Thromboembolic Event - Venous	0	1 (3.6%)	5 (3.2%)	10 (3.0%)
Thromboembolic Event - Arterial	0	1 (3.6%)	2 (1.3%)	9 (2.7%)
Congestive Heart Failure	1 (5.6%)	0	2 (1.3%)	1 (0.3%)
Wound Healing Complications	0	0	0	2 (0.6%)
Fistula/Abscess (Non GI)	1 (5.6%)	0	1 (0.6%)	0
Gastrointestinal Perforation	0	0	0	1 (0.3%)

AESIs=adverse events of special interest
Note: Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.

E.2.2 Haemorrhagic adverse events – IMBrave150

The assessment report (35) concluded on page 109 that:

"despite attempts to exclude all patients with prior bleeding due to esophageal and/or gastric varices within 6 months prior to study treatment and perform esophagogastroduodenoscopy (EGD) on all patients in order to treat all size varices, a considerable number of patients experienced gastrointestinal bleedings in the atezolizumab and bevacizumab arm in study IMbrave150".

The EPAR also concluded that:

"Patients treated with bevacizumab have an increased risk of hemorrhage, and cases of severe gastrointestinal hemorrhage, including fatal events, were reported in patients with hepatocellular carcinoma (HCC) treated with atezolizumab in combination with bevacizumab".

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

Table 79: Overview of parameters in the PSA

Input parameter	Distribution	Lower	Upper	Point estimate
Control: Patient Characteristics - Age at model start	Normal	62.482	63.718	63
Control: Patient Characteristics - Patient weight	Normal	70.049	71.751	71
Control: Patient Characteristics - Patient height	Normal	167.233	168.167	167.7
Subsequent treatment, mean time on treatment - Lenvatinib	Normal	256.132	368.068	312.1
Subsequent treatment, mean time on treatment - Regorafenib	Normal	135.7	199.9	167.8
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Appointment with oncologist	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Appointment with hepatologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Appointment with Gastroenterologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Appointment with Radiologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Appointment within clinician nurse specialist	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Appointment with palliative care physician/nurse	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - AFP test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Liver function test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - INR	Gamma	0.186	0.276	0.23

Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Complete blood count	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Biochemistry	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Endoscopy	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Abdominal CT	Gamma	0.062	0.092	0.08
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Abdominal MRI	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Hospitalisation	Gamma	0.008	0.011	0.01
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Hospital follow-up: Specialist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - GP visit follow-up	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - DurvaTrem - Hospital follow-up: Nurse	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Appointment with oncologist	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Appointment with hepatologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Appointment with Gastroenterologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Appointment with Radiologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Appointment within clinician nurse specialist	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Appointment with palliative care physician/nurse	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - AFP test	Gamma	0.186	0.276	0.23

Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Liver function test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - INR	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Complete blood count	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Biochemistry	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Endoscopy	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Abdominal CT	Gamma	0.062	0.092	0.08
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Abdominal MRI	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Hospitalisation	Gamma	0.008	0.011	0.01
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Hospital follow-up: Specialist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - GP visit follow-up	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - DurvaTrem - Hospital follow-up: Nurse	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - Appointment with oncologist	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - DurvaTrem - Appointment with hepatologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - Appointment with Gastroenterologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - Appointment with Radiologist	Gamma	0	0	0

Resource Use - Itemized Frequency - PD - DurvaTrem - Appointment within clinician nurse specialist	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - DurvaTrem - Appointment with palliative care physician/nurse	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - AFP test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - DurvaTrem - Liver function test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - DurvaTrem - INR	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - DurvaTrem - Complete blood count	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - DurvaTrem - Biochemistry	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - Endoscopy	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - Abdominal CT	Gamma	0.062	0.092	0.08
Resource Use - Itemized Frequency - PD - DurvaTrem - Abdominal MRI	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - Hospitalisation	Gamma	0.008	0.011	0.01
Resource Use - Itemized Frequency - PD - DurvaTrem - Hospital follow-up: Specialist	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - GP visit follow-up	Gamma	0	0	0
Resource Use - Itemized Frequency - PD - DurvaTrem - Hospital follow-up: Nurse	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - AtezoBev - Appointment with oncologist	Gamma	0.268	0.399	0.33
Resource Use - Itemized Frequency - PFS, First - AtezoBev - Appointment with Gastroenterologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, First - AtezoBev - Appointment within clinician nurse specialist	Gamma	0.268	0.399	0.33
Resource Use - Itemized Frequency - PFS, First - AtezoBev - AFP test	Gamma	0.186	0.276	0.23

Resource Use - Itemized Frequency - PFS, First - AtezoBev - Liver function test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, First - AtezoBev - INR	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, First - AtezoBev - Complete blood count	Gamma	0.268	0.399	0.33
Resource Use - Itemized Frequency - PFS, First - AtezoBev - Endoscopy	Gamma	0.804	1.196	1
Resource Use - Itemized Frequency - PFS, First - AtezoBev - Abdominal CT	Gamma	0.067	0.1	0.08
Resource Use - Itemized Frequency - PFS, First - AtezoBev - Hospitalisation	Gamma	0.008	0.011	0.01
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - Appointment with oncologist	Gamma	0.268	0.399	0.33
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - Appointment with Gastroenterologist	Gamma	0	0	0
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - Appointment within clinician nurse specialist	Gamma	0.268	0.399	0.33
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - AFP test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - Liver function test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - INR	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - Complete blood count	Gamma	0.268	0.399	0.33
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - Abdominal CT	Gamma	0.067	0.1	0.08
Resource Use - Itemized Frequency - PFS, Subsequent - AtezoBev - Hospitalisation	Gamma	0.008	0.011	0.01
Resource Use - Itemized Frequency - PD - AtezoBev - Appointment with oncologist	Gamma	0.201	0.299	0.25

Resource Use - Itemized Frequency - PD - AtezoBev - Appointment within clinician nurse specialist	Gamma	0.201	0.299	0.25
Resource Use - Itemized Frequency - PD - AtezoBev - AFP test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - AtezoBev - Liver function test	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - AtezoBev - INR	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - AtezoBev - Complete blood count	Gamma	0.186	0.276	0.23
Resource Use - Itemized Frequency - PD - AtezoBev - Abdominal CT	Gamma	0.067	0.1	0.08
Resource Use - Itemized Frequency - PD - AtezoBev - Hospitalisation	Gamma	0.008	0.011	0.01
OS MultinormInv random number 1 - DurTrem				0.5
OS MultinormInv random number 2 - DurTrem				0.5
OS MultinormInv random number 3 - DurTrem				0.5
OS MultinormInv random number 4 - DurTrem				0.5
OS MultinormInv random number 5 - DurTrem				0.5
PFS MultinormInv random number 1 - DurTrem				0.5
PFS MultinormInv random number 2 - DurTrem				0.5
PFS MultinormInv random number 3 - DurTrem				0.5
PFS MultinormInv random number 4 - DurTrem				0.5
PFS MultinormInv random number 5 - DurTrem				0.5
TTD MultinormInv random number 1 - DurTrem				0.5
TTD MultinormInv random number 2 - DurTrem				0.5
TTD MultinormInv random number 3 - DurTrem				0.5
TTD MultinormInv random number 4 - DurTrem				0.5

TTD MultinormInv random number 5 - DurTrem				0.5
Adverse event - Mean treatment exposure (years) - Durvalumab plus tremelimumab	Normal	1.072	1.595	1.33
Adverse event - Mean treatment exposure (years) - Atezolizumab plus bevacizumab	Normal	0.496	0.738	0.62
Adverse event - Durvalumab plus tremelimumab - Aspartate aminotransferase increased	Normal	16.080	23.920	20
Adverse event - Durvalumab plus tremelimumab - Hypertension	Normal	5.628	8.372	7
Adverse event - Durvalumab plus tremelimumab - Lipase increased	Normal	19.296	28.704	24
Adverse event - Atezolizumab plus bevacizumab - Aspartate aminotransferase increased	Normal	18.492	27.508	23
Adverse event - Atezolizumab plus bevacizumab - Hypertension	Normal	40.200	59.800	54
Adverse event - Atezolizumab plus bevacizumab - Lipase increased	Normal	0.00	2.156	0

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

For the SLR update, the following key biomedical databases were searched.

Table 80: Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	31.08.20 to 05.11.21	05.11.21
Medline	Embase.com	31.08.20 to 05.11.21	05.11.21
Medline-in-process	PubMed	31.08.20 to 05.11.21	05.11.21
CENTRAL	Cochrane Library	31.08.20 to 05.11.21	05.11.21
CDSR	Cochrane Library	31.08.20 to 05.11.21	05.11.21

Abbreviations: Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews (CDSR)

In addition to searches of electronic databases, hand searches were conducted to capture data from recent unpublished studies. The retrieval of unpublished clinical trials and other studies through the search of registries and conference proceedings is recommended by the Cochrane Handbook for Systematic Reviews of Interventions.

