Durvalumab (hepatocellular carcinoma)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A23-138 Version: 1.0 Status: 8 Mar 2024 DOI: 10.60584/A23-138_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Durvalumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Durvalumab (hepatocellular carcinoma) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

15 December 2023

Internal Project No.

A23-138

DOI-URL

https://doi.org/10.60584/A23-138_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Ivona Djuric
- Anna-Katharina Barnert
- Benjamin Becker
- Reza Fathollah-Nejad
- Petra Kohlepp
- Christopher Kunigkeit
- Dorothea Sow
- Volker Vervölgyi

Keywords

Durvalumab, Carcinoma – Hepatocellular, Benefit Assessment, NCT03298451, NCT03434379

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of figures

Page

I List of abbreviations

Abbreviation	Meaning
AASLD	American Association for the Study of Liver Diseases
ACT	appropriate comparator therapy
AE	adverse event
AFP	alpha fetoprotein
BCLC	Barcelona Clinic Liver Cancer
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MWA	microwave ablation
PEI	percutaneous ethanol injection
PGIC	Patient Global Impression of Change
PFS	progression-free survival
PRO	patient-reported outcome
PVE	portal vein embolization
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFA	radiofrequency ablation
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TACE	transarterial chemoembolization
TAE	transarterial embolization
TARE	transarterial radioembolization
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug durvalumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 December 2023.

Research question

The aim of the present report is to assess the added benefit of durvalumab as first-line treatment in comparison with the appropriate comparator therapy (ACT) of advanced or unresectable hepatocellular carcinoma in adult patients (HCC).

The research questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of durvalumab

Research question	Therapeutic indication[a]	ACT[b]
1	First-line treatment of advanced or unresectable hepatocellular carcinoma in adult patients ▪ with Child-Pugh A or no hepatic cirrhosis	Atezolizumab in combination with bevacizumab
2	First-line treatment of advanced or unresectable hepatocellular carcinoma in adult patients ▪ with Child-Pugh B	Best supportive care[c]

a. For this therapeutic indication, it is assumed according to G-BA that neither curative treatment (for BLCL stages 0 and A) nor locoregional therapy in BLCL stage B, particularly transarterial (chemo)embolization (TACE or TAE), is an option (any longer). It is also assumed that patients in BCLC stage D are ineligible for durvalumab monotherapy.
b. Presentation of the respective ACT specified by the G-BA.
c. BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BCLC: Barcelona Clinic Liver Cancer; BSC: best supportive care; G-BA: Joint Federal Committee; TACE: transarterial chemoembolization; TAE: transarterial embolization

The company followed the specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Research question 1: Patients with Child-Pugh A or no hepatic cirrhosis

Study pool and study design

No study on the direct comparison of durvalumab versus atezolizumab + bevacizumab in the present therapeutic indication was identified from the check of completeness of the study pool.

The company presented an adjusted indirect comparison for the assessment of durvalumab versus atezolizumab + bevacizumab via the common comparator sorafenib. For the adjusted indirect comparison, the company identified the HIMALAYA study on the intervention side and the IMbrave150 study on the atezolizumab + bevacizumab side.

HIMALAYA study

The HIMALAYA study is an open-label RCT comparing durvalumab monotherapy or tremelimumab + durvalumab versus sorafenib in 4 treatment arms. The study enrolled adults with advanced or unresectable HCC for whom locoregional therapy is not therapeutically indicated and who have not received prior systemic therapy for HCC. Further requirements for study inclusion were a Barcelona Clinic Liver Cancer (BCLC) stage B or C, as well as a Child-Pugh stage A and an ECOG PS of 0 or 1.

A total of 778 patients were included in the arms relevant for the benefit assessment: 389 patients in the durvalumab arm and 389 in the sorafenib arm.

Treatment was continued in both arms largely in accordance with the Summary of Product Characteristics (SPC): until disease progression, unacceptable toxicity, or the occurrence of another discontinuation criterion. Under certain conditions, treatment beyond progression was possible.

The primary outcome of the study was overall survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and adverse events (AEs).

IMbrave150 study

The IMbrave150 study is an open-label RCT comparing atezolizumab + bevacizumab versus sorafenib. The study included adults with locally advanced or metastatic and/or unresectable HCC who had not previously received systemic treatment. Further prerequisites for study inclusion were a classification in Child-Pugh stage A and general health as measured by ECOG PS of 0 or 1.

A total of 558 patients were randomly allocated in a 2:1 ratio to treatment with either atezolizumab + bevacizumab (N = 375) or with sorafenib (N = 183).

Treatment in both arms was conducted largely in accordance with the SPCs. Treatment was continued until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, or death. Under certain conditions, treatment beyond progression was possible.

Co-primary outcomes of the study were overall survival and progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and AEs.

Similarity of the studies for the indirect comparison

The overall analysis shows some differences in the study and patient characteristics between the HIMALAYA and IMbrave150 studies, but none of them fundamentally calls into question their sufficient similarity for conducting an adjusted indirect comparison via the common comparator sorafenib.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

In the present scenario, an indirect comparison can be conducted only for the outcome of overall survival. The outcome-specific risk of bias of the results on the outcome of overall survival was rated as low for each of the studies HIMALAYA and IMbrave150.

There was 1 RCT each on both sides of this adjusted indirect comparison. Hence, the check of homogeneity was no longer required. As there is no directly comparative study for the comparison of durvalumab versus the ACT, it is impossible to check the consistency of results. Therefore, the results of the adjusted indirect comparison are associated, at best, with a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived on the basis of the data available from the adjusted indirect comparison.

Results

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between durvalumab and atezolizumab + bevacizumab for the outcome of overall survival. This results in no hint of an added benefit of durvalumab in comparison with atezolizumab + bevacizumab; an added benefit is therefore not proven.

Morbidity

No suitable data are available for outcomes in the morbidity category. This results in no hint of an added benefit of durvalumab in comparison with atezolizumab + bevacizumab; an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for outcomes in the health-related quality of life category. This results in no hint of an added benefit of durvalumab in comparison with atezolizumab + bevacizumab; an added benefit is therefore not proven.

Side effects

Due to an insufficient certainty of results in the HIMALAYA and IMbrave150 studies, no indirect comparison was calculated for the outcomes of serious AEs (SAEs), severe AEs, or discontinuation due to AEs. Furthermore, no (suitable) data are available for the outcomes of patient-reported outcome (PRO)-CTCAE, immune-mediated AEs, or haemorrhage. Hence, no suitable data on the AE outcomes are available for the indirect comparison. This results in no hint of greater or lesser harm from durvalumab in comparison with atezolizumab + bevacizumab; greater or lesser harm is therefore not proven.

Research question 2: Patients with Child-Pugh B

The company has presented no data for assessing the added benefit of durvalumab as first-line treatment in comparison with the ACT in adult patients with advanced or unresectable HCC with Child-Pugh B.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug durvalumab in comparison with the ACT is assessed as follows:

Research question 1: Patients with Child-Pugh A or no hepatic cirrhosis

Overall, based on the adjusted indirect comparison using the common comparator sorafenib, there are neither favourable nor unfavourable effects of durvalumab in comparison with atezolizumab + bevacizumab. However, it should be noted that usable results with sufficient certainty of results for conducting an indirect comparison are available only for the outcome of overall survival. For the overall population, there is no hint of an added benefit of durvalumab for this outcome. For each of the outcomes of the categories of morbidity, health-

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

related quality of life, and side effects, no suitable data are available for the indirect comparison.

In summary, for adult patients with advanced or unresectable HCC with Child-Pugh A or no hepatic cirrhosis, there is no hint of an added benefit of durvalumab as first-line treatment compared with the ACT atezolizumab + bevacizumab; an added benefit is therefore not proven for this patient group.

Research question 2: Patients with Child-Pugh B

The company has presented no data for the assessment of added benefit of durvalumab as first-line treatment of advanced or unresectable HCC in adult patients with Child-Pugh B. An added benefit of durvalumab in comparison with the ACT is therefore not proven for these patients.

Table 3 shows a summary of the probability and extent of added benefit of durvalumab.

Table 3: Durvalumab – probability and extent of added benefit

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	First-line treatment of advanced or unresectable hepatocellular carcinoma in adult patients with Child-Pugh A or no hepatic cirrhosis	Atezolizumab in combination with bevacizumab	Added benefit not proven
2	First-line treatment of advanced or unresectable hepatocellular carcinoma in adult patients with Child-Pugh A	Best supportive care[c]	Added benefit not proven

a. For this therapeutic indication, it is assumed according to G-BA that neither curative treatment (for BLCL stages 0 and A) nor locoregional therapy in BLCL stage B, particularly transarterial (chemo)embolization (TACE or TAE), is an option (any longer). It is also assumed that patients in BCLC stage D are ineligible for durvalumab monotherapy.
b. Presentation of the respective ACT specified by the G-BA.
c. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BCLC: Barcelona Clinic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; TAE: transarterial embolization

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of durvalumab as first-line treatment in comparison with the ACT of advanced or unresectable hepatocellular carcinoma in adult patients (HCC).

