IQWiG Reports – Commission No. A20-97

Atezolizumab (hepatocellular carcinoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Atezolizumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2021). 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.

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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
AFP	alpha fetoprotein
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire Cancer-30
EORTC QLQ-HCC18	European Organization for Research and Treatment of Cancer – HCC-specific Quality of Life Questionnaire
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed model for repeated measures
PFS	progression-free survival
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 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 atezolizumab. 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 30 November 2020.

Research question

The aim of this report is to assess the added benefit of combination therapy of atezolizumab plus bevacizumab (hereinafter atezolizumab + bevacizumab) in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who received no prior systemic therapy.

The G-BA's specification of the ACT results in 2 research questions, which are presented in Table 2 below.

Table 2: Research questions of the benefit assessment of atezolizumab + bevacizumab

Research question	Indication[a]	ACT[b]
1	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class A or no hepatic cirrhosis	**Sorafenib** or lenvatinib
2	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class B	Best supportive care[c]

a. For this therapeutic indication, it is assumed that neither curative treatment (for BLCL stage 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 treatment with atezolizumab in combination with bevacizumab.
b. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
c. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BCLC: Barcelona Clinic Liver Cancer; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; TAE: transarterial embolization

The company followed the specification of the ACT. For research question 1, the company selected sorafenib from the options named.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

Results on research question 1: Patients with Child-Pugh class A or no hepatic cirrhosis

Study pool and study characteristics

The study pool for the benefit assessment of atezolizumab + bevacizumab in comparison with the ACT consists of the RCT IMbrave150.

IMbrave150 is an open-label, randomized, controlled study comparing atezolizumab + bevacizumab with sorafenib. The study included adults with locally advanced or metastatic and/or unresectable HCC who received no prior systemic therapy. Further inclusion criteria were Child-Pugh class A and general condition rated as an Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) score of 0 or 1.

In the global cohort, a total of 501 patients were randomly allocated in a 2:1 ratio to treatment with atezolizumab + bevacizumab (N = 336) or sorafenib (N = 165). In addition to this global cohort, there was a Chinese cohort with an identical study protocol. This cohort is described below.

Atezolizumab + bevacizumab treatment was administered in compliance with the Summary of Product Characteristics (SPC). Virtually the same is true for sorafenib treatment.

Treatment was continued until loss of clinical benefit, unacceptable toxicity, revocation of consent, or death.

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

Chinese cohort

In an extended inclusion phase carried out in China, additional patients were randomized in a 2:1 ratio to the treatment arms. The Chinese cohort (N = 194) very strongly overlaps (n = 137) with the global cohort. The patients of the Chinese cohort were treated using the identical study protocol and statistical analysis plan of the global study population, but according to the company, the data were analysed in a separate study report.

Patients who are included in the Chinese cohort but not in the global cohort (n = 57) represent a relevant subpopulation of the IMbrave150 study and are factored into the present benefit assessment.

In general, the benefit assessment is based on the summary analysis of both IMbrave150 cohorts at the data cut-offs 29 August 2019 or 29 November 2019. The analysis of the global cohort as per the 31 August 2020 data cut-off was used only for the outcome of overall survival. The

summary analysis is available only for the 29 August 2019 data cut-off. The increase in follow-up period by almost 1 year results in a higher information content.

Risk of bias

The risk of bias across outcomes is rated as low for the IMbrave150 study. At outcome level, the risk of bias was rated as low for overall survival and as high for all other outcomes for which usable data are available.

The available data allow deriving no more than indications, e.g. of an added benefit, for the outcome of overall survival. Due to the high risk of bias, only a hint, e.g. of added benefit, can be derived for the results of the remaining outcomes. Conversely, there may be no need to downgrade the certainty of results for specific outcomes (see description of results below).