HTA reports were searched via the INHATA database, which covers the following agencies:

- UK: National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG)
- France: Haute Autorité de Santé (HAS)
- Germany: Gemeinsamer Bundesausschuss (GBA) and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis (IQWiG)
- Spain: Agencia española del medicamento (AEM) y Grupo Genesis
- Italy: Agenzia Italiana del Farmaco (AIFA)
- Australia: Pharmaceutical Benefits Advisory Committee (PBAC)
- Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)
- NIHR HTA Programme

Bibliographic search was also conducted by checking the reference list of included studies and any relevant SLRs identified looking for any relevant additional studies. A hand search was performed on an SLR bibliography (i.e., Recent Advances in Systemic Therapies for Advanced Hepatocellular Carcinoma (113)) but no relevant studies were identified.

Table 81: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	https://www.clinicaltrials.gov/	sorafenib OR Nexavar OR lenvatinib OR Lenvima OR atezolizumab OR tecentriq OR bevacizumab OR avastin OR nivolumab OR Opdivo OR durvalumab OR Imfinzi OR tremelimumab OR ticilimumab | Studies With Results | Hepatocellular Carcinoma	31st Aug 2020 – 29th Oct 2021
EU Clinical Trials Register (EUCTR)	https://www.clinicaltrialsregister.eu/ctr-search/search	Hepatocellular carcinoma AND (sorafenib OR Nexavar OR lenvatinib OR Lenvima OR atezolizumab OR tecentriq OR bevacizumab OR avastin OR nivolumab OR Opdivo OR durvalumab OR Imfinzi OR tremelimumab OR ticilimumab)	31st Aug 2020 – 29th Oct 2021
World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP)	https://trialsearch.who.int/AdvSearch.aspx	Hepatocellular carcinoma AND (sorafenib OR Nexavar OR lenvatinib OR Lenvima OR atezolizumab OR tecentriq OR bevacizumab OR avastin OR nivolumab OR Opdivo OR durvalumab OR Imfinzi OR tremelimumab OR ticilimumab)	31st Aug 2020 – 29th Oct 2021

Source name	Location/source	Search strategy	Date of search
INAHTA	https://www.inahta.org/	("Carcinoma, Hepatocellular"[mh]) OR (HCC) OR ("hepatocellular carcinoma")	20th October 2021

Conference proceedings were hand searched to retrieve the latest studies, which have not been published in journal articles or to supplement results of previously published studies. Abstracts from the following conferences were searched from 2016 to November 2021.

Table 82: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search (Year searched)
Gastrointestinal Cancers Symposium (ASCO GI)	*	Manual search	Hepatocellular carcinoma	2021/2022
American Society of Clinical Oncology (ASCO) annual meeting	**	Manual search	Hepatocellular carcinoma	2021/2022
European Association for the Study of Liver (EASL) congress	***	Manual search	Hepatocellular carcinoma	2020/2021
American Association for the Study of Liver Diseases (AASLD) annual meeting	****	Manual search	Hepatocellular carcinoma	2020/2021
European Society for Medical Oncology (ESMO) congress	*****	Manual search	Hepatocellular carcinoma	2020/2021

* https://meetings.asco.org/abstracts-presentations/search?query=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D%7D&q=
** https://meetings.asco.org/abstracts-presentations/search?query=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20Meeting%22%7D%5D%7D&q=
*** https://easl.eu/event/the-international-liver-congress-2021/ILC-Resources/
**** https://aasldpubs.onlinelibrary.wiley.com/journal/15273350
***** link for year 2020: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020?event_resources_filter_form%5Bformat%5D%5B%5D=abstract&event_resources_filter_form%5Bsearch%5D=
link for year 2021: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021?event_resources_filter_form%5Bformat%5D%5B%5D=abstract&event_resources_filter_form%5Bsearch%5D=

H.1.1 Search strategies

Table 83: Search strategy table for Embase and MEDLINE via embase.com

No.	Query	Results
#1	'liver cell carcinoma'/exp	180663
#2	'liver cancer'/exp	280406
#3	((hepato* OR hepatic OR liver) NEAR/3 (carcinoma* OR cancer* OR neoplasm* OR tumour* OR tumor* OR malign*)):ab,ti	232296
#4	hepatocarcinoma*:ab,ti OR hepatoma*:ab,ti	40179
#5	'liver tumor'/mj	36005
#6	#1 OR #2 OR #3 OR #4 OR #5	368932
#7	'sorafenib'/syn OR 'bay 43 9006' OR 'bay 43-9006' OR 'bay 439006' OR 'bay43 9006' OR bay439006 OR nexavar	33663
#8	'lenvatinib'/syn OR lenvima	3864
#9	'atezolizumab'/syn OR 'mpdl 3280a' OR mpdl3280a OR 'rg 7446' OR rg7446 OR tecentriq OR tecntriq	9259
#10	'bevacizumab'/syn OR abevmy OR 'abp 215' OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR 'ask b1202' OR askb1202 OR avastin OR aybintio OR 'bat 1706' OR bat1706 OR 'bcd 021' OR bcd021 OR bevax OR 'bevz 92' OR bevz92 OR 'bi 695502' OR bi695502 OR boyounuo OR bryxta OR byvasda OR 'cbt 124' OR cbt124 OR 'chs 5217' OR chs5217 OR cizumab OR 'ct p16' OR ctp16 OR equidacent OR 'fkb 238' OR fkb238 OR 'gb 222' OR gb222 OR 'hd 204' OR hd204 OR 'hlx 04' OR hlx04 OR 'ibi 305' OR ibi305 OR 'jyv028' OR jy028 OR krabeva OR kyomarc OR lextemy OR 'ly 01008' OR ly01008 OR 'mb 02' OR mb02 OR 'milv0' OR mil60 OR mvasi OR 'myl 14020' OR 'myl 1402o' OR myl14020 OR myl1402o OR 'nsc 704865' OR nsc704865 OR onbevzi OR 'ons 1045' OR 'ons 5010' OR ons1045 OR ons5010 OR oyavas OR 'pf 06439535' OR 'pf 6439535' OR pf06439535 OR pf6439535 OR pusintin OR 'ql 1101' OR ql1101 OR 'r 435' OR r435 OR 'rg 435' OR rg435 OR 'rhumab vegf' OR 'ro 4876646' OR ro4876646 OR 'rph 001' OR rph001 OR 'sb 8' OR sb8 OR 'sct 510' OR sct510 OR 'stc 103' OR stc103 OR 'tab 008' OR tab008 OR 'tot 102' OR tot102 OR 'trs 003' OR trs003 OR 'tx 16' OR tx16 OR versavo OR zirabev OR 'zrc 113' OR zrc113	66230
#11	'nivolumab'/syn OR 'bms 936558' OR bms936558 OR 'cmab 819' OR cmab819 OR 'mdx 1106' OR mdx1106 OR 'ono 4538' OR ono4538 OR opdivo	26320
#12	'durvalumab'/syn OR imfinzi OR 'medi 4736' OR medi4736	6208
#13	'ticilimumab'/syn OR 'cp 675 206' OR 'cp 675, 206' OR 'cp 675206' OR 'cp675 206' OR 'cp675, 206' OR cp675206 OR tremelimumab	3057
#14	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	120351
#15	'clinical trial'/exp	1650490
#16	'randomized controlled trial'/de	680287
#17	'controlled clinical trial'/de	435176
#18	'multicenter study'/de	300910
#19	'phase 1 clinical trial'/de	60588
#20	'phase 2 clinical trial'/de	91442
#21	'phase 3 clinical trial'/de	56353
#22	'phase 4 clinical trial'/de	4497

#23	'randomization'/exp	92231
#24	'single blind procedure'/de	44081
#25	'double blind procedure'/de	188893
#26	'crossover procedure'/de	68297
#27	'placebo'/de	379503
#28	'randomi?ed controlled trial?':ti,ab,kw	127736
#29	rct:ti,ab,kw OR random* OR sham:ti,ab,kw OR placebo*:ti,ab,kw	2145564
#30	(random* NEAR/2 allocat*):ti,ab,kw	47905
#31	(allocated NEAR/2 random*) OR (random* NEAR/1 assign*) OR random*	1949922
#32	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	331547
#33	'prospective study'/de OR 'control group'/de	822418
#34	((control* OR equivalence OR superiority OR 'non inferiority' OR noninferiority OR pragmatic OR practical OR quasiexperimental OR 'quasi experimental' OR experimental OR phase) NEAR/3 (study OR studies OR trial* OR group*)):ab,ti	1919328
#35	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	4548623
#36	'case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de OR editorial:it OR letter:it OR note:it	5453633
#37	#35 NOT #36	4339745
#38	#6 AND #14 AND #37	6794
#39	#38 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)	157
#40	#38 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [conference abstract]/lim)	4174
#41	#39 OR #40	4237
#42	#38 NOT #41	2557
#43	#38 NOT #41 AND [31-8-2020]/sd	493
#44	#43 AND [english]/lim	484