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of durvalumab

Research question	Therapeutic indication[a]	ACT[b]
1	First-line treatment of advanced or unresectable hepatocellular carcinoma in adult patients ▪ with Child-Pugh A or no hepatic cirrhosis	Atezolizumab in combination with bevacizumab
2	First-line treatment of advanced or unresectable hepatocellular carcinoma in adult patients ▪ with Child-Pugh B	Best supportive care[c]

a. For this therapeutic indication, it is assumed according to G-BA that neither curative treatment (for BLCL stages 0 and A) nor locoregional therapy in BLCL stage B, particularly transarterial (chemo)embolization (TACE or TAE), is an option (any longer). It is also assumed that patients in BCLC stage D are ineligible for durvalumab monotherapy.
b. Presentation of the respective ACT specified by the G-BA.
c. BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BCLC: Barcelona Clinic Liver Cancer; BSC: best supportive care; G-BA: Joint Federal Committee; TACE: transarterial chemoembolization; TAE: transarterial embolization

The company followed the specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: Patients with Child-Pugh A or no hepatic cirrhosis

I 3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on durvalumab (status: 18 October 2023)
- bibliographical literature search on durvalumab (last search on 16 October 2023)
- search in trial registries/trial results databases for studies on durvalumab (last search on 20 October 2023)
- search on the G-BA website for durvalumab (last search on 20 October 2023)
- bibliographical literature search on the ACT (last search on 16 October 2023)
- search in trial registries/trial results databases for studies on the ACT (last search on 20 October 2023)
- search on the G-BA website for the ACT (last search on 20 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on durvalumab (last search on 21 December 2023); for search strategies, see Appendix I A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 4 January 2024); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no study on the direct comparison of durvalumab versus atezolizumab + bevacizumab in the present therapeutic indication was identified from the check of completeness of the study pool.

The company therefore presented an adjusted indirect comparison according to Bucher [3] for the assessment of durvalumab versus atezolizumab + bevacizumab via the common comparator sorafenib. For the adjusted indirect comparison, the company identified the HIMALAYA study on the intervention side and the IMbrave150 study on the atezolizumab + bevacizumab side.

The check of the study pool did not reveal any additional relevant study for the adjusted indirect comparison presented by the company.

I 3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Durvalumab vs. sorafenib						
D419CC00002 (HIMALAYA[d])	Yes	Yes	No	Yes [4,5]	Yes [[6,7]	Yes [8-10]
Atezolizumab + bevacizumab vs. sorafenib						
IMbrave150	No	No	Yes	No [11]	Yes [12,13]	Yes [14-25]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that selected by the company. The IMbrave150 study has already been submitted and evaluated for a previous benefit assessment of atezolizumab [20,21].

The indirect comparison is shown schematically in Figure 1.

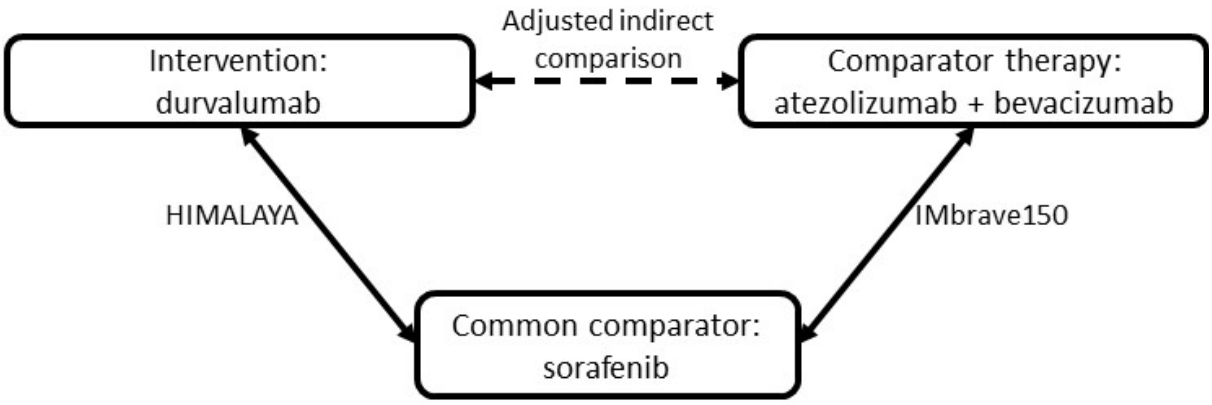

Figure 1: Study pool for the adjusted indirect comparison between durvalumab and atezolizumab + bevacizumab using sorafenib as the common comparator

I 3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characterization of the included studies – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Durvalumab vs. sorafenib						
HIMALAYA	RCT, open-label, parallel-group	Adults (≥ 18 years) with advanced or unresectable HCC[b] ▪ without prior systemic therapy ▪ and with ▪ Child-Pugh score A ▪ ECOG-PS 0 or 1 ▪ ≥ 1 measurable non-irradiated lesions as per RECIST version 1.1	Global cohort[c] ▪ Durvalumab monotherapy (n = 389) ▪ Durvalumab (1500 mg) + tremelimumab (75 mg)d (n = 153) ▪ Durvalumab (1500 mg) + tremelimumab (300 mg)d (n = 393) ▪ Sorafenib (n = 389)	Screening: 28 days Treatment: until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, study end, or death[e] Observation[f]: at the longest until death	170 study centres in Brazil, Canada, France, Germany, Hong Kong, India, Italy, Japan, Russia, South Korea, Spain, Taiwan, Thailand, Ukraine, United States, and Vietnam 10/2017–ongoing Data cut-offs: ▪ 2 September 2019 ▪ 22 May 2020 ▪ 27 Aug 021 (final analysis for overall survival) ▪ 23 Jan 2023 (long-term follow-up data)g	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Atezolizumab + bevacizumab vs. sorafenib						
IMbrave150	RCT, open-label, parallel-group	Adults with locally advanced or metastatic and/or unresectable HCC[h] ▪ without prior systemic therapy and with ▪ Child-Pugh score A ▪ ECOG PS 0 or 1 ▪ ≥ 1 measurable untreated lesion according to RECIST version 1.1	Global cohort: ▪ Atezolizumab + bevacizumab (N = 336) ▪ Sorafenib (N = 165) Cohort in China[i]: ▪ Atezolizumab + bevacizumab (N = 133) ▪ Sorafenib (N = 61) Total[j]: ▪ Atezolizumab + bevacizumab (N = 375) ▪ Sorafenib (N = 183)	Screening: 28 days Treatment: until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, or death[e] Observation[f]: at the longest until death	111 study centres[k] in Australia, Canada, China, Czech Republic, France, Germany, Hong Kong, Italy, Japan, Poland, Russia, Singapore, South Korea, Spain, Taiwan, United Kingdom, United States 03/2018–11/2022 Data cut-offs: ▪ 29 Aug 2019[l] ▪ 29 Nov 2019[m] ▪ 31 Aug 2020[n]	Primary: overall survival, PFS Secondary: morbidity, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. Confirmed by histology.
c. In addition to the global cohort, a Chinese cohort was also planned for the HIMALAYA study, into which 180 patients were randomized. According to the company, no results were available for this cohort at the time of the benefit assessment.
d. This arm is irrelevant for the assessment and is not presented in the following tables.
e. Treatment beyond progression was allowed as long as the patient showed clinical benefit as assessed by the investigator.
f. Outcome-specific information is provided in Table 8.
g. Data cut-off for exploratory analysis of overall survival and serious AEs. According to protocol version 7, long-term follow-up data can be collected for about 3 years after the final primary analysis).
h. Diagnosis in cirrhotic patients confirmed by histology/cytology or as per AASLD criteria or by histology in patients with no cirrhosis.
i. To support a marketing authorization in China, patients of Chinese descent who resided in China, Hong Kong, or Taiwan were enrolled in the IMbrave150 study. Hereinafter, this cohort is referred to as "expansion cohort".
j. The global cohort and the expansion cohort are no longer presented separately in the following, as the analyses of the entire IMbrave150 study population are considered, where available.
k. Data based on the global cohort of the IMbrave150 study.
l. Final/Primary analysis of PFS and overall survival.
m. Three-month safety update for the FDA.
n. Analysis of effectiveness outcomes at the request of the EMA for the global cohort.

AASLD: American Association for the Study of Liver Diseases; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; EMA: European Medicines Agency; FDA: Food and Drug Administration; HCC: hepatocellular carcinoma; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 7: Characterization of the intervention – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	Intervention	Comparison
Durvalumab vs. sorafenib		
HIMALAYA	Durvalumab 1500 mg, i.v., on Day 1 of the 28-day cycle[a] ▪ Dose reduction was not allowed[b].	Sorafenib 400 mg orally, twice daily[a] ▪ Dose reductions were allowed as per SPC[c]
	Disallowed prior and concomitant treatment ▪ Any systemic HCC therapy ▪ Allogenic organ transplantation (e.g liver transplantation) ▪ Therapies directed against PD1, PD-L1, or CTLA-4 ▪ ≤ 4 weeks before start of the study medication and during the study: ▫ Attenuated live vaccines[d] ▫ Radiotherapy of more than 30% of the bone marrow or with a wide irradiation field ▫ Major surgery as defined by the investigator ▫ Other investigational drugs ▪ ≤ 2 weeks before start of the study medication and during the study: ▫ Systemic immunosuppressants[e] **Allowed concomitant treatment** ▪ Best supportive care, including: ▫ Antibiotics ▫ Nutritional support ▫ Correction of metabolic disorders ▫ Symptom control and pain management, including palliative radiotherapy for non-target lesions ▫ Acetaminophen, diphenhydramine, or other medications deemed necessary by the investigator for appropriate prophylactic or supportive treatment ▪ Diuretics for ascites, if received at a stable dose for ≥ 2 months	
Atezolizumab + bevacizumab vs. sorafenib		
IMbrave150	Atezolizumab 1200 mg, i.v., on Day 1 of the 21-day cycles[a] + Bevacizumab 15 mg/kg, i.v., on Day 1 of the 21-day cycles[a]	Sorafenib 400 mg orally, twice daily[a]
	▪ Dose reduction was disallowed ▪ In case of toxicity, the dosing of atezolizumab or bevacizumab can be interrupted independently of each other.	▪ Dose reductions were allowed as per SPC[f]