Results

Mortality

Overall survival

For the outcome of all-cause mortality, a statistically significant difference between treatment groups was found for the global cohort at the 31 August 2020 data cut-off. In addition, there is an effect modification by the characteristic of HCC aetiology. For the individual subgroups, an indication of added benefit of atezolizumab + bevacizumab in comparison with sorafenib was found only for patients with a viral aetiology (hepatitis B or C). For patients with non-viral aetiology, in contrast, there is no hint of any added benefit of atezolizumab + bevacizumab in comparison with sorafenib; an added benefit is therefore not proven.

Morbidity

Nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhoea (symptom scales of the European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire Cancer-30 [EORTC QLQ-C30]), icterus, abdominal swelling (symptom scales of the European Organization for Research and Treatment of Cancer – HCC-specific Quality of Life Questionnaire EORTC QLQ-HCC18]), and fatigue (EORTC QLQ-C30 and EORTC QLQ-HCC18)

A statistically significant difference in favour of atezolizumab + bevacizumab in comparison with sorafenib was found for each of the EORTC QLQ-C30 symptom scales of nausea and vomiting, dyspnoea, appetite loss, constipation, and diarrhoea, the EORTC QLQ-HCC18 symptom scales of icterus and abdominal swelling, and the fatigue symptom scales of EORTC QLQ-C30 and EORTC QLQ-HCC18. For each of these symptom scales, there is therefore a hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

Pain (EORTC QLQ-C30 and -HCC18)

The pain symptom scale is surveyed using the two questionnaires EORTC QLQ-C30 and -HCC18. The results are therefore interpreted in light of the overall picture. For both symptom scales, there is a statistically significant difference in favour of atezolizumab +

bevacizumab in comparison with sorafenib. For the outcome of pain, as measured with the EORTC-HCC18, the effect is at most minor. Nevertheless, the effects are viewed as being in the same direction. Differences in extent are taken into account in the overall picture when deriving added benefit on the outcome level. Overall, for the outcome of pain, there is a hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

Insomnia (EORTC QLQ-C30), fever (EORTC QLQ-HCC18)

No statistically significant difference between treatment groups was found for the EORTC QLQ-C30 insomnia symptom scale or for the EORTC QLQ-HCC18 fever symptom scale. This did not result in any added benefit of atezolizumab + bevacizumab in comparison with sorafenib for these symptom scales; an added benefit is therefore not proven for any of them.

Health status (European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS], EQ-5D VAS)

For the outcome of health status (as measured with EQ-5D VAS), the difference in mean change from baseline over the course of the study is analysed by means of a mixed model for repeated measures (MMRM). A statistically significant difference was found in favour of atezolizumab + bevacizumab. However, the 95% confidence interval of the SMD in the form of Hedges' g is not fully outside of the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. Hence, there is no hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib; an added benefit is therefore not proven.

Health-related quality of life

Global health status and physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (EORTC QLQ-C30 functioning scales), body image, nutrition (EORTC QLQ-HCC18 functioning scales)

A statistically significant difference in favour of atezolizumab + bevacizumab in comparison with sorafenib was each shown for global health status, the EORTC QLQ-C30 functional scales of physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning as well as the EORTC QLQ-HCC18 functional scales of body image and nutrition. For each of these outcomes, this results in a hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

Sex life (EORTC QLQ-HCC18)

For the sex life functional scale of the EORTC QLQ-HCC18, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib for this symptom scale; an added benefit is therefore not proven.

AEs

Serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3), and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, and discontinuation due to AEs. Consequently, there is no hint of greater or lesser harm from atezolizumab + bevacizumab in comparison with sorafenib for these outcomes; greater or lesser harm is therefore not proven for any of them.

Immune-mediated AEs and bleeding (AEs, SAEs, severe AEs for each)

No usable data are available for immune-mediated AEs and bleeding (AEs, SAEs, severe AEs for each). Consequently, there is no hint of greater or lesser harm from atezolizumab + bevacizumab in comparison with sorafenib for any of these outcomes; greater or lesser harm is therefore not proven for any of them.