Table 84: Search strategy for CDSR and CENTRAL via cochranelibrary.com

No.	Query	Results
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	1856
#2	((hepato* OR hepatic OR liver) AND (carcinoma* OR cancer* OR neoplasm* OR tumour* OR tumor* OR malign*)):ti,ab,kw (Word variations have been searched)	20815
#3	(hepatocarcinoma* OR hepatoma* OR "Liver tumor" OR "Liver tumour"):ti,ab,kw (Word variations have been searched)	763
#4	MeSH descriptor: [Liver Neoplasms] explode all trees	3107
#5	#1 OR #2 OR #3 OR #4	20874
#6	sorafenib OR nexavar OR lenvatinib OR lenvima OR nivolumab OR opdivo OR atezolizumab OR tecentriq OR durvalumab OR imfinzi OR tremelimumab OR bevacizumab OR Avastin (Word variations have been searched)	12153
#7	MeSH descriptor: [Sorafenib] explode all trees	507

#8	MeSH descriptor: [Nivolumab] explode all trees	512
#9	MeSH descriptor: [Bevacizumab] explode all trees	2065
#10	#6 OR #7 OR #8 OR #9	12153
#11	#5 AND #10	2242
#12	#5 AND #10 with Cochrane Library publication date Between Aug 2020 and Oct 2021, in Cochrane Reviews, Trials	345

Table 85: Search strategy for MEDLINE In Process via Pubmed.com

No.	Query	Results
1	carcinoma, hepatocellular[MeSH Terms]	92,721
2	(hepato* OR hepatic OR liver) AND (carcinoma* OR cancer* OR neoplasm* OR tumour* OR tumor* OR malign*)	448,435
3	hepatocarcinoma*[TIAB] OR hepatoma*[TIAB] OR "Liver tumo*"[TIAB]	48,326
4	#1 OR #2 OR #3	452,957
5	sorafenib OR "bay 43 9006" OR "bay 43-9006" OR "bay 439006" OR "bay43 9006" OR bay439006 OR nexavar	10,135
6	lenvatinib OR lenvima	1,221
7	atezolizumab OR "mpdl 3280a" OR mpdl3280a OR "rg 7446" OR rg7446 OR tecentriq OR tecntriq	1,932
8	bevacizumab OR abevmy OR "abp 215" OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR "ask b1202" OR askb1202 OR avastin OR aybintio OR "bat 1706" OR bat1706 OR "bcd 021" OR bcd021 OR bevax OR "bevz 92" OR bevz92 OR "bi 695502" OR bi695502 OR boyounuo OR bryxta OR byvasda OR "cbt 124" OR cbt124 OR "chs 5217" OR chs5217 OR cizumab OR "ct p16" OR ctp16 OR equidacent OR "fkb 238" OR fkb238 OR "gb 222" OR gb222 OR "hd 204" OR hd204 OR "hlx 04" OR hlx04 OR "ibi 305" OR ibi305 OR "jyv028" OR jy028 OR krabeva OR kyomarc OR lextemy OR "ly 01008" OR ly01008 OR "mb 02" OR mb02 OR "milv0" OR mil60 OR mvasi OR "myl 14020" OR "myl 1402o" OR myl14020 OR myl1402o OR "nsc 704865" OR nsc704865 OR onbevzi OR "ons 1045" OR "ons 5010" OR ons1045 OR ons5010 OR oyavas OR "pf 06439535" OR "pf 6439535" OR pf06439535 OR pf6439535 OR pusintin OR "ql 1101" OR ql1101 OR "r 435" OR r435 OR "rg 435" OR rg435 OR "rhumab vegf" OR "ro 4876646" OR ro4876646 OR "rph 001" OR rph001 OR "sb 8" OR sb8 OR "sct 510" OR sct510 OR "stc 103" OR stc103 OR "tab 008" OR tab008 OR "tot 102" OR tot102 OR "trs 003" OR trs003 OR "tx 16" OR tx16 OR versavo OR zirabev OR "zrc 113" OR zrc113	44,358
9	nivolumab OR "bms 936558" OR bms936558 OR "cmab 819" OR cmab819 OR "mdx 1106" OR mdx1106 OR "ono 4538" OR ono4538 OR opdivo	7,216
10	durvalumab OR imfinzi OR "medi 4736" OR medi4736	947
11	ticilimumab OR "cp 675 206" OR "cp 675, 206" OR "cp 675206" OR "cp675 206" OR "cp675, 206" OR cp675206 OR tremelimumab	373
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	62,556
13	"clinical trial" OR clinical trial [pt]	1,016,085
14	"randomized controlled trial" OR randomized controlled trial [pt] OR "randomised controlled trial" OR "randomized controlled trials" OR "randomised controlled trials"	775,961
15	"controlled clinical trial" OR controlled clinical trial [pt]	641,701
16	"multicenter study" OR multicenter study [pt]	313,615

17	"phase 1 clinical trial" OR 'phase 1 clinical trial'[MeSH Major Topic]	2,050
18	"phase 2 clinical trial" OR 'phase 2 clinical trial'[MeSH Major Topic]	3,408
19	"phase 3 clinical trial" OR 'phase 3 clinical trial'[MeSH Major Topic]	3,867
20	"phase 4 clinical trial" OR 'phase 4 clinical trial'[MeSH Major Topic]	393
21	randomization OR "random allocation"[MeSH Terms]	1,313,844
22	"single blind procedure" OR "Single-Blind Method"[Mesh]	30,978
23	"double blind procedure" OR "double-blind procedure" OR Double-Blind Method[Mesh]	167,547
24	"crossover procedure" OR "Cross-Over Studies"[Mesh]	51,657
25	placebo OR "Placebos"[Mesh]	246,734
26	"rct"[tiab]	27,747
27	random* AND allocat*	165,213
28	(allocated AND random*) OR (random* AND assign*) OR random*	1,500,849
29	(double [tiab] OR single [tiab] OR doubly [tiab] OR singly [tiab] OR triple[tiab] OR treble[tiab]) AND (blind [tiab] OR blinded [tiab] OR blindly [tiab] OR mask [tiab] OR masked [tiab])	201,301
30	placebo [tiab]	228,263
31	(control* OR equivalence OR superiority OR "non inferiority" OR noninferiority OR pragmatic OR practical OR quasiexperimental OR "quasi experimental" OR experimental OR phase) AND (study OR studies OR trial* OR group*)	6,143,179
32	"prospective study" OR "Prospective Studies"[Mesh]	641,342
33	controlled [tiab] AND (study [tiab] OR design [tiab] OR trial [tiab])	519,221
34	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	7,173,889
35	#4 AND #12 AND #34	3586
36	#35 AND (inprocess[sb] OR pubstatusaheadofprint)	178

H.1.2 Systematic selection of studies

Table 86: Inclusion and exclusion criteria used for assessment of studies

Category	Inclusion criteria	Exclusion criteria
Population	Patients (aged ≥18 years) with unresectable advanced or metastatic HCC receiving systemic treatment in the 1st line setting	Persons with HCC undergoing loco-regional treatment, resection, ablation, or liver transplant
Interventions	• Durvalumab + tremelimumab • Durvalumab	Studies not evaluating at least one relevant intervention/comparator
Comparators	• Sorafenib • Lenvatinib • Nivolumab • Atezolizumab + bevacizumab	Studies not evaluating at least one relevant intervention/comparator
Outcomes	• **Efficacy**: DOR, OS, PFS, TTP, tumour response	Outcomes other than listed

	• **Safety and tolerability**: Withdrawals, specific AEs, incidence of Grade 3 and 4 AEs, serious AEs, and AEs leading to discontinuation	
Study type	Randomized controlled trials‡	• Single arm trials • Non-randomized trials • Observational studies • Case reports/case series • Non-systematic reviews • Trials terminated due to clinical efficacy/safety outcomes • Post-hoc or pooled analyses of original trial data
Publication type	• Journal articles • Conference abstracts	• Notes/Editorials/Letters • Newspaper articles
Language	English	Non-English
Publication year	• August 2020 – present	-

AEs, adverse events; DCR, disease control rate; DOR, duration of response; EORTC-QLQC30, European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire; HRQoL, Health related quality of life; FACT-HEP, Functional Assessment of Cancer Therapy – Hepatobiliary, HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; TTP, time to progression
‡ The inclusion/exclusion of dose-ranging and dose escalation studies will be assessed, and their inclusion/exclusion will be documented