Table 7: Characterization of the intervention – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	Intervention	Comparison
	Disallowed prior and concomitant treatment ▪ Any systemic HCC therapy ▪ Allogeneic stem cell transplantation or solid organ transplantation ▪ Treatment with CD137 agonists or immune checkpoint blockade therapies ▪ Long-term daily use of NSAIDs ▪ ≤ 60 days before start of study medication: ▫ radiotherapy in the area of the abdomen/pelvis ▫ abdominal surgery ▪ ≤ 4 weeks before start of the study medication and during the study: ▫ major surgery[g] ▫ other radiotherapy[h] ▫ local therapies of the liver ▫ systemic immunostimulants (including interferons or interleukin-2)[i] ▫ attenuated live vaccines[d] ▪ ≤ 2 weeks before start of the study medication and during the study: ▫ strong CYP3A4-inducing substances[j] ▫ systemic immunosuppressants[k] ▫ oral and intravenous antibiotics[l] ▪ ≤ 10 days before start of the study medication and during the study: ▫ aspirin (> 325 mg/day) or dipyramidol, ticlopidine, clopidogrel and cilostazol ▫ therapeutic use of full-dose oral or parenteral anticoagulants or thrombolytic drugs ▪ From the start of study medication: ▫ herbal therapies / traditional Chinese medicine with proven anti-cancer activity in the therapeutic indication **Allowed concomitant treatment** ▪ For uncontrolled tumour pain: pain medication in a stable dose at the start of the study ▪ Prophylactic anticoagulation if the drug effect leads to an INR < 1.5 times ULN and aPTT in the normal range within 14 days before the start of the study medication, and prophylactic low molecular weight heparin ▪ Premedication with antihistamines, antipyretics, and analgesics at the discretion of the investigator in case of infusion-related reactions ▪ Palliative radiotherapy if the target lesion is not treated locally[m]	

Table 7: Characterization of the intervention – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	Intervention	Comparison
a. Treatment beyond progression was possible as long as the patient showed clinical benefit as assessed by the investigator. b. Patients with a body weight of 30 kg or less should receive a weight-based dosage of 20 mg/kg every 4 weeks until the body weight has increased to over 30 kg. c. If necessary, a further dose reduction to 400 mg every 2nd day is possible, beyond the reduction specified in the SPC. d. Not Allowed for 30 days after the last study treatment (HIMALAYA) or for 5 months after the last dose of atezolizumab (IMbrave150). e. Allowed are intranasal, inhaled, topical steroids or local steroid injections, systemic corticosteroids in physiological doses of no more than 10 mg/day of prednisone or equivalent or steroids as premedication for hypersensitivity reactions. f. In addition, the study protocol describes that sorafenib can also be reduced to a single 400 mg dose every 2 days if necessary. g. Surgical interventions for diagnostic reasons are allowed. h. Except for palliative radiotherapy of bone lesions ≤ 7 days before the start of the study medication. i. Five half-lives or ≤ 4 weeks of the drugs before the start of the study, whichever was longer. j. During treatment with sorafenib, concomitant treatment is not expressly prohibited, but caution is recommended with the concomitant use of strong CYP3A4-inducing substances. k. Therapy with acute low-dose immunosuppressants or a single high-dose therapy with a systemic immunosuppressant is allowed before the start of the study. Also allowed, even during the study: mineralocorticoids, corticosteroids for COPD or asthma, and low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency. l. The prophylactic use of antibiotics (e.g. to prevent urinary tract infections or exacerbations of COPD) is allowed. m. During radiotherapy, it was possible to continue treatment with atezolizumab, while treatment with bevacizumab and sorafenib had to be interrupted. aPTT: activated partial thromboplastin time; CD: cluster of differentiation; COPD: chronic obstructive pulmonary disease; CYP3A4: cytochrome P450 3A4; HCC: hepatocellular carcinoma; INR: international normalized ratio; i.v.: intravenous; NSAID: non-steroidal anti-inflammatory drugs; RCT: randomized controlled trial; ULN: upper limit of normal		

HIMALAYA

The HIMALAYA study is an open-label RCT comparing durvalumab monotherapy or tremelimumab + durvalumab versus sorafenib in 4 treatment arms. The study enrolled adults with advanced or unresectable HCC for whom locoregional therapy is not therapeutically indicated and who have not received prior systemic therapy for HCC. Further requirements for study inclusion were a Barcelona Clinic Liver Cancer (BCLC) stage B or C, as well as a Child-Pugh stage A and an ECOG-PS of 0 or 1.

A total of 778 patients were included in the arms relevant for the benefit assessment: 389 patients in the durvalumab arm and 389 in the sorafenib arm. Allocation to the study arms was stratified according to macrovascular invasion (yes/no), aetiology of liver disease (hepatitis B / hepatitis C / other), and ECOG PS (0/1).

An expansion cohort was to be implemented in China once global recruitment was complete. A total of 180 Chinese patients were to be randomized into it. As no results for this cohort were available at the time of the benefit assessment, this cohort was disregarded in the benefit assessment.

In the relevant intervention arm, patients were treated with 1500 mg durvalumab every 4 weeks, in accordance with the SPC [26]. In the comparator arm, sorafenib 400 mg twice daily was administered largely as per SPC [27]. If adverse drug reactions occurred, a dose reduction to 400 mg sorafenib once daily and, if necessary, to 400 mg sorafenib every 2 days was allowed (the SPC provides for a reduction to 400 mg sorafenib once daily. Treatment was continued in both arms until disease progression, unacceptable toxicity, or the occurrence of another discontinuation criterion. Under certain conditions, treatment beyond progression was possible. This aspect is addressed in detail below.

The primary outcome of the study was overall survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and adverse events (AEs).

IMbrave150

The IMbrave150 study is an open-label RCT comparing atezolizumab + bevacizumab versus sorafenib. The study included adults with locally advanced or metastatic and/or unresectable HCC who had not previously received systemic treatment. Further prerequisites for study inclusion were a classification in Child-Pugh stage A and general health as measured by ECOG PS of 0 or 1.

A total of 558 patients were randomly allocated in a 2:1 ratio to treatment with either atezolizumab + bevacizumab (N = 375) or with sorafenib (N = 183). Stratification was implemented by region (Asia excluding Japan / rest of the world), macrovascular invasion and/or extrahepatic spread (present/absent), alpha-fetoprotein (AFP; < 400 ng/mL / ≥ 400 ng/mL), ECOG PS (0/1). The study population of the IMbrave150 study is composed of a global cohort (N = 501) and a cohort in China (N = 194). Hereinafter, the cohort in China is referred to as "expansion cohort". The expansion cohort has a very large overlap of n = 137 with the global cohort. The patients in the expansion cohort were treated in accordance with an identical study protocol and statistical analysis plan as the global study population, but the data were analysed in a separate CSR. If not indicated otherwise, the data in this benefit assessment refer to the total population (combined population of the global and extension cohorts).

Treatment with atezolizumab + bevacizumab was in compliance with the specifications of the SPC [28]. This also largely applies to treatment with sorafenib [27]. The IMbrave150 study allowed reducing the dose to 400 mg every 2 days if adverse drug reactions occurred (the SPC provides for a reduction to 400 mg sorafenib once daily).

Treatment was continued until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, or death. Patients who met the criteria for disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 were allowed to be treated further if they met certain criteria (see below).

Co-primary outcomes of the study were overall survival and progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and AEs.

Treatment beyond disease progression

In both the HIMALAYA study and the IMbrave150 study, treatment with the respective intervention (durvalumab or atezolizumab + bevacizumab or sorafenib) was allowed to be continued in all treatment arms even after disease progression if certain criteria were met – for instance, if there was evidence of clinical benefit in the investigator's opinion and if there was no unacceptable toxicity. This contradicts the recommendations of the current S3 guideline on the diagnosis and treatment of HCC and biliary carcinomas [29]. According to the above, ongoing systemic therapy should not be continued beyond radiological progression since several different drug-based tumour therapies are available for HCC.

In the HIMALAYA study, 48.3% of the patients in the intervention arm and 34.4% of the patients in the comparator arm received treatment (≥ 1 cycle) beyond disease progression. In the IMbrave150 study, 39.3% of patients in the atezolizumab + bevacizumab arm received treatment beyond disease progression [15]; no information is available for the comparator arm. Thus, treatment beyond disease progression was administered in both study arms of both studies. It remains unclear whether treatment beyond disease progression influences the effects observed in the studies. Overall, however, this uncertainty presumably does not fundamentally call into question the indirect comparison.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
Durvalumab vs. sorafenib	
HIMALAYA	
Mortality	
Overall survival	Until death, lost-to-follow-up, withdrawal of informed consent, or termination of the study by the sponsor
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-HCC18)	Until 3 months after discontinuation of study medication or progression or until withdrawal of informed consent or termination of the study by the sponsor
Health status (EQ-5D VAS)	
Health-related quality of life	
EORTC QLQ-C30 and EORTC QLQ-HCC18	Until 3 months after discontinuation of study medication or progression or until withdrawal of informed consent or termination of the study by the sponsor
Side effects	
PRO-CTCAE	Until 3 months after discontinuation of study medication or progression or until withdrawal of informed consent or termination of the study by the sponsor
All outcomes in the side effects category	Until 90 days after the last dose of the study medication
Atezolizumab + bevacizumab vs. sorafenib	
IMbrave150	
Mortality	
Overall survival	Until death, lost-to-follow-up, withdrawal of informed consent, or termination of the study by the sponsor
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-HCC18)	After discontinuation of the study medication or progression, every 3 months for 1 year[a] or until withdrawal of informed consent or termination of the study by the sponsor
Health status (EQ-5D VAS)	
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-HCC18)	After discontinuation of the study medication or progression, every 3 months for 1 year[a] or until withdrawal of informed consent or termination of the study by the sponsor
Side effects	
SAEs	Up to 90 days after the last dose of the study medication or initiation of new systemic treatment[b]
Further AEs	Up to 30 days after the last dose of the study medication or initiation of new systemic treatment

a. As per information provided in the study protocol.
b. Beyond this period, only SAEs related to the study medication are observed.

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

Only the outcome "overall survival" was to be recorded until the end of the study participation in both studies.