Palmar-plantar erythrodysaesthesia syndrome (severe AEs)

For the outcome of palmar-plantar erythrodysaesthesia syndrome (severe AEs), a statistically significant difference was found in favour of atezolizumab + bevacizumab in comparison with sorafenib. Due to the size of the effect and the fact that, despite a longer follow-up time, no event was observed in the intervention arm, this outcome is associated with a high certainty of results even though the risk of bias of results was high. This results in an indication of lesser harm from atezolizumab + bevacizumab in comparison with sorafenib.

Further specific AEs

Alopecia (preferred term [PT], AEs)

For the outcome of alopecia (PT, AEs), a statistically significant difference was found in favour of atezolizumab + bevacizumab in comparison with sorafenib. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size. Hence, there is an indication of lesser harm from atezolizumab + bevacizumab in comparison with sorafenib.

Diarrhoea, blood bilirubin increased (PT, severe AEs each), general disorders and administration site conditions, metabolic and nutritional disorders, respiratory, thoracic, and mediastinal disorders (System Organ Class [SOC], severe AEs each)

A statistically significant difference was found in favour of atezolizumab + bevacizumab in comparison with sorafenib for each of the outcomes of diarrhoea and blood bilirubin increased (PT, severe AEs for each) and for the outcomes of general disorders and administration site conditions, metabolic and nutritional disorders as well as respiratory, thoracic, and mediastinal disorders (SOC, severe AEs for each). Hence, there is a hint of lesser harm from atezolizumab + bevacizumab in comparison with sorafenib for each outcome.

Infections and infestations (SOC, SAEs)

For the outcome of infections and infestations (SOC, SAEs), a statistically significant difference was found to the disadvantage of atezolizumab + bevacizumab in comparison with sorafenib. Hence, there is a hint of greater harm from atezolizumab + bevacizumab in comparison with sorafenib.

Results on research question 2: Patients with Child-Pugh class B

For adult patients with advanced or unresectable HCC of Child-Pugh class B who received no prior systemic treatment, the company presents no data for the assessment of added benefit of atezolizumab + bevacizumab in comparison with the ACT. This results in no hint of added benefit of atezolizumab + bevacizumab in comparison with the ACT. An added benefit is therefore not proven.

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

On the basis of the presented results, the probability and extent of added benefit of atezolizumab + bevacizumab in comparison with the ACT are assessed as follows:

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

The overall picture shows several favourable effects, in some cases only for subgroups, and one unfavourable effect; these effects have a probability of a hint or indication and vary in their extents.

The favourable effects in overall survival are found only in patients with HCC of viral aetiology. For this reason, hereinbelow, the favourable and unfavourable effects are weighed separately by aetiology.

Patients with HCC of viral aetiology (hepatitis B or C)

For adult patients with HCC of viral aetiology (hepatitis B or C), there is an indication of major added benefit for the outcome of overall survival. This favourable effect is supported by the hints of added benefit for the symptom and health-related quality of life outcomes, some of major extent. Furthermore, various specific AEs result in hints and indications of lesser harm with an extent up to major. As to the unfavourable effects, a hint of greater harm of minor extent was found in the outcome category of serious/severe AEs. Further, no usable data are available for atezolizumab-specific or bevacizumab-specific AEs, immune-mediated AEs, and bleeding

[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].

(AEs, SAEs, severe AEs for each). It is believed that, even if unfavourable effects were found concerning these outcomes, the favourable effects would not be called into question. Overall, the extent of added benefit is deemed major in this situation. For adult patients with advanced or unresectable HCC of viral aetiology and Child-Pugh class A or no hepatic cirrhosis who received no prior systemic therapy, this results in an indication of major added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