Figure 50: PRISMA diagram for global SLR

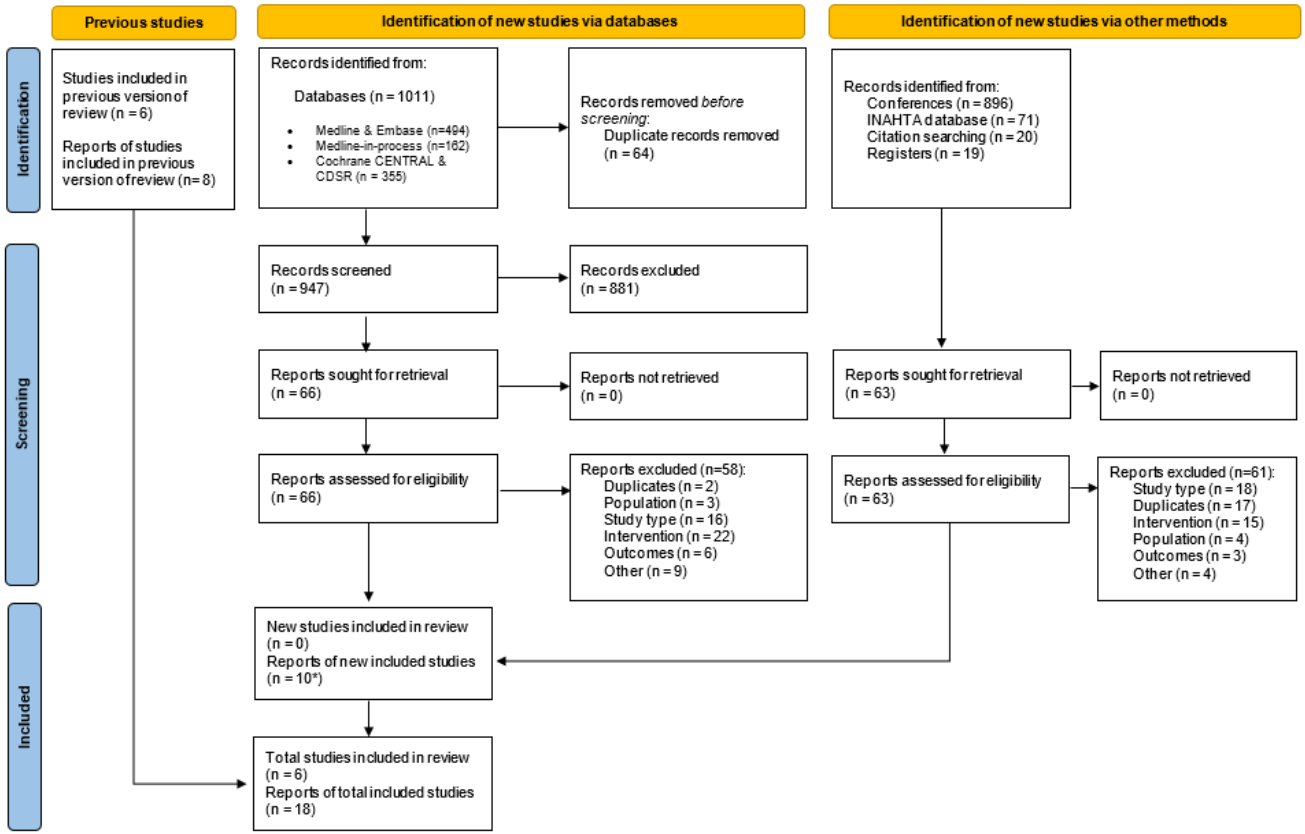


Table 87: Overview of study design for studies included in the global SLR

Study/ID	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome	Local SLR adaption
REFLECT **Kudo (2018)**	Randomized, open label	Advanced HCC	Lenvatinib (478) vs sorafenib (476)	OS median duration of follow-up 27·7 months in the lenvatinib group and 27·2 months in the sorafenib group	progression-free survival, time to progression, and objective response rate	Excluded due to irrelevant comparison
CheckMate 459 **Yau (2019)**	Randomized, open label	Advanced HCC	Nivolumab vs sorafenib			Excluded due to irrelevant comparison
IMbrave150 **Finn (2020)**	Randomized, open label	Locally advanced or metastatic and/or unresectable HCC	Atezolizumab + bevacizumab vs sorafenib			Included for local assessment
SHARP **(Llovet 2008)**	Randomized, double blind	Advanced HCC	Sorafenib vs placebo			Excluded due to irrelevant comparison
Sorafenib AP **Cheng (2009)**	Randomized, double blind	Advanced HCC	Sorafenib vs placebo			Excluded due to irrelevant comparison

Study/ID	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcom e and follow-up period	Secondary outcome	Local SLR adaption
Ji (2014)	Randomize d, open label	Liver function impaired advanced HCC	Sorafenib vs soc			
HIMALAY A	Randomize d, open label	Advanced HCC	Druvalumab/STRI DE vs sorafenib			Included for local assessmen t

H.1.3 Excluded full text references

Table 88: Excluded reference in full-text review in global SLR

Author	Title	Reason for exclusion
Zhang, H.-//-Li, J.-//-Zeng, W.	Frequent fragility of randomized controlled trials for HCC treatment	Not study type of interest
Xie, Y.-//-Tian, H.-//-Xiang, B.-//-Zhang, Y.-//-Liu, J.-//-Cai, Z.-//-Xiang, H.	Transarterial chemoembolization plus sorafenib versus sorafenib for intermediate-advanced hepatocellular carcinoma: A meta-analysis comparing clinical outcomes	Not study type of interest
Vogel, A.-//-Rimassa, L.-//-Sun, H. C.-//-Abou-Alfa, G. K.-//-El-Khoueiry, A.-//-Pinato, D. J.-//-Sanchez Alvarez, J.-//-Daigl, M.-//-Orfanos, P.-//-Leibfried, M.-//-Blanchet Zumofen, M. H.-//-Gaillard, V. E.-//-Merle, P.	Comparative efficacy of atezolizumab plus bevacizumab and other treatment options for patients with unresectable hepatocellular carcinoma: A network meta-analysis	Not study type of interest
Vogel, A.-//-Qin, S.-//-Kudo, M.-//-Su, Y.-//-Hudgens, S.-//-Yamashita, T.-//-Yoon, J. H.-//-Fartoux, L.-//-Simon, K.-//-López, C.-//-et al.,	Lenvatinib versus sorafenib for first-line treatment of unresectable hepatocellular carcinoma: patient-reported outcomes from a randomised, open-label, non-inferiority, phase 3 trial	Not including outcomes of interest
Shemesh, C.-//-Chan, P.-//-Shao, H.-//-Xu, D.-//-Combs, D.-//-Vadhavkar, S.-//-Bruno, R.-//-Wu, B.	Atezolizumab and bevacizumab in patients with unresectable hepatocellular carcinoma: assessment of hepatic impairment and region	Not including outcomes of interest

Ryoo, B. Y.-//-Cheng, A. L.-//-Ren, Z.-//-Kim, T. Y.-//-Pan, H.-//-Rau, K. M.-//-Choi, H. J.-//-Park, J. W.-//-Kim, J. H.-//-Yen, C. J.-//-et al.,	Randomised Phase 1b/2 trial of tepotinib vs sorafenib in Asian patients with advanced hepatocellular carcinoma with MET overexpression	Not intervention/comparator of interest
Rossi, A. J.-//-Khan, T. M.-//-Saif, A.-//-Marron, T. U.-//-Hernandez, J. M.	Treatment of Hepatocellular Carcinoma with Neoadjuvant Nivolumab Alone Versus in Combination with a CCR2/5 Inhibitor or an Anti-IL-8 Antibody	Not population of interest
Ricke, J.-//-Schinner, R.-//-Seidensticker, M.-//-Gasbarrini, A.-//-van Delden, O. M.-//-Amthauer, H.-//-Peynircioglu, B.-//-Bargellini, I.-//-Iezzi, R.-//-De Toni, E. N.-//-Malfertheiner, P.-//-Pech, M.-//-Sangro, B.	Liver function after combined selective internal radiation therapy or sorafenib monotherapy in advanced hepatocellular carcinoma	Not intervention/comparator of interest
Ren, Z.-//-Xu, J.-//-Bai, Y.-//-Xu, A.-//-Cang, S.-//-Du, C.-//-Li, Q.-//-Lu, Y.-//-Chen, Y.-//-Guo, Y.-//-et al.,	Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study	Not intervention/comparator of interest
Regmi, P.-//-Hu, H. J.-//-Lv, T. R.-//-Paudyal, A.-//-Sah, R. B.-//-Ma, W. J.-//-Jin, Y. W.-//-Li, F. Y.	Efficacy and safety of sorafenib plus hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma	Not study type of interest
Qin, S.-//-Bi, F.-//-Gu, S.-//-Bai, Y.-//-Chen, Z.-//-Wang, Z.-//-Ying, J.-//-Lu, Y.-//-Meng, Z.-//-Pan, H.-//-et al.,	Donafenib Versus Sorafenib in First-Line Treatment of Unresectable or Metastatic Hepatocellular Carcinoma: a Randomized, Open-Label, Parallel-Controlled Phase II-III Trial	Not intervention/comparator of interest
Pollock, R. F.-//-Brennan, V. K.-//-Shergill, S.-//-Colaone, F.	A systematic literature review and network meta-analysis of first-line treatments for unresectable hepatocellular carcinoma based on data from randomized controlled trials	Not study type of interest
Park, R.-//-da Silva, L. L.-//-Nissaisorakarn, V.-//-Riano, I.-//-Williamson, S.-//-Sun, W.-//-Saeed, A.	Comparison of efficacy of systemic therapies in advanced hepatocellular carcinoma: Updated systematic ~~review~~ and frequentist network meta-analysis of randomized controlled trials	Not study type of interest
Pan, Y.-//-Wang, R.-//-Hu, D.-//-Xie, W.-//-Fu, Y.-//-Hou, J.-//-Xu, L.-//-Zhang, Y.-//-Chen, M.-//-Zhou, Z.	Comparative safety and efficacy of molecular-targeted drugs, immune checkpoint inhibitors, hepatic arterial infusion chemotherapy and their combinations in advanced hepatocellular carcinoma: findings from advances in landmark trials	Not study type of interest