In both studies, the observation durations for the morbidity, health-related quality of life, and side effects outcomes are systematically shortened because they were surveyed only for the period of treatment with the study medication (HIMALAYA: plus up to 3 months; IMbrave150: plus 1 year [morbidity and health-related quality of life], or 30 days [AEs] or 90 days [serious AEs [SAEs]). To be able to draw a reliable conclusion on the total study period or the time until patient death, it would be necessary, however, to record these outcomes over the total period.

Data cut-offs

HIMALAYA

A total of 4 data cut-offs are available for the HIMALAYA study:

- 1st data cut-off on 2 September 2019: predefined interim analysis for objective response rate and duration of response of the durvalumab monotherapy arm and the tremelimumab + durvalumab arm (planned to occur after 32 weeks of observation in approximately 100 patients in each treatment arm)
- 2nd data cut-off on 22 May 2020: interim analysis for overall survival (planned to occur after approximately 404 deaths in the tremelimumab + durvalumab and sorafenib arms combined, after approximately 30 months)
- 3rd data cut-off on 27 August 2021: final analysis of overall survival (planned to occur after 515 deaths in the tremelimumab + durvalumab and sorafenib arms combined, after approximately 37.5 months)
- 4th Data cut-off 23 January 2023: exploratory long-term follow-up data on overall survival and SAEs (up to 90 days after last dose)

The company presented analyses on the 3rd data cut-off from 27 August 2021 and on the 4th data cut-off from 23 January 2023 for the outcomes "overall survival" and "SAEs". The 4th data

cut-off for the exploratory long-term follow-up data was only specified in protocol version 7 of 22 September 2021, 1 month after the final analysis of overall survival. As this data cut-off was not prespecified, the results are not used for the benefit assessment.

The 3rd data cut-off from 27 August 2021, also available in Module 4 A, is the prespecified final analysis of overall survival, which occurred after 555 deaths. At this point, analyses of all other outcomes were conducted in addition to the analyses of the primary outcome. This data cut-off is used for the benefit assessment.

IMbrave150

A total of 3 data cut-offs are available for the IMbrave150 study:

- 1st data cut-off on 29 August 2019: primary analysis of PFS (planned to occur after approximately 308 events) and final analysis of overall survival, as the prespecified statistical stop rule for overall survival was reached
- 3-month safety update from the Food and Drug Administration (FDA) on 29 November 2019: analyses of AEs only
- 2nd data cut-off on 31 August 2020: analysis of overall survival, PFS, etc., as part of the marketing authorization at the request of the European Medicines Agency (EMA)

In Module 4 A, the 31 August 2020 data cut-off is presented for the overall population for the outcome of overall survival. This data cut-off was implemented at the request of the EMA as part of the marketing authorization process and represents the most up-to-date analysis for overall survival. Results on the outcomes of the category morbidity and health-related quality of life are available for the 1st data cut-off [20,21], but the company does not present them in Module 4 A. The analysis of the total population's AE outcomes is based on the 29 November 2019 data cut-off (3-month safety update for the FDA) for the global cohort and for the cohort in China on the 29 August 2019 data cut-off; it represents the most recent analysis for the AE outcomes.

Study population

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	**HIMALAYA**		**IMbrave150**	
Characteristic				
Category				
	Durvalumab	**Sorafenib**	**Atezolizumab + bevacizumab**	**Sorafenib**
	N[a] = 389	**N[a] = 389**	**N[a] = 375**	**N[a] = 183**
Age [years], median [min; max]	64 [20; 86]	64 [18; 88]	62 [26; 88]	65 [31; 87]
Sex [F/M], %	17/83	13/87	16/84	17/83
Family origin, n (%)				
Asian	212 (54.5)	189 (48.6)	227 (60.5)	114 (62.3)
Caucasian	160 (41.1)	179 (46.0)	123 (32.8)	52 (28.4)
Black or African American	2 (0.5)	10 (2.6)	0 (0)	0 (0)
Other	15 (3.9)	5 (1.3)	6 (1.6)	5 (2.7)
Unknown	0 (0)	6 (1.5)	19 (5.1)	12 (6.6)
Region, n (%)				
Asia (without Japan)	167 (42.9)	156 (40.1)	172 (45.9)	86 (47.0)
Rest of the world	222 (57.1)	233 (59.9)	203 (54.1)	97 (53.0)
ECOG PS, n (%)				
0	237 (60.9)	241 (62.0)	234 (62.4)	112 (61.2)
1	150 (38.6)	147 (37.8)	141 (37.6)	71 (38.8)
2	2 (0.5)	1 (0.3)	0 (0)	0 (0)
BCLC stage at baseline (IMbrave150) / screening (HIMALAYA), n (%)				
Stage A1	0 (0)	0 (0)	6 (1.6)	3 (1.6)
Stage A4	0 (0)	0 (0)	4 (1.1)	3 (1.6)
Stage B	80 (20.6)	66 (17.0)	55 (14.7)	26 (14.2)
Stage C	309 (79.4)	323 (83.0)	310 (82.7)	151 (82.5)
Extrahepatic spread and macrovascular invasion at baseline (IMbrave150) / screening (HIMALAYA), n (%)				
Macrovascular invasion	94 (24.2)	100 (25.7)	141 (37.6)	78 (42.6)
Extrahepatic spread	212 (54.5)	203 (52.2)	239 (63.7)	106 (57.9)
Macrovascular invasion and/or extrahepatic spread	255 (65.6)	251 (64.5)	290 (77.3)	136 (74.3)

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	**HIMALAYA**		**IMbrave150**	
Characteristic				
Category				
	Durvalumab	**Sorafenib**	**Atezolizumab + bevacizumab**	**Sorafenib**
	N[a] = 389	**N[a] = 389**	**N[a] = 375**	**N[a] = 183**
Child-Pugh score, n (%)				
A5	284 (73.0)	277 (71.2)	268 (71.8)	137 (74.9)
A6	96 (24.7)	102 (26.2)	103 (27.6)	46 (25.1)
B7	8 (2.1)	10 (2.6)	ND	ND
B7 or B8	ND	ND	2 (0.6)	0 (0)
Other	1 (0.3)	0 (0)	ND	ND
HCC aetiology, n (%)				
Hepatitis B	119 (30.6)	119 (30.6)	200 (53.3)	91 (49.7)
Hepatitis C	107 (27.5)	104 (26.7)	72 (19.2)	37 (20.2)
Nonviral	163 (41.9)	166 (42.7)	103 (27.4)	55 (30.1)
AFP at screening, n (%)				
< 400 ng/mL	247 (63.5)	256 (65.8)	231 (61.6)	112 (61.2)
≥ 400 ng/mL	137 (35.2)	124 (31.9)	144 (38.4)	71 (38.8)
Unknown	5 (1.3)	9 (2.3)	0 (0)	0 (0)
Prior local therapy[b] of HCC, n (%)				
Microwave ablation (MWA)	3 (0.8)	4 (1.0)	ND	ND
Percutaneous ethanol injection (PEI)	7 (1.8)	3 (0.8)	13 (3.5)	3 (1.6)
Radiofrequency ablation (RFA)	40 (10.3)	33 (8.5)	55 (14.7)	28 (15.3)
Transarterial embolization (TAE)	16 (4.1)	11 (2.8)	13 (3.5)	8 (4.4)
Transarterial chemoembolization (TACE)	122 (31.4)	132 (33.9)	155 (41.3)	77 (42.1)
Transarterial radioembolization (TARE)	8 (2.1)	5 (1.3)	ND	ND
Portal vein embolization (PVE)	1 (0.3)	2 (0.5)	ND	ND
Other ablation therapy	9 (2.3)	8 (2.1)	ND	ND
Other therapeutic embolization	0 (0)	0 (0)	ND	ND
Other	ND	ND	28 (7.5)	17 (9.3)
Treatment discontinuation, n (%)	342 (87.9[c])[b]	353 (90.7[c])[b]	ND[d]	ND[d]
Study discontinuation, n (%)	ND	ND	ND	ND

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Study	HIMALAYA		IMbrave150	
Characteristic Category				
	Durvalumab	Sorafenib	Atezolizumab + bevacizumab	Sorafenib
	N[a] = 389	N[a] = 389	N[a] = 375	N[a] = 183

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Common reasons for treatment discontinuation in the intervention arm versus the control arm were: objective progression of the disease (57.5% vs. 45.5%), subjective progression of the disease (11.4% vs. 17.6%), adverse events (8.2% vs. 16.8%).
c. Institute's calculation.
d. In the IMbrave150 study's global cohort, 183 (54.5 %) patients in the intervention arm and 132 (80.0 %) patients in the control arm discontinued treatment (data cut-off on 29 August 2019).

AFP: alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; f: female; HCC: hepatocellular carcinoma; m: male; max: maximum; min: minimum; MWA: microwave ablation; n: number of patients in the category; N: number of randomized patients; ND no data; PEI: percutaneous ethanol injection; PVE: portal vein embolization; RCT: randomized controlled trial; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; TAE: transarterial embolization; TARE: transarterial radioembolization

The characteristics of the patients are largely balanced between the arms of both studies. In both studies, the median patient age was around 64 years; the majority of patients were male, and most were of Asian descent (approximately 52% [HIMALAYA] and 61% [IMbrave150]). In both studies, approximately 61% of all patients had an ECOG PS of 0. Approximately 82% of the patients included in both studies were in BCLC stage C. In the HIMALAYA study, the HCC aetiology was hepatitis B or C infection in slightly more than half of the patients, while around 42% of patients had a nonviral aetiology. In the IMbrave150 study, around 2/3 of patients had a hepatitis B or C aetiology, and around 29% had a nonviral aetiology.

A detailed description of the similarity of patient characteristics between the studies can be found in Section I 3.1.3.

Treatment duration and observation period

Table 10 shows the mean and median treatment durations of the patients and the mean and median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, indirect comparison of durvalumab versus sorafenib (multipage table)

Comparison **Study** **Duration of the study phase** **Outcome category**	**Durvalumab or atezolizumab + bevacizumab**	**Sorafenib**
Durvalumab vs. sorafenib		
HIMALAYA, 3rd data cut-off on 27 August 2021[a]	N = 388	N = 374
Treatment duration [months]		
Median [min; max]	5.5 [0.2; 44.4]	4.1 [0.1; 38.6]
Mean (SD)	9.7 (10.2)	7.5 (8.5)
Observation period [months]		
Overall survival		
Median [min; max][b]	16.5 [0.2; 45.7]	13.3 [0.0; 43.6]
Mean (SD)	ND	
Morbidity	ND	
Health-related quality of life	ND	
Side effects[c]		
Median [min; max]	6.1 [0.0; 44.4]	5.6 [0.2; 38.6]
Mean (SD)	ND	
Atezolizumab + bevacizumab vs. sorafenib		
IMbrave150 (global cohort), data cut-off: 29 August 2019	N = 336	N = 165
Treatment duration [months]		
Median [Q1; Q3]	Atezolizumab: 7.4 [ND] Bevacizumab: 6.8 [ND]	2.8 [ND]
Mean (SD)	ND	
Observation period [months]		
Overall survival		
Median [min; max][b, d]	17.6 [0.1; 28.6]	10.4 [0; 27.9]
Mean (SD)	ND	
Morbidity	ND	
Health-related quality of life	ND	
Side effects	ND	

a. Final analysis for overall survival.
b. It is unclear how the observation period was calculated. Presumably, deaths and censorings were equally counted as complete observations.
c. The observation period for adverse events is defined as the time from the first dose of study medication to the earliest of the following events: data cut-off, treatment discontinuation + 90 days, start of subsequent therapy, or death.
d. Follow-up for the global cohort; data cut-off: 31 August 2020 from Cheng [15].

Table 10: Information on the course of the study – RCT, indirect comparison of durvalumab versus sorafenib (multipage table)

Comparison **Study** **Duration of the study phase** **Outcome category**	**Durvalumab or atezolizumab + bevacizumab**	**Sorafenib**
CI: confidence interval; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1, Q3: 25% and 75% quartile, respectively; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation;		

Within the HIMALAYA study, the median treatment duration was 5.5 months in the intervention arm and 4.1 months in the comparator arm. The median observation duration for the outcome "overall survival" was 16.5 months and 13.3 months, respectively. For the outcomes regarding side effects, the median observation time was 6.1 months and 5.6 months, respectively. Notably, despite the planned 90-day follow-up observation of side effects, the actual observation period is only approximately 0.6 months and 1.5 months longer than the treatment period. Information on the observation periods of the outcomes on morbidity and health-related quality of life is lacking.

At the 29 August 2019 data cut-off of the IMbrave150 study, the duration of intervention-arm treatment with atezolizumab (7.4 months) or bevacizumab (6.8 months) was significantly longer than in the sorafenib arm (2.8 months). Information on the 31 August 2020 data cut-off is not available. The median observation period for the outcome "overall survival" as of the 31 August 2020 data cut-off differs between the intervention arm at 17.6 months and the comparator arm at 10.4 months. Information on the observation duration for the outcomes of morbidity, health-related quality of life, and side effects is missing.

A detailed description of the similarity of treatment and observation duration between the studies can be found in Section I 3.1.3.

Subsequent therapies

Table 11 and Table 12show the subsequent therapies patients received after discontinuation of the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥ 3% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: durvalumab versus sorafenib (HIMALAYA study)

Study	**Patients with subsequent therapy, n (%)**	
Therapy	**Durvalumab**	**Sorafenib**
Drug	**N = 389**	**N = 389**
HIMALAYA[a]		
Systemic therapy	168 (43.2)	175 (45.0)
Immunotherapy	20 (5.1)	89 (22.9)
Atezolizumab	11 (2.8)	14 (3.6)
Nivolumab	5 (1.3)	47 (12.1)
Pembrolizumab	1 (0.3)	17 (4.4)
Cytotoxic chemotherapy	18 (4.6)	25 (6.4)
Targeted therapy	155 (39.8)	108 (27.8)
Cabozantinib	20 (5.1)	26 (6.7)
Lenvatinib	68 (17.5)	32 (8.2)
Regorafenib	26 (6.7)	62 (15.9)
Sorafenib	98 (25.2)	12 (3.1)
Antiangiogenic therapy	20 (5.1)	19 (4.9)
Bevacizumab	12 (3.1)	16 (4.1)
Therapeutic embolization	29 (7.5)	20 (5.1)
Transarterial chemoembolization (TACE)	28 (7.2)	18 (4.6)

a. Data cut-off: 27 August 2021.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: atezolizumab + bevacizumab versus sorafenib (IMbrave150 study)

Study	Patients with subsequent therapy, n (%)	
Therapy Drug	Atezolizumab + bevacizumab N = 336	Sorafenib N = 165
IMbrave150 (global cohort)[a]		
Systemic therapy	120 (35.7)	86 (52.1)
Tyrosine kinase inhibitor	108 (32.1)	54 (32.7)
Angiogenesis inhibitor (monoclonal antibodies)	6 (1.8)	10 (6.1)
Chemotherapy	11 (3.3)	15 (9.1)
Immunotherapy	11 (3.3)	43 (26.1)
Other	6 (1.8)	6 (3.6)
Local therapy	21 (6.3)	17 (10.3)
Radiofrequency ablation (RFA)	3 (0.9)	4 (2.4)
Transarterial embolization (TAE)	4 (1.2)	3 (1.8)
Transarterial chemoembolization (TACE)	12 (3.6)	8 (4.8)
Transcatheter arterial infusion (TAI)	1 (0.3)	4 (2.4)
Transarterial radioembolization (TARE)	1 (0.3)	0 (0)
Other	1 (0.3)	2 (1.2)
Surgical procedure	11 (3.3)	1 (0.6)
Radiotherapy	17 (5.1)	10 (6.1)

a. Data cut-off: 31 August 2020.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In the HIMALAYA study, approximately 43% or 45% of patients received subsequent systemic therapy. In the durvalumab arm, the most common subsequent therapy was sorafenib (approximately 25%). In the sorafenib arm, the most common subsequent therapies were regorafenib (approximately 16%) and nivolumab (12%). For patients who received subsequent therapy, this corresponds to the recommendations of the S3 guideline on the diagnosis and therapy of HCC and biliary carcinomas [29], with the exception of treatment with nivolumab, which is not approved for this therapeutic indication. It remains unclear, however, how many of the patients did not receive subsequent therapy despite being eligible for it. Overall, around 90% of patients discontinued therapy (see Table 9), while only just under half of patients received subsequent therapy. The company has not provided any information on why these patients did not receive subsequent therapy.

For the IMbrave150 study, data on subsequent therapies are available only for the global cohort. In this cohort, approximately 36% or 52% of patients received systemic subsequent

therapy. The most common subsequent therapy in both arms was treatment with tyrosine kinase inhibitors (approximately 32% and 33% respectively); in the comparator arm, a relevant proportion also received immunotherapy (approximately 26%). Details of the drugs used are not available for the IMbrave150 study. However, it remains unclear whether all patients received subsequent therapy since a total of approximately 55% of patients in the intervention arm and 80% in the control arm discontinued treatment, resulting in a discrepancy to the proportion of patients receiving subsequent therapy.

A detailed description of the similarity of subsequent therapies between the studies can be found in Section I 3.1.3.

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab

Comparison Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Durvalumab vs. sorafenib							
HIMALAYA	Yes	Yes	No	No	Yes	Yes	Low
Atezolizumab + bevacizumab vs. sorafenib							
IMbrave150	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for both studies.

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company reports that the epidemiological characteristics of the HIMALAYA and IMbrave150 participants are largely comparable to the characteristics of the corresponding patients in Germany. It explains that the majority of patients in both the included studies and in Germany are male. Likewise, the mean body mass index (BMI) of the HIMALAYA patient

population is reportedly comparable to the mean BMI of the German population. The company further states that the median age of HIMALAYA and IMbrave150 participants (HIMALAYA: 64 years each; IMbrave150: 62 and 65 years, respectively) is slightly below the median age of the German patient population with liver tumours in general (women: 75 years; men: 71 years). However, the participant age is reportedly comparable to that found in other clinical studies and real-world studies in the German context with a similar study population.

The company adds that the proportion of patients with a hepatitis C infection underlying the HCC was 27.5% (durvalumab monotherapy arm) and 26.7% (sorafenib arm) in the HIMALAYA study. It argues that this adequately reflects the healthcare context in Germany. The company reports that there are differences in the aetiology of HCC between the regions Asia, Africa and Europe. In patients from Africa and South-East Asia, HCC is typically based on hepatitis B infections, while hepatitis C infections are prevalent among patients from Japan, North America, and Western Europe. In Germany, nonviral aetiologies, which include high alcohol consumption as well as metabolic causes, are the main cause of liver tumours. The proportion of nonviral HCC genesis in the HIMALAYA study was 41.9% (durvalumab monotherapy arm) and 42.7% (sorafenib arm). According to the company, 45.2% of patients in the HIMALAYA study's durvalumab monotherapy arm and 46.8% in its sorafenib arm reported a history of alcohol consumption.

Due to the proportion of Asian participants, the proportion of participants with HCC due to an underlying hepatitis B virus infection (30% in the durvalumab monotherapy arm and 30.6% in the sorafenib arm) is reportedly higher in both studies. However, the significant proportions of hepatitis C aetiology and nonviral risk factors were reportedly adequately mapped in the HIMALAYA and IMbrave150 studies.

Overall, the most common disease-related local therapies before the start of each study were in line with what would typically be expected in the target population in the German healthcare context when treated according to the S3 guideline.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 3.1.3 Similarity of the studies for the indirect comparison

Similarity is a key requirement for the inclusion of studies in an adjusted indirect comparison via a common comparator. Overall, the HIMALAYA and IMbrave150 studies share a very similar study design, and the patient populations are also sufficiently similar. This is described in detail below.