Oranratnachai, S.-//-Rattanasiri, S.-//-Pooprasert, A.-//-Tansawet, A.-//-Reungwetwattana, T.-//-Attia, J.-//-Thakkinstian, A.	Efficacy of First Line Systemic Chemotherapy and Multikinase Inhibitors in Advanced Hepatocellular Carcinoma: A Systematic ~~Review~~ and Network Meta-Analysis	Not study type of interest
Nct	A Study of Camrelizumab Combined With Rivoceranib Mesylate Versus Investigator's Choice of Regimen in Treatment of Patients With Advanced Hepatocellular Carcinoma (HCC)	Other (No results posted)
Nct	A Study to Compare the Effectiveness and Safety of IBI310 Combined With Sintilimab Versus Sorafenib in the First-line Treatment of Advanced HCC	Other (No results posted)
Nct	Radiotherapy Plus Toripalimab vs. Sorafenib in Advanced Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis	Other (No results posted)
Nct	Evaluate the Safety and Efficacy of Toripalimab Combined With Bevacizumab Versus Sorafenib Therapy for HCC	Other (No results posted)
Kelley, R. K.-//-Sangro, B.-//-Harris, W.-//-Ikeda, M.-//-Okusaka, T.-//-Kang, Y. K.-//-Qin, S.-//-Tai, Dw- M.-//-Lim, H. Y.-//-Yau, T.-//-et al.,	Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: randomized Expansion of a Phase I/II Study	Not population of interest
Haruna, Y.-//-Yakushijin, T.-//-Kawamoto, S.	Efficacy and safety of sorafenib plus vitamin K treatment for hepatocellular carcinoma: A phase II, randomized study	Not intervention/comparator of interest
Haber, P. K.-//-Puigvehí, M.-//-Castet, F.-//-Lourdusamy, V.-//-Montal, R.-//-Tabrizian, P.-//-Buckstein, M.-//-Kim, E.-//-Villanueva, A.-//-Schwartz, M.-//-Llovet, J. M.	Evidence-Based Management of Hepatocellular Carcinoma: Systematic Review and Meta-analysis of Randomized Controlled Trials (2002-2020)	Not study type of interest
Galle, P. R.-//-Finn, R. S.-//-Qin, S.-//-Ikeda, M.-//-Zhu, A. X.-//-Kim, T. Y.-//-Kudo, M.-//-Breder, V.-//-Merle, P.-//-Kaseb, A.-//-et al.,	Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial	Not including outcomes of interest
Finn, R. S.-//-Qin, S.-//-Ikeda, M.-//-Galle, P. R.-//-Ducreux, M.-//-Kim, T. Y.-//-Lim, H. Y.-//-Kudo, M.-//-Breder, V. V.-//-Merle, P.-//-et al.,	IMbrave150: updated overallsurvival (OS) data from a global, randomized, open-label phase IIIstudy of atezolizumab (Atezo) +bevacizumab (Bev)	Duplicates

	versussorafenib (Sor) in patients (PTS)with unresectable hepatocellularcarcinoma (HCC)	
Facciorusso, A.-//-Tartaglia, N.-//-Villani, R.-//-Serviddio, G.-//-Ramai, D.-//-Mohan, B. P.-//-Chandan, S.-//-El Aziz, M. A. A.-//-Evangelista, J.-//-Cotsoglou, C.-//-et al.,	Lenvatinib versus sorafenib as first-line therapy of advanced hepatocellular carcinoma: a systematic review and meta-analysis	Not study type of interest
Euctr, P. L.	A clinical study to compare Toripalimab (JS001) combined with Lenvatinib versus placebo combined with Lenvatinib as the 1st-line therapy for advanced hepatocellular carcinoma (HCC)	Other (No results posted)
Euctr, C. Z.	A Study of Relatlimab in Combination with Nivolumab in Participants with Advanced Liver Cancer who have never been been Treated with Immuno-oncology Therapy after Prior Treatment with Tyrosine Kinase Inhibitors	Other (No results posted)
El Shorbagy, S.-//-abuTaleb, F.-//-Labib, H. A.-//-Ebian, H.-//-Harb, O. A.-//-Mohammed, M. S.-//-Rashied, H. A.-//-Elbana, K. A.-//-Haggag, R.	Prognostic Significance of VEGF and HIF-1 α in Hepatocellular Carcinoma Patients Receiving Sorafenib Versus Metformin Sorafenib Combination	Not intervention/comparator of interest
Blanc, J. F.-//-Khemissa, F.-//-Bronowicki, J. P.-//-Monterymard, C.-//-Perarnau, J. M.-//-Bourgeois, V.-//-Obled, S.-//-Abdelghani, M. B.-//-Mabile-Archambeaud, I.-//-Faroux, R.-//-et al.,	Phase 2 trial comparing sorafenib, pravastatin, their combination or supportive care in HCC with Child–Pugh B cirrhosis	Not intervention/comparator of interest
Bi, F.-//-Qin, S.-//-Gu, S.-//-Bai, Y.-//-Chen, Z.-//-Wang, Z.-//-Ying, J.-//-Lu, Y.-//-Meng, Z.-//-Pan, H.-//-et al.,	An exploratory subgroup analysis of a phase II/III trial of donafenib versus sorafenib in the first-line treatment of advanced hepatocellular carcinoma	Not intervention/comparator of interest
Bi, F.-//-Qin, S.-//-Xu, J.-//-Du, C.-//-Fan, Q.-//-Zhang, L.-//-Tao, M.-//-Jiang, D.-//-Wang, S.-//-Chen, Y.-//-et al.,	P-89 The correlation between adverse events and survival benefits of donafenib in the first-line treatment of advanced hepatocellular carcinoma	Not intervention/comparator of interest
	Correction to Lancet Oncol 2021; 22: 977–90 (The Lancet Oncology (2021) 22(7) (977–990), (S1470204521002527), (10.1016/S1470-2045(21)00252-7))	Not study type of interest
Wang, X.-//-Zheng, K.-//-Cao, G.-//-Xu, L.-//-Zhu, X.-//-Chen, H.-//-Fu, S.-//-Wu, D.-//-Yang, R.-//-Wang, K.-//-et al.,	Sorafenib plus hepatic arterial infusion chemotherapy versus sorafenib alone for advanced hepatocellular carcinoma with major portal vein tumor	Not intervention/comparator of interest