Study design

The HIMALAYA and IMbrave150 studies are multicentre, open-label RCTs, each of which included patients with advanced or unresectable HCC. In both studies, patients were not allowed to have received any prior systemic therapy and had to be in Child-Pugh stage A. Only patients with BCLC stage B or C were allowed to be included in the HIMALAYA study. There was no corresponding restriction in the IMbrave150 study. However, approximately 97% of the patients included in the study had BCLC stage B or C at the start of the study (see Table 9).

The periods during which the studies were conducted are comparable as well. While the HIMALAYA study began in October 2017 (currently still ongoing), the IMbrave150 study began in March 2018 and was completed in November 2022.

Planned duration of follow-up observation

The outcome of overall survival was observed until study end in both studies. The planned observation of patient-reported outcomes on morbidity and health-related quality of life differs between the studies. After discontinuation of the study medication, the corresponding outcomes were recorded for up to 3 months in the HIMALAYA study and up to 1 year in the IMbrave150 study. The duration of follow-up for severe AEs also differed between the studies. In the HIMALAYA study, this outcome was recorded for up to 90 days after discontinuation of the study medication, whereas the IMbrave150 study provided merely for a follow-up observation for up to 30 days after discontinuation of the study medication. SAEs were recorded in both studies up to 90 days after discontinuation of the study medication.

In the present assessment, these differences in the planned duration of follow-up observation have no consequences since there are no suitable data for the indirect comparison for the outcomes on morbidity and side effects (see Section I 3.2.1).

Patient population

The demographic and clinical characteristics of the included patients, e.g. age, family origin, BCLC stage, and prior treatment, are sufficiently comparable between the HIMALAYA and IMbrave150 studies.

There are minor differences in the proportion of patients affected by macrovascular invasion and/or extrahepatic spread, which are slightly lower in the HIMALAYA study (approximately 65%) compared to the study population of the IMbrave150 study (approximately 76%). Since no relevant effect modifications are known for this characteristic, the differences for the indirect comparison of the 2 studies are negligible. There are major differences between the 2 study populations with regard to the aetiology of HCC. In around half of the patients in the IMbrave150 study, HCC was the result of hepatitis B infection. In the HIMALAYA study, in contrast, this was the case in only around 31% of patients. A nonviral aetiology was present in

approximately 28% of IMbrave150 participants and approximately 42% of HIMALAYA participants. These differences are also partly reflected in the studies' slightly different proportions of Asian patients: in the HIMALAYA study, the proportion of patients from Asia is lower (approximately 42%) than in the IMbrave150 study (46%). Since aetiology is a known relevant effect modifier, these differences must be taken into account in subgroup analyses (see also Section I 3.2.4).

Subsequent therapies

The data on subsequent therapies available in the HIMALAYA and Imbrave150 studies as presented in Table 12 are not comparable per se due to the different categorization of the subsequent therapies. However, it can be inferred from the data that similar therapies were generally available and used – predominantly targeted therapies with tyrosine kinase inhibitors (e.g. sorafenib and lenvatinib) and immunotherapies.

Common comparator

Patients in the common comparator arms of both studies received sorafenib largely in accordance with the SPC (see Table 7 and description in the text below). For the common comparator sorafenib, the similarity between the HIMALAYA study and the IMbrave150 study was therefore generally sufficient.

Treatment duration and observation period

There are differences between the sorafenib arms of the HIMALAYA and IMbrave150 studies, both in the median duration of treatment and in the median observation period for the overall survival outcome. For example, patients in the sorafenib arm of the HIMALAYA study were treated for a median of 4.1 months and observed for the overall survival outcome of 13.3 months. In the IMbrave150 study, patients in the sorafenib arm were treated for 2.8 months at the 29 August 2019 data cut-off and observed for 10.4 months for the overall survival outcome. No information is available on the duration of treatment of patients in the sorafenib arm of the IMbrave150 study at the 2nd data cut-off (31 August 2020); therefore, it remains unclear whether the differences will also persist at this data cut-off. It is unclear how the observation periods for overall survival were calculated or estimated. Since the median survival times actually observed for the outcome of overall survival do not differ between the studies (13.8 versus 13.4 months), the observation periods are presumed to be sufficiently similar.

Summary on the comparability of the studies

The overall analysis shows some differences in study and patient characteristics between the HIMALAYA and IMbrave150 studies, but none of them fundamentally calls into question their sufficient similarity for conducting an adjusted indirect comparison via the common comparator sorafenib.

This concurs with the company's assessment in that the company likewise deems the HIMALAYA and IMbrave150 studies to be sufficiently similar for conducting an adjusted indirect comparison.

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-HCC18
  - Health status, surveyed using the EQ-5D visual analogue scale (VAS) and Patient Global Impression of Change (PGIC)
- Health-related quality of life
  - surveyed using the EORTC QLQ-C30 and EORTC QLQ-HCC 18
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Patient Reported Outcome(PRO) CTCAE
  - Immune-related AEs (AEs, SAEs, severe AEs)
  - Bleeding (AEs, SAEs, severe AEs)
  - Other specific AEs, if any

Table 14 shows the outcomes for which data were available in the studies included.

Table 14: Matrix of outcomes – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab

Comparison / Study	Outcomes													
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-HCC18)	Health status (EQ-5D VAS)	Health status (PGIC)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-HCC18)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Immune-related AEs (AEs, SAEs, severe AEs)	Bleeding (AEs, SAEs, severe AEs)	Other specific AEs
Durvalumab vs. sorafenib														
HIMALAYA	Yes	No[b]	No[b]	No[b]	No[c]	No[b]	No[b]	Yes	Yes	Yes	No[c]	No[c]	No[c]	No[d]
Atezolizumab + bevacizumab vs. sorafenib														
IMbrave150	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	No[e]	No[f]	No[c]	No[d]
Indirect comparison possible	Yes	No[g]	No[g]	No[g]	No[g]	No[g]	No[g]	No[h]	No[h]	No[h]	No[g]	No[i]	No[g]	No[h]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Outcome was surveyed, but no analyses of the relevant operationalizations are available (see continuous text below).
c. The outcome was recorded in the HIMALAYA and/or IMbrave150 studies, but the company presented no data on the outcome in Module 4 A (see body of text below).
d. The certainty of results required to perform an adjusted indirect comparison is not reached. Therefore, no specific AEs were selected.
e. Outcome not recorded.
f. The outcome was recorded in the IMbrave150 study, but no adequate analyses are available for it (see body of text below).
g. Not possible as (suitable) data are not available for at least 1 side of the indirect comparison.
h. Certainty of results required to perform an adjusted indirect comparison is not reached (see Section I 3.2.2).
i. For the outcome, no indirect comparison is feasible in the present assessment due to the information being insufficient for a similarity check of the operationalizations (see body of text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Morbidity and health-related quality of life

For the patient-reported outcomes on morbidity (EORTC QLQ-C30, EORTC QLQ-HCC18, and VAS of EQ-5D) and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-HCC18), no suitable data are available for an indirect comparison.

The company reports excluding the results for this outcome from an adjusted indirect comparison because during the treatment phase, the patient-reported outcomes were collected at shorter intervals in the IMbrave150 study (every 3 weeks) than in the HIMALAYA study (every 8 weeks). The company argues further that, as a result, potential deteriorations in the IMbrave150 study would be systematically recorded at an earlier stage than in the HIMALAYA study.

This rationale is not appropriate. Since the 2 studies use the same data collection time points, a valid effect estimate for these outcomes can be calculated for each of the 2 studies. Thus, an adjusted indirect comparison is possible if the outcome operationalizations are sufficiently similar.

However, the available data on symptoms, health status, and health-related quality of life are unsuitable for conducting an adjusted indirect comparison for other reasons. For the HIMALAYA study, the only analyses available regarding the cited outcomes are those on the time to confirmed deterioration. Differences in observation periods are found in both the HIMALAYA study and the IMbrave150 study. In light of different observation periods and thus different numbers of possible follow-up surveys, analyses of the time until confirmed deterioration exhibit greater uncertainties compared to analyses of initial deterioration. In this situation, analyses of time to first deterioration are therefore needed. However, such analyses are available only for the IMbrave150 study. Furthermore, for all cited outcomes on morbidity and health-related quality of life, the risk of bias is high already because of the lack of blinding in the presence of subjective recording of outcomes. Irrespective of the fact that the operationalization lacks similarity, the certainty of results criterion for adjusted indirect comparisons would therefore not be met. Hence, an indirect comparison is not calculated for the patient-reported outcomes on symptoms and health-related quality of life.

Immune-related AEs

The company has not presented any indirect comparisons for the outcome of immune-related AEs because, as a result of the study-specific definitions implemented in the studies, it deems any comparisons to be not meaningful. This approach is not appropriate because the comparability of the operationalization of immune-related AEs between the studies has not been analysed. In addition, the company correctly describes that no suitable data are available for the IMbrave150 study, partly due to the lack of a summary analysis of immune-mediated AEs. However, the company would still be expected to present the operationalization and

results of immune-related AEs for the HIMALAYA study, which are completely missing from Module 4 A. In the present assessment, an indirect comparison was not conducted for the outcome.

I 3.2.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias on the outcome level and outcome-specific risk of bias – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab

Comparison Study		Outcomes													
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-HCC18)	Health status (EQ-5D VAS)	Health status (PGIC)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-HCC18)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Immune-related AEs (AEs, SAEs, severe AEs)	Bleeding (AEs, SAEs, severe AEs)	Other specific AEs
Durvalumab vs. sorafenib															
HIMALAYA	L	L	–[b]	–[b]	–[b]	–[c]	–[b]	–[b]	H[d]	H[d]	H[e]	–[c]	–[c]	–[c]	–[f]
Atezolizumab + bevacizumab vs. sorafenib															
IMbrave150	L	L	–[g]	–[g]	–[g]	–[h]	–[g]	–[g]	H[d]	H[d]	H[e]	–[h]	–[i]	–[c]	–[f]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No analyses of initial deterioration are available (see Section I 3.2.1).
c. The outcome was surveyed in the HIMALAYA and/or Imbrave150 studies, but the company presented no data on the outcome in Module 4 A (see Section I 3.2.1).
d. Potential difference in observation periods between the treatment arms; potentially informative censoring.
e. Lack of blinding in subjective recording of outcomes.
f. Requirement for the certainty of results to perform an adjusted indirect comparison is not met. Therefore, no specific AEs were selected.
g. Not assessed because no (suitable) data are available for at least 1 side of the indirect comparison (see Section I 3.2.1).
h. Outcome not recorded.
i. The outcome was recorded in the IMbrave150 study, but no adequate data are available for it (see Section I 3.2.1).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The outcome-specific risk of bias of the results on the outcome of overall survival was rated as low for each of the studies HIMALAYA and IMbrave150.

For the results on the outcomes of SAEs and severe AEs, the risk of bias was rated as high for both the HIMALAYA and IMbrave150 studies. Side effect outcomes were surveyed only for the period of treatment with the study medication (plus 3 months for the HIMALAYA study or plus 30 days [AEs] or 90 days [SAEs] or until the start of a subsequent antineoplastic treatment, whichever occurred first for the IMbrave150 study). Regarding the outcomes mentioned, this results for both studies in marked differences in the observation periods of individual patients with potentially informative censoring. The open-label study design leads to a high risk of bias for the results of the outcome of discontinuation due to AEs.

If only 1 study is available on 1 side of an indirect comparison and results of individual outcomes of this study have a high risk of bias, the certainty of results required to conduct an adjusted indirect comparison is insufficient. Thus, the certainty of results is insufficient for an adjusted indirect comparison in all of the outcomes of the side effects category for which suitable data are available in the individual studies.

Data for the present assessment which allow a meaningful adjusted indirect comparison are available only for overall survival. This deviates from the approach of the company, which, in addition to the outcome of overall survival, also used the outcomes of AEs, SAEs, discontinuation due to AEs, and severe AEs for an adjusted indirect comparison.

I 3.2.3 Results

Table 16 summarizes the results comparing durvalumab versus atezolizumab + bevacizumab as first-line treatment of advanced or unresectable HCC in adult patients with Child-Pugh A or no hepatic cirrhosis. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. Kaplan-Meier curves for time-to-event analyses can be found in I Appendix B, results for common AEs in I Appendix D of the full dossier assessment. No Kaplan-Meier curves for the entire study population are available for the IMbrave150 study; the Kaplan-Meier curves for the global cohort can be found in I Appendix B of the full dossier assessment as an approximation of the results for the entire study population.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Durvalumab or atezolizumab + bevacizumab** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Sorafenib** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Between-group difference** **HR [95% CI]; p-value**
Mortality					
Overall survival					
Durvalumab vs. sorafenib					
HIMALAYA (data cut-off from 27 August 2021)	389	16.6 [14.1; 19.1] 280 (72.0)	389	13.8 [12.3; 16.1] 293 (75.3)	0.86 [0.73; 1.01]; 0.068[a]
Atezolizumab + bevacizumab vs. sorafenib					
IMbrave150 (data cut-off from 31 August 2020)	375	19.4 [17.1; 23.7] 196 (52.3)	183	13.4 [11.4; 16.9] 110 (60.1)	0.66 [0.52; 0.83]; < 0.001[b]
Indirect comparison using common comparators[c]:					
Durvalumab vs. atezolizumab + bevacizumab					1.30 [0.98; 1.72]; 0.064
Morbidity					
Symptoms (EORTC QLQ-C30, EORTC-QLQ-HCC 18)	No suitable data[d]				
Health status (EQ-5D VAS, PGIC)	No suitable data[d]				
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-HCC18)	No suitable data[d]				
Side effects[e]					
AEs (supplementary information)					
Durvalumab vs. sorafenib					
HIMALAYA	388	1.0 [0.9; 1.1] 345 (88.9)	374	0.3 [0.3; 0.4] 357 (95.5)	–
Atezolizumab + bevacizumab vs. sorafenib					
IMbrave150	368	ND 361 (98.1)	174	ND 171 (98.3)	–

Table 16: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Outcome category Outcome Comparison Study	Durvalumab or atezolizumab + bevacizumab N	Median time to event in months [95% CI] Patients with event n (%)	Sorafenib N	Median time to event in months [95% CI] Patients with event n (%)	Between-group difference HR [95% CI]; p-value
SAEs					
Durvalumab vs. sorafenib					
HIMALAYA	388	NA [NC; NC] 115 (29.6)	374	31.2 [23.8; NC] 111 (29.7)	0.91 [0.70;1.18]; 0.463[f]
Atezolizumab + bevacizumab vs. sorafenib					
IMbrave150	368	ND 146 (39.7)	174	ND 52 (29.9)	1.10 [0.80; 1.51]; 0.570[f]
Indirect comparison using common comparators:					
Durvalumab vs. atezolizumab + bevacizumab					–[g]
Severe AEs[h]					
Durvalumab vs. sorafenib					
HIMALAYA	388	16.3 [11.1; NC] 158 (40.7)	374	4.5 [2.8; 6.1] 210 (56.1)	0.54 [0.44; 0.67]; < 0.001[f]
Atezolizumab + bevacizumab vs. sorafenib					
IMbrave150	368	ND 236 (64.1)	174	ND 104 (59.8)	0.80 [0.63; 1.01]; 0.065[f]
Indirect comparison using common comparators:					
Durvalumab vs. atezolizumab + bevacizumab					–[g]
Discontinuation due to AEs					
Durvalumab vs. sorafenib					
HIMALAYA	388	NA [NC; NC] 32 (8.2)	374	NA 63 (16.8)	0.45 [0.29; 0.68]; < 0.001[f]
Atezolizumab + bevacizumab vs. sorafenib					
IMbrave150	368	ND 62 (16.8)	174	ND 19 (10.9)	1.06 [0.63; 1.79]; 0.815[f]
Indirect comparison using common comparators:					
Durvalumab vs. atezolizumab + bevacizumab					–[g]
PRO-CTCAE	No suitable data[i]				
Immune-related AEs	No suitable data[j]				
Bleeding (AEs, SAEs, severe AEs)	No suitable data[j]				

Table 16: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, indirect comparison: durvalumab versus atezolizumab + bevacizumab (multipage table)

Outcome category Outcome Comparison Study	Durvalumab or atezolizumab + bevacizumab N	Durvalumab or atezolizumab + bevacizumab Median time to event in months [95% CI] Patients with event n (%)	Sorafenib N	Sorafenib Median time to event in months [95% CI] Patients with event n (%)	Between-group difference HR [95% CI]; p-value

a. HR and 95% CI from a Cox proportional hazards model, stratified by aetiology of liver disease (hepatitis B vs. hepatitis C vs. other), ECOG PS (0 vs. 1), macrovascular invasion (yes vs. no); p-value from stratified log-rank test.
b. HR and 95% CI from a Cox proportional hazards model stratified by geographical region (Asia without Japan/rest), extrahepatic spread and/or macrovascular invasion (yes/no), and AFP at screening (< 400 ng/mL / ≥ 400 ng/mL); p-value: stratified log-rank test.
c: Indirect comparison according to Bucher [3].
d. No analyses of first-time deterioration are available for the HIMALAYA study.
e. For outcomes in the side effects category, the data cut-off date of 27 August 2021 was used for the HIMALAYA study and the data cut-off date of 29 November 2019 for the IMbrave150 study.
f. Effect estimate and 95% CI from an unstratified Cox proportional hazards model; p-value from unstratified log-rank test.
g. An indirect comparison was not calculated because the certainty of results required for conducting an adjusted indirect comparison was not met (see Section I 3.2.2). The effect estimates are presented as supplementary information in I Appendix C of the full dossier assessment.
h. Operationalized as CTCAE grade ≥ 3.
i. Surveyed only in the HIMALAYA study.
j. No data are available in Module 4 A.

AE: adverse event; AFP: alpha-fetoprotein; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HCC: hepatocellular carcinoma; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NC: not calculable; NR: not reached; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

There was 1 RCT each on both sides of this adjusted indirect comparison. Hence, the check of homogeneity was no longer required. As there is no directly comparative study for the comparison of durvalumab versus the ACT, it is impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived on the basis of the data available from the adjusted indirect comparison.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between durvalumab and atezolizumab + bevacizumab for the outcome of overall survival. This results in no hint of an added benefit of durvalumab in comparison with atezolizumab + bevacizumab; an added benefit is therefore not proven.

Morbidity

No suitable data are available for outcomes in the morbidity category. This results in no hint of an added benefit of durvalumab in comparison with atezolizumab + bevacizumab; an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for outcomes in the health-related quality of life category. This results in no hint of an added benefit of durvalumab in comparison with atezolizumab + bevacizumab; an added benefit is therefore not proven.

Side effects

Due to an insufficient certainty of results in the HIMALAYA and IMbrave150 studies, no indirect comparison was calculated for the outcomes of SAEs, severe AEs, and discontinuation due to AEs. Furthermore, no (suitable) data are available for the outcomes of PRO-CTCAE, immune-mediated AEs, or haemorrhage. Hence, no suitable data on the AE outcomes are available for the indirect comparison. This results in no hint of greater or lesser harm from durvalumab in comparison with atezolizumab + bevacizumab; greater or lesser harm is therefore not proven.