	thrombosis (Vp3/4): a randomized phase II trial	
Schütte, K.-//-Schinner, R.-//-Fabritius, M. P.-//-Möller, M.-//-Kuhl, C.-//-Iezzi, R.-//-Öcal, O.-//-Pech, M.-//-Peynircioglu, B.-//-Seidensticker, M.-//-Sharma, R.-//-Palmer, D.-//-Bronowicki, J. P.-//-Reimer, P.-//-Malfertheiner, P.-//-Ricke, J.	Impact of Extrahepatic Metastases on Overall Survival in Patients with Advanced Liver Dominant Hepatocellular Carcinoma: A Subanalysis of the SORAMIC Trial	Not intervention/comparator of interest
Riano, I.-//-Martin, L.-//-Varela, M.-//-Serrano, T.-//-Nunez, O.-//-Minguez, B.-//-Rodrigues, P. M.-//-Perugorria, M. J.-//-Banales, J. M.-//-Arenas, J. I.	Efficacy and safety of the combination of pravastatin and sorafenib for the treatment of advanced hepatocellular carcinoma (Estahep clinical trial)	Not intervention/comparator of interest
Ren, Z.-//-Fan, J.-//-Xu, J.-//-Bai, Y.-//-Xu, A.-//-Cang, S.-//-Du, C.-//-Liu, B.-//-Li, Q.-//-Lu, Y.-//-et al.,	LBA2 Sintilimab plus bevacizumab biosimilar vs sorafenib as first-line treatment for advanced hepatocellular carcinoma (ORIENT-32)2	Not intervention/comparator of interest
Qin, S.-//-Bi, F.-//-Xu, J.-//-Du, C.-//-Fan, Q.-//-Zhang, L.-//-Tao, M.-//-Jiang, D.-//-Wang, S.-//-Chen, Y.-//-et al.,	P-86 Comparison of the pharmacokinetics of donafenib and sorafenib in patients with advanced hepatocellular carcinoma: an open-label, randomized, parallel-controlled, multicentre phase II/III trial	Not including outcomes of interest
Qin, S.-//-Bi, F.-//-Cui, C.-//-Zhu, B.-//-Wu, J.-//-Xin, X.-//-Wang, J.-//-Shan, J.-//-Chen, J.-//-Zheng, Z.-//-et al.,	Comparison of donafenib and sorafenib as advanced hepatocellular carcinoma first-line treatments: subgroup analysis of an open-label, randomized, parallel-controlled, multicentre phase II/III trial	Not intervention/comparator of interest
Nct	Phase III Study of Toripalimab（ JS001） Combined With Lenvatinib for Advanced HCC	Other (No results posted)
Nct	SCT-I10A Plus SCT510 Versus Sorafenib as First-Line Therapy for Advanced Hepatocellular Carcinoma	Other (No results posted)
Kobayashi, S.-//-Kondo, M.-//-Morimoto, M.-//-Hidaka, H.-//-Nakazawa, T.-//-Aikata, H.-//-Hatanaka, T.-//-Takizawa, D.-//-Matsunaga, K.-//-Okuse, C.-//-et al.,	SO-6 The influence of liver function on the outcomes of phase II trial of sorafenib vs. hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma	Not intervention/comparator of interest
Juloori, A.-//-Liao, C. Y.-//-Lemons, J. M.-//-Singh, A. K.-//-Iyer, R.-//-Robbins, J. R.-//-George, B.-//-Fung, J.-//-Pillai, A.-//-Arif, F.-//-et al.,	Phase I Study of Stereotactic Body Radiotherapy followed by Ipilimumab with Nivolumab vs. Nivolumab alone in Unresectable Hepatocellular Carcinoma	Not including outcomes of interest
Julien, K.-//-Leung, H. T.-//-Fuertes, C.-//-Mori, M.-//-Wang, M. J.-//-Teo, J.-//-Weiss, L.-//-Hamilton, S.-//-DiFebo, H.-	Nivolumab in Advanced Hepatocellular Carcinoma: Safety Profile and Select Treatment-	Not study type of interest

//-Noh, Y. J.-//-Galway, A.-//-Koh, J.-//-Brutcher, E.-//-Zhao, H.-//-Shen, Y.-//-Tschaika, M.-//-To, Y. Y.	Related Adverse Events From the CheckMate 040 Study	
Jia, F.-//-Ren, Z.-//-Xu, J.-//-Shao, G.-//-Dai, G.-//-Liu, B.-//-Xu, A.-//-Yang, Y.-//-Wang, Y.-//-Zhou, H.-//-et al.,	Sintilimab plus IBI305 as first-line treatment for advanced hepatocellular carcinoma	Not intervention/comparator of interest
Gordan, J. D.-//-Kennedy, E. B.-//-Abou-Alfa, G. K.-//-Beg, M. S.-//-Brower, S. T.-//-Gade, T. P.-//-Goff, L.-//-Gupta, S.-//-Guy, J.-//-Harris, W. P.-//-et al.,	Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline	Not study type of interest
Euctr, B. E.	A Study to Evaluate SHR-1210 in Combination With Apatinib (Rivoceranib) as First-Line Therapy in Patients With Advanced HCC	Other (No results posted)
Ding, W.-//-Tan, Y.-//-Qian, Y.-//-Xue, W.-//-Wang, Y.-//-Jiang, P.-//-Xu, X.	First-line targ veted therapies of advanced hepatocellular carcinoma: A Bayesian network analysis of randomized controlled trials	Not study type of interest
Chen, J.-//-Wang, J.-//-Pan, Y.-//-Chen, J.-//-Tuo-Heti, Y. M. J.-//-Wang, X.-//-Fu, Y.-//-Zhang, Y.-//-Xu, L.-//-Chen, M.-//-et al.,	Preventive effect of celecoxib in sorafenib-related hand-foot syndrome in hepatocellular carcinoma patients, a single-center, open-label, randomized, controlled clinical phase III trial	Not intervention/comparator of interest
Casadei-Gardini, A.-//-Marisi, G.-//-Dadduzio, V.-//-Gramantieri, L.-//-Faloppi, L.-//-Ulivi, P.-//-Foschi, F. G.-//-Tamburini, E.-//-Vivaldi, C.-//-Rizzato, M. D.-//-Ielasi, L.-//-Canale, M.-//-Conti, F.-//-Rudnas, B.-//-Fornaro, L.-//-Silvestris, N.-//-Silletta, M.-//-Cardellino, G. G.-//-Lonardi, S.-//-Fornari, F.-//-Orsi, G.-//-Rovesti, G.-//-Zagonel, V.-//-Cascinu, S.-//-Scartozzi, M.	Association of NOS3 and ANGPT2 gene polymorphisms with survival in patients with hepatocellular carcinoma receiving sorafenib: Results of the multicenter prospective INNOVATE study	Not study type of interest
Bi, F.-//-Qin, S.-//-Gu, S.-//-Bai, Y.-//-Chen, Z.-//-Wang, Z.-//-Ying, J.-//-Lu, Y.-//-Meng, Z.-//-Pan, H.-//-et al.,	Donafenib versus sorafenib as first-line therapy in advanced hepatocellular carcinoma: an open-label, randomized, multicenter phase II/III trial	Not intervention/comparator of interest
	Effect of pembrolizumab (pembro) on hepatitis B and hepatitis C viral load and aminotransferase levels in patients with advanced hepatocellular carcinoma in keynote-224 and KEYNOTE-240	Not including outcomes of interest
Guo, T.-//-Liu, P.-//-Yang, J.-//-Wu, P.-//-Chen, B.-//-Liu, Z.-//-Li, Z.	Evaluation of targeted agents for advanced and unresectable hepatocellular carcinoma: A network meta-analysis	Not study type of interest

Kudo, M.-//-Ueshima, K.-//-Yokosuka, O.-//-Ogasawara, S.-//-Obi, S.-//-Izumi, N.-//-Aikata, H.-//-Nagano, H.-//-Hatano, E.-//-Sasaki, Y.-//-Hino, K.-//-Kumada, T.-//-Yamamoto, K.-//-Imai, Y.-//-Iwadou, S.-//-Ogawa, C.-//-Okusaka, T.-//-Kanai, F.-//-Akazawa, K.-//-Yoshimura, K. I.-//-Johnson, P.-//-Arai, Y.	Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial	Not intervention/comparator of interest
Kudo, M.-//-Finn, R. S.-//-Qin, S.-//-Han, K. H.-//-Ikeda, K.-//-Piscaglia, F.-//-Baron, A.-//-Park, J. W.-//-Han, G.-//-Jassem, J.-//-Blanc, J. F.-//-Vogel, A.-//-Komov, D.-//-Evans, T. R. J.-//-Lopez, C.-//-Dutcus, C.-//-Guo, M.-//-Saito, K.-//-Kraljevic, S.-//-Tamai, T.-//-Ren, M.-//-Cheng, A. L.	Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial	Duplicates
B.-Y. Ryoo//Z. Ren T.//Y. Kim H. Pan K.//M. Rau H.J. Choi J.//W. Park J.H. Kim C.//J. Yen B.//H. Kim//D. Zhou//J. Straub//C. Zhao//S. Qin	Phase II trial of tepotinib vs sorafenib in Asian patients (pts) with advanced hepatocellular carcinoma (HCC)	Not intervention/comparator of interest
Ikeda, M.-//-Shimizu, S.-//-Sato, T.-//-Morimoto, M.-//-Kojima, Y.-//-Inaba, Y.-//-Hagihara, A.-//-Kudo, M.-//-Nakamori, S.-//-Kaneko, S.-//-Sugimoto, R.-//-Tahara, T.-//-Ohmura, T.-//-Yasui, K.-//-Sato, K.-//-Ishii, H.-//-Furuse, J.-//-Okusaka, T.	Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: Randomized phase II trial	Not intervention/comparator of interest
Cheng, A. L.-//-Thongprasert, S.-//-Lim, H. Y.-//-Sukeepaisarnjaroen, W.-//-Yang, T. S.-//-Wu, C. C.-//-Chao, Y.-//-Chan, S. L.-//-Kudo, M.-//-Ikeda, M.-//-Kang, Y. K.-//-Pan, H.-//-Numata, K.-//-Han, G.-//-Balsara, B.-//-Zhang, Y.-//-Rodriguez, A. M.-//-Zhang, Y.-//-Wang, Y.-//-Poon, R. T. P.	Randomized, open-label phase 2 study comparing frontline dovitinib versus sorafenib in patients with advanced hepatocellular carcinoma	Not intervention/comparator of interest
Abdel-Rahman, O.-//-Abdel-Wahab, M.-//-Shaker, M.-//-Abdel-Wahab, S.-//-Elbassiony, M.-//-Ellithy, M.	Sorafenib versus capecitabine in the management of advanced hepatocellular carcinoma	Not population of interest

Table 89: Excluded publications in local adaption of SLR

References Title	Reason for exclusion
Finn RS. IMbrave150: updated overall survival (OS) data from a global, randomized, open-label phase IIIstudy of atezolizumab (Atezo) +bevacizumab (Bev) versussorafenib (Sor) in patients (PTS)with unresectable hepatocellularcarcinoma (HCC). J Clin Oncol. 2021;39(3 SUPPL). doi:10.1200/JCO.2021.39.3_suppl.267.	Poster
Salem R. Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: Results from the IMbrave150 trial. Cancer Med. 2021;10(16):5437-5447. doi:10.1002/cam4.4090.	Not relevant endpoint

Qin S. Atezolizumab plus Bevacizumab versus Sorafenib in the Chinese Subpopulation with Unresectable Hepatocellular Carcinoma: Phase 3 Randomized, Open-Label IMbrave150 Study. Liver Cancer. 2021;10(4):296-308. doi:10.1159/000513486.	Not relevant subgroup
Finn RS et al. IMbrave150: updated efficacy and safety by risk status in patients (pts) receiving atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment for unresectable hepatocellular carcinoma (HCC). Cancer Res. 2021;81(13 SUPPL). doi:10.1158/1538-7445.AM2021-CT009.	Not relevant subgroup
Andrew X Zhu RF. IMbrave150: EXPLORATORY EFFICACY AND SAFETY OF ATEZOLIZUMAB (ATEZO) + BEVACIZUMAB (BEV) VS SORAFENIB (SOR) IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) WITH NON-VIRAL ETIOLOGY IN A GLOBAL PHASE III STUDY. Presented at: 2021.	Poster
Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet. 2018;391(10126):1163-1173.	Not relevant comparator
Rimini M, Lenvatinib versus Sorafenib as first-line treatment in hepatocellular carcinoma: A multi-institutional matched case-control study. Hepatol Res. 2021 Dec;51(12):1229-1241. doi: 10.1111/hepr.13718. Epub 2021 Oct 21. PMID: 34591334.	Not relevant comparator
Vogel A, Lenvatinib versus sorafenib for first-line treatment of unresectable hepatocellular carcinoma: patient-reported outcomes from a randomised, open-label, non-inferiority, phase 3 trial. LANCET G&H. VOLUME 6, ISSUE 8, P649-658, AUGUST	Not relevant comparator
Rimini M, Shimose S, Lonardi S, Tada T, Masi G, Iwamoto H, et al. Lenvatinib versus Sorafenib as first-line treatment in hepatocellular carcinoma: a multi-institutional matched case-control study. Hepatol Res. 2021; 51(12): 1229–41. https://doi.org/10.1111/hepr.13718	Not relevant comparator
Yau T, Park J, Finn R, et al. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol. 2019;30: v874-v875	Not relevant comparator
Yau T,. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022	Not relevant comparator
Sangro B. LBA-3 CheckMate 459: Long-term (minimum follow-up 33.6 months) survival outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. Annals of Onc. VOLUME 31, SUPPLEMENT 3, S241-S242, JULY 2020	Not relevant comparator
Ji Y xin, Zhang Z fa, Lan K tao, et al. Sorafenib in liver function impaired advanced hepatocellular carcinoma. Chin Med Sci J. 2014;29(1):7-14.	Not relevant comparator
Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-390.	Not relevant comparator
Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. Expert Rev Anticancer Ther. 2009 Jun;9(6):739-45. doi: 10.1586/era.09.41. PMID: 19496710.	Not relevant comparator
Clinicaltrials.gov: An Investigational Immuno-therapy Study of Nivolumab Compared to Sorafenib as a First Treatment in Patients With Advanced Hepatocellular Carcinoma	Not relevant comparator

Li D, Toh HC, Merle P, et al. Atezolizumab plus Bevacizumab versus Sorafenib for Unresectable Hepatocellular Carcinoma: Results from Older Adults Enrolled in the IMbrave150 Randomized Clinical Trial. *Liver Cancer*. 2022;11(6):558-571.	Not relevant subgroup

H.1.4 Quality assessment

Risk of bias assessments were conducted on the six trials included in the review and the HIMALAYA trial. The overall risk of bias across included studies was either low or unclear with a few studies with high-risk of bias in blinding and imbalance withdrawals (Figure 51).

Table 90 presents the quality assessment per individual study. An adequate method of randomization was reported in six studies, while the remaining study did not report the methodology for randomization sequence generation. Allocation concealment was adequately reported in six studies and was unclear in remaining 1 study.

Baseline characteristics were reported to be well balanced between treatment groups in six studies. Remaining one study had a few baseline characteristics that differed between groups. Three studies were blinded in design and four studies were open label. The risk of bias was high in a trial which was open label in design. It was unclear in five out of six studies if the authors reported more outcomes than they reported.

All studies presented with an unclear risk of bias for statistical analysis. In these trials, no methods for imputing missing data were reported. No conflicts of interest were found.

Figure 51: Risk of bias summary of included studies

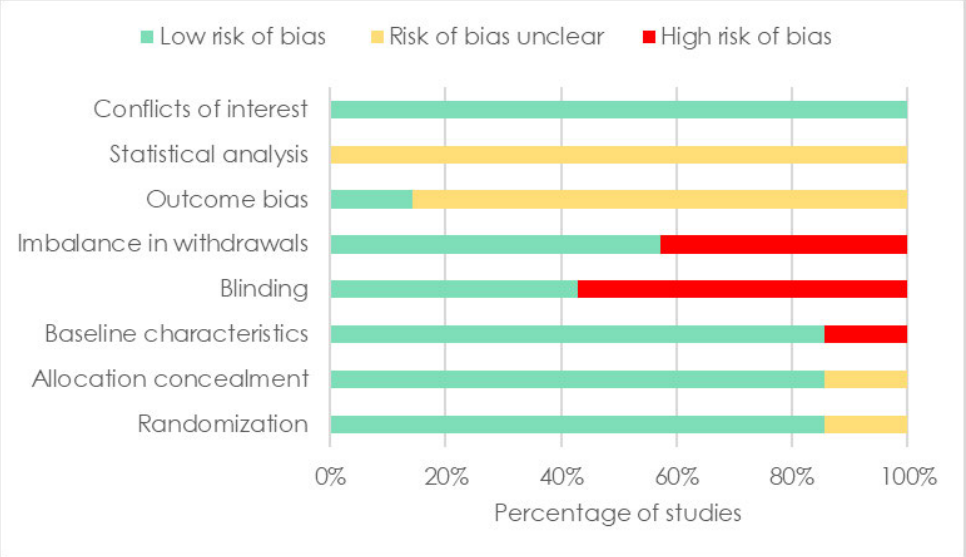


Table 90: Critical appraisal

Study name	Was the randomisation method adequate?	Was the allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Also consider whether the authors of the study publication declared any conflicts of interest.
Finn, 2020b (IMbrave150)	Low risk	Low risk	Low risk	High risk	High risk[a]	Unclear	Unclear	Low risk
Kudo, 2018 (REFLECT)	Low risk	Low risk	High risk[b]	High risk	Low risk	Unclear	Unclear	Low risk
Yau, 2019 (CheckMate 459)	Low risk	Low risk	Low risk	High risk	High risk	Low risk[c]	Unclear	Low risk
Cheng, 2009 (Sorafenib AP)	Low risk	Low risk	Low risk	Low risk	High risk[d]	Unclear	Unclear	Low risk
Ji, 2014 (NR)	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Llovet, 2008 (SHARP)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
AstraZeneca (HIMALAYA)	Low risk	Low risk	Low risk	High risk	Low risk	Unclear	Unclear	Low risk