I 3.2.4 Subgroups and other effect modifiers

The following potential effect modifiers should be taken into account for the present benefit assessment:

- Age (< 65 years/≥ 65 years)
- Sex (female/male)
- Extrahepatic spread and/or macrovascular invasion at baseline (present/absent)
- Aetiology of HCC (hepatitis B/hepatitis C/nonviral)

The company presented no subgroup analyses for the indirect comparison. The company argues that indirect comparisons have limited interpretive value as they are based on the overall population and, therefore, subgroup analyses relying on indirect comparisons would not be meaningfully interpretable. This approach is not appropriate.

Particularly in the present data constellation, it is advisable to consider subgroup analyses. For example, subgroup analyses in the benefit assessment of atezolizumab in the present therapeutic indication [20,21] showed a relevant effect modification for the outcome of overall survival for the characteristic of HCC aetiology (hepatitis B or C vs. nonviral aetiology). In addition, the analysis of the similarity between the HIMALAYA and IMbrave150 studies showed that the distribution of this characteristic differs between the studies (see Section I 3.1.3). It is unclear whether there is an effect modification for the outcome of overall survival in the present indirect comparison. Due to the lack of subgroup analyses for the indirect comparison, no conclusions can be drawn on potential effect modifications for the comparison of durvalumab versus atezolizumab + bevacizumab.

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 17).

Table 17: Extent of added benefit at outcome level: durvalumab versus atezolizumab + bevacizumab

Outcome category **Outcome**	**Durvalumab vs. atezolizumab + bevacizumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	16.6 vs. 19.4 HR: 1.30 [0.98; 1.72] p = 0.064	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, EORTC-QLQ-HCC 18)	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS, PGIC)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-HCC18)	No suitable data[c]	Lesser/added benefit not proven
Side effects		
SAEs	No suitable data[d]	Greater/lesser harm not proven
Severe AEs[e]	No suitable data[d]	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data[d]	Greater/lesser harm not proven
PRO-CTCAE	No suitable data[c]	Greater/lesser harm not proven
Immune-related AEs (AEs, SAEs, severe AEs)	No suitable data[c]	Greater/lesser harm not proven
Bleeding (AEs, SAEs, severe AEs)	No suitable data[c]	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Indirect comparison not possible as results are not available for at least 1 edge of the indirect comparison.
d. Effect estimation from indirect comparison not presented due to insufficient certainty of results.
e. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; HCC: hepatocellular carcinoma; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; SAE: serious adverse event; VAS: visual analogue scale

I 3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of durvalumab in comparison with atezolizumab + bevacizumab

Positive effects	**Negative effects**
–	–
For each of the outcomes of the categories of morbidity, health-related quality of life, and side effects, no suitable data are available for the indirect comparison.	

Overall, based on the adjusted indirect comparison using the common comparator sorafenib, there are neither favourable nor unfavourable effects of durvalumab in comparison with atezolizumab + bevacizumab. However, it should be noted that usable results with sufficient certainty of results for conducting an indirect comparison are available only for the outcome of overall survival. For the overall population, there is no hint of an added benefit of durvalumab for this outcome. For each of the outcomes of the categories of morbidity, health-related quality of life, and side effects, no suitable data are available for the indirect comparison.

In summary, for adult patients with advanced or unresectable HCC with Child-Pugh A or no hepatic cirrhosis, there is no hint of an added benefit of durvalumab as first-line treatment compared with the ACT atezolizumab + bevacizumab; an added benefit is therefore not proven for this patient group.

The assessment described above concurs with that of the company, which did not claim any added benefit for this patient group.

I 4 Research question 2: Patients with Child-Pugh B

I 4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on durvalumab (status: 18 October 2023)
- bibliographical literature search on durvalumab (last search on 16 October 2023)
- search in trial registries/trial results databases for studies on durvalumab (last search on 20 October 2023)
- search on the G-BA website for durvalumab (last search on 20 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on durvalumab (last search on 21 December 2023); for search strategies, see Appendix I A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCT for the direct comparison of durvalumab versus best supportive care.

I 4.2 Results on added benefit

The company has presented no data for assessing the added benefit of durvalumab as first-line treatment in comparison with the ACT in adult patients with advanced or unresectable HCC with Child-Pugh B. This resulted in no hint of an added benefit of durvalumab in comparison with the ACT. An added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

The company has presented no data for the assessment of added benefit of durvalumab as first-line treatment of advanced or unresectable HCC in adult patients with Child-Pugh B. An added benefit of durvalumab in comparison with the ACT is therefore not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for this patient group.

I 5 Probability and extent of added benefit – summary

Table 19 summarizes the result of the assessment of added benefit of durvalumab in comparison with the ACT.

Table 19: Durvalumab – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	First-line treatment of adult patients with advanced or unresectable hepatocellular carcinoma with Child-Pugh A or no liver cirrhosis	Atezolizumab in combination with bevacizumab	Added benefit not proven
2	First-line treatment of advanced or unresectable hepatocellular carcinoma in adult patients with Child-Pugh A	Best supportive care[c]	Added benefit not proven

a. For this therapeutic indication, it is assumed according to G-BA that neither curative treatment (for BLCL stages 0 and A) nor locoregional therapy in BLCL stage B, particularly transarterial (chemo)embolization (TACE or TAE), is an option (any longer). It is also assumed that patients in BCLC stage D are ineligible for durvalumab monotherapy.
b. Presentation of the respective ACT specified by the G-BA.
c. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BCLC: Barcelona Clinic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; TAE: transarterial embolization

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691. https://doi.org/10.1016/S0895-4356(97)00049-8.

4. AstraZeneca. A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA); study D419CC00002; Clinical Study Report [unpublished]. 2022.

5. AstraZeneca. A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA); study D419CC00002; Zusatzanalysen [unpublished]. 2023.

6. AstraZeneca. A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with advanced Hepatocellular Carcinoma (HIMALAYA) [online]. [Accessed: 09.01.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-005126-11.

7. AstraZeneca. Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA) [online]. 2023 [Accessed: 09.10.2024]. URL: https://clinicaltrials.gov/study/NCT03298451.

8. Abou-Alfa GK, Lau G, Kudo M et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid 2022; 1(8): EVIDoa2100070. https://doi.org/10.1056/EVIDoa2100070.

9. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Durvalumab (Neues Anwendungsgebiet: hepatozelluläres Karzinom, Erstlinie, Kombination mit Tremelimumab) [online]. 2023 [Accessed: 09.02.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/941/.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Tremelimumab und Durvalumab (hepatozelluläres Karzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 23.08.2023]. URL: https://www.iqwig.de/download/a23-27-und-a23-30_tremelimumab-und-durvalumab_nutzenbewertung-35a-sgb-v_v1-1.pdf.

11. AstraZeneca. A Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150); study YO40245; Zusatzanalysen [unpublished]. 2023.

12. F. Hoffmann-La Roche. A Phase III, Open-Label, Randomized Study of Atezolizumab in Combination with Bevacizumab Compared with Sorafenib in Patients with Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma [online]. [Accessed: 09.01.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-003691-31.

13. Hoffmann-La Roche. A Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150) [online]. 2023 [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT03434379.

14. Casak SJ, Donoghue M, Fashoyin-Aje L et al. FDA Approval Summary: Atezolizumab Plus Bevacizumab for the Treatment of Patients with Advanced Unresectable or Metastatic Hepatocellular Carcinoma. Clin Cancer Res 2021; 27(7): 1836-1841. https://doi.org/10.1158/1078-0432.CCR-20-3407.

15. 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. https://doi.org/10.1016/j.jhep.2021.11.030.

16. Finn RS, Qin S, Ikeda M et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382(20): 1894-1905. https://doi.org/10.1056/NEJMoa1915745.

17. Galle PR, Finn RS, Qin S 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. Lancet Oncol 2021; 22(7): 991-1001. https://doi.org/10.1016/s1470-2045(21)00151-0.

18. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Atezolizumab (Neues Anwendungsgebiet: hepatozelluläres Karzinom, Kombination mit Bevacizumab) [online]. 2021 [Accessed: 09.02.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/613/.

19. Hsu C, Ducreux M, Zhu AX et al. Hepatic Events and Viral Kinetics in Hepatocellular Carcinoma Patients Treated with Atezolizumab plus Bevacizumab. Liver Cancer 2023; 12(1): 44-56. https://doi.org/10.1159/000525499.

20. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a20-97_atezolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

21. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (hepatozelluläres Karzinom) – Addendum zum Auftrag A20-97 [online]. 2021 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a21-45_atezolizumab_addendum-zum-auftrag-a20-97_v1-0.pdf.

22. Kudo M, Finn RS, Galle PR et al. IMbrave150: Efficacy and Safety of Atezolizumab plus Bevacizumab versus Sorafenib in Patients with Barcelona Clinic Liver Cancer Stage B Unresectable Hepatocellular Carcinoma: An Exploratory Analysis of the Phase III Study. Liver Cancer 2023; 12(3): 238-250. https://doi.org/10.1159/000528272.

23. 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. https://doi.org/10.1159/000525671.

24. Qin S, Ren Z, Feng YH et al. 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. https://doi.org/10.1159/000513486.

25. Salem R, Li D, Sommer N et al. Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: Results from the IMbrave150 trial. Cancer Med 2021; 10(16): 5437-5447. https://doi.org/10.1002/cam4.4090.

26. AstraZeneca. Fachinformation IMFINZI 50 mg/ml Konzentrat zur Herstellung einer Infusionslösung. Stand der Information: November. 2023.

27. Bayer. Nexavar 200 mg Filmtabletten [online]. 2023 [Accessed: 19.12.2023]. URL: https://www.fachinfo.de.

28. Roche Pharma. Fachinformation Tecentriq 840mg/1.200mg. Stand: August. 2023.

29. Leitlinienprogramm Onkologie. S3-Leitlinie Diagnostik und Therapie des Hepatozellulären Karzinoms und biliärer Karzinome (Langversion). Version 4.0 [online]. 2023. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/HCC/Version_4/LL_Hepatozelluläres_Karzinom_und_biliäre_Karzinome_Langversion_4.0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-138.html.