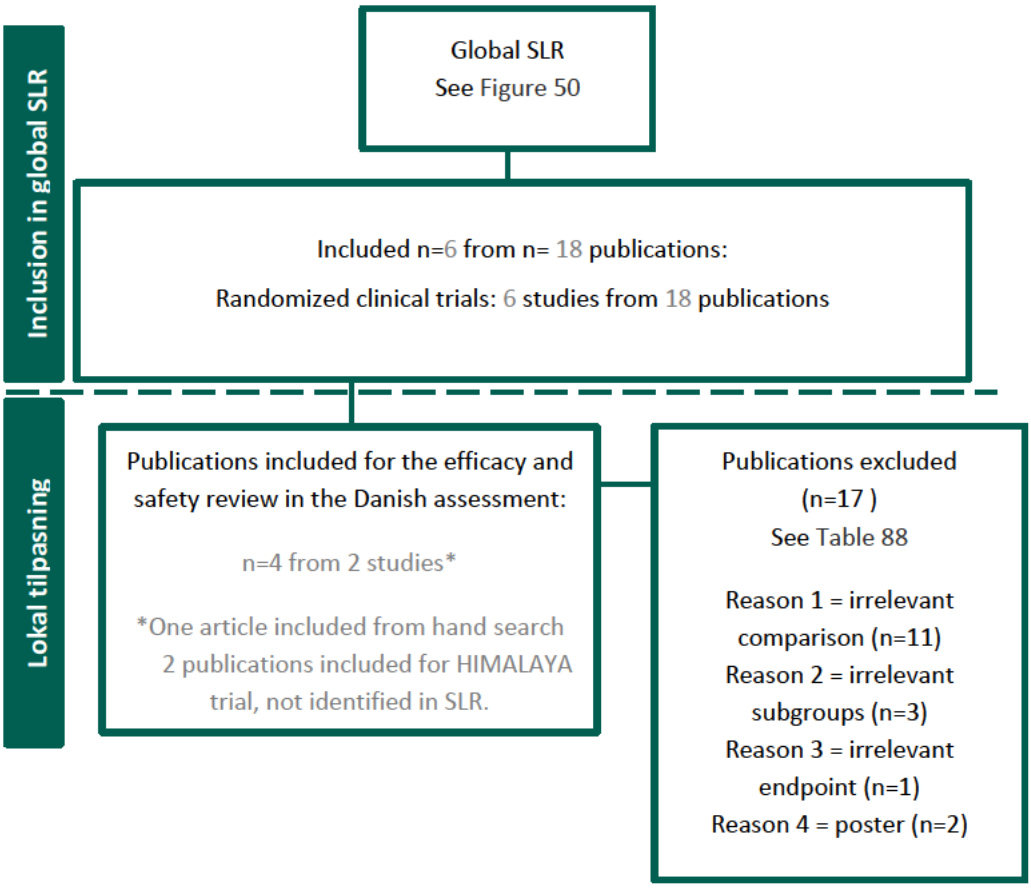
Abbreviations: AE, adverse events; RCT, randomized controlled trial.
Adapted from the Centre for Reviews and Dissemination guidelines
a Of patients assigned to atezolizumab + bevacizumab (n = 336) and sorafenib (n = 165), the sorafenib group had a higher proportion of patients who withdrew consent (12% versus 4%).
b Lenvatinib and sorafenib groups differed in proportions with hepatitis B (19% versus 26%) and α-fetoprotein < 200 ng/mL (53% versus 60%).
c The protocol is available at the trial registry entry, and all outcomes measured appear to have been reported.
d Of patients assigned to sorafenib (n = 149) and placebo (n = 75), the sorafenib group experienced a higher proportion of patients who discontinued due to AEs (15% versus 9%) and a higher proportion of deaths (8% versus 3%).

Local adaption of SLR

For this Danish assessment, the relevant comparison is between STRIDE and Atezo-bev, requiring a further local adaption of the SLR. 15 publications from 4 studies were excluded in this local adaption; refer to Figure 52 for more information. The included publications are from the HIMALAYA study and the IMbrave150 study. A hand search was conducted to include data from the OS update of IMbrave150 **(1)**. This data was included in the MAIC analysis on OS

Refer to Table 9 for the list of included literature for the assessment of efficacy and safety.

Figure 52: Local SLR adaption



H.1.5 Unpublished data

N.A.

Appendix I. Literature searches for health-related quality of life

N/A as it is a cost-minimization analysis. No SLR was needed.

I.1 Health-related quality-of-life

Table 91: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	NA	NA	dd.mm.yyyy
Medline	NA	NA	dd.mm.yyyy
Specific health economics databases[1]	NA	NA	dd.mm.yyyy

Table 92: Other Sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	dd.mm.yyyy
NA	NA	NA	dd.mm.yyyy

Table 93: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	dd.mm.yyyy
NA	NA	NA	NA	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

I.1.1 Search strategies

Table 94: Search strategy

No.	Query	Results
#1		N.A.
#2		N.A.

I.1.2 Quality assessment and generalizability of estimates

N.A.

I.1.3 Unpublished data

N.A.

Appendix J. Literature searches for input to the health economic model

NA. No literature review was needed.

J.1 External literature for input to the health economic model

N.A.

Appendix K. Additional input for health economic model

Additional input for subsequent treatments for alternative analysis.

Table 95: Medicine costs of subsequent treatments – from Himalaya trial

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment [days]
Atezolizumab	60 mg/ml	20 ml (vial)	28 952.64 kr	100%*	135.2
Nivolumab	10 mg/ml	4 ml (vial)	3 431.27 kr	100%*	206.3
	10 mg/ml;	10 ml (vial)	8 325.80 kr	100%*	
	10 mg/ml	24 ml (vial)	20 457.13 kr	100%*	
Pembrolizumab	25 mg/ml	4 ml (vial)	21 573.58 kr	100%*	282.9
Capecitabine	150 mg	60 (tablet)	634.00 kr	100%*	93.0
	500 mg	120 (tablet)	565.50 kr	100%*	
Fluorouracil	50 mg/ml	100 ml (vial)	300.00 kr	100%*	139.4

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment [days]
Oxaliplatin	5 mg/ml	10 ml (vial)	41.18 kr	100%*	112.1
Cabozantinib	20 mg	84 (tablet)	40 251.25 kr	100%*	183.5
	40 mg	30 (tablet)	49 400.00 kr	100%*	
	60 mg	30 (tablet)	49 400.00 kr	100%*	
Lenvatinib	10.7 mg	30 x 4 mg (tablet)	11 669.47 kr	100%*	312.1
Regorafenib	40 mg	84 (tablet)	19 218.06 kr	100%*	167.8
Sorafenib	200 mg	112 (tablet)	17 438.48 kr	100%*	242.6
Bevacizumab	25 mg/ml	4 ml (vial)	1 895.27 kr	100%*	154.7
	25 mg/ml	16 ml (vial)	6 986.84 kr	100%*	
Ramucirumab	10 mg/ml	10 ml (vial)	3 809.56 kr	100%*	124.0
	10 mg/ml	50 ml (vial)	18 545.33 kr	100%*	

*assumption

Table 96: Distribution of subsequent treatment in HIMALAYA trial

Anticancer therapy	Subsequent treatment after STRIDE	
Immunotherapy	Atezolizumab	2.98%
	Nivolumab	2.48%
	Pembrolizumab	0.00%
Cytotoxic chemotherapy	Capecitabine	3.27%
	Fluorouracil	5.45%
	Oxaliplatin	2.18%
Targeted therapy	Cabozantinib	8.89%
	Lenvatinib	20.38%
	Regorafenib	10.74%
	Sorafenib	38.90%
Antiangiogenic therapy	Bevacizumab	2.18%
	Ramucirumab	2.55%

Table 97: Subsequent treatment costs

Mean time on treatment (days)	Drug cost per admin	Admin cost per admin	Dose schedule	Total admin cost
135.2	28 952.64 kr	1 947 kr	Q3W. *Assumed equal to primary treatment*	12 534.97 kr

206.3	20 457.12 kr	1 947 kr	240 mg every 2 weeks	28 690.44 kr
282.9	43 147.16 kr	1 947 kr	200 mg every 3 weeks	26 228.87 kr
93	21.68 kr	0 kr	1250 mg/m^2, twice daily. 14 days, followed by a 7-day rest period	0.00 kr
139.4	300.00 kr	1 947 kr	15 mg/kg, once a week	38 773.11 kr

112.1	4 982.78 kr	1 947 kr	Q2W	15 589.91 kr
183.5	1 646.67 kr	0 kr	60 mg once daily	0.00 kr
312.1	1 040.53 kr	0 kr	Once daily. *Assumed equal to primary treatment*	0.00 kr
167.8	915.15 kr	0 kr	160 mg once daily, for 21 of 28-day cycle	0.00 kr

242.6	311.40 kr	0.00 kr	Twice daily. *Assumed equal to primary treatment*	0.00 kr
154.7	19 659.49 kr	1 947.00 kr	Q3W. *Assumed equal to primary treatment*	14 342.90 kr
124	22 857.36 kr	1 947.00 kr	8 mg/kg every 2 weeks	17 244.86 kr

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