Patients with HCC of non-viral aetiology

For adult patients with HCC of non-viral aetiology, several favourable effects were found as well. Hints of added benefit, some of them of major extent, were found for the categories of symptoms and health-related quality of life. For various specific AEs, there are hints and indications of lesser harm with an extent of up to major. These favourable effects are offset by a hint of greater harm with an extent of minor for the outcome category of serious/severe AEs (as was the case for patients with HCC of viral aetiology). Further, no usable data are available for atezolizumab-specific or bevacizumab-specific AEs, immune-mediated AEs, and bleeding (AEs, SAEs, and severe AEs for each). In this situation as well, it is thought that even if unfavourable effects were found for these outcomes, they would not call the favourable effects into question. Overall, the extent of added benefit in this situation is deemed considerable. For adult patients with advanced or unresectable HCC of non-viral aetiology and Child-Pugh class A or no hepatic cirrhosis who received no prior systemic therapy, this results in a hint of considerable added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

Research question 2: Patients with Child-Pugh class B

The company has not presented any data for the assessment of added benefit of atezolizumab + bevacizumab in adult patients with advanced or unresectable HCC of Child-Pugh class B who received no prior systemic therapy. An added benefit of atezolizumab + bevacizumab in comparison with the ACT is therefore not proven for these patients.

Table 3 presents a summary of the probability and extent of added benefit of atezolizumab + bevacizumab.

Table 3: Atezolizumab + bevacizumab – probability and extent of added benefit

Research question	Indication[a]	ACT [b]	Probability and extent of added benefit
1	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class A or no hepatic cirrhosis	**Sorafenib** or lenvatinib	▪ Patients with HCC of viral aetiology: Indication of major added benefit[c] ▪ Patients with HCC of non-viral aetiology: Hint of considerable added benefit[c]
2	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class B	BSC[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. For this therapeutic indication, it is assumed that neither curative treatment (for BLCL stage 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 treatment with atezolizumab in combination with bevacizumab.
c. Only patients with an ECOG-PS of 0 or 1 were included in the IMbrave150 study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.
d. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BCLC: Barcelona Clinic Liver Cancer; BSC: best supportive care; 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 deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of atezolizumab in combination with bevacizumab (hereinafter atezolizumab + bevacizumab) in comparison with the ACT in adult patients with advanced or unresectable HCC who received no prior systemic therapy.

The G-BA's specification of the ACT results in 2 research questions, which are presented in Table 4 below.

Table 4: Research questions of the benefit assessment of atezolizumab + bevacizumab

Research question	Indication[a]	ACT[b]
1	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class A or no hepatic cirrhosis	**Sorafenib** or lenvatinib
2	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class B	Best supportive care[c]

a. For this therapeutic indication, it is assumed that neither curative treatment (for BLCL stage 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 treatment with atezolizumab in combination with bevacizumab.
b. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
c. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BCLC: Barcelona Clinic Liver Cancer; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; TAE: transarterial embolization

The company followed the specification of the ACT. For research question 1, the company selected sorafenib from the options mentioned.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

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

2.3.1 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on atezolizumab (as of 2 October 2020)
- Bibliographic literature search on atezolizumab (most recent search on 2 October 2020)
- Search in trial registries / study results databases on atezolizumab (most recent search on 5 October 2020)
- Search on the G-BA website on atezolizumab (most recent search on 2 October 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on atezolizumab (most recent search on 1 December 2020)

The check did not identify any additional relevant studies.

2.3.1.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication (yes/no [reference])
IMbrave150	Yes	Yes	No	No[c]	Yes [3,4]	Yes [5]

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. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the study report in Module 5 of the dossier.

RCT: randomized controlled trial

The study pool for the benefit assessment of atezolizumab + bevacizumab in comparison with the ACT for research question 1 consists of the IMbrave150 RCT and coincides with the study pool of the company.

2.3.1.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
IMbrave150	RCT, open-label, parallel-group	Adults with locally advanced or metastatic and/or unresectable HCC[b] ▪ without systemic prior therapy and with ▪ Child-Pugh class A ▪ ECOG-PS 0 or 1 ▪ ≥ 1 according to RECIST Version 1.1 measurable untreated lesion	Global cohort: Atezolizumab + bevacizumab (N = 336) Sorafenib (N = 165) Chinese cohort[c, d]: Atezolizumab + bevacizumab (N = 133) Sorafenib (N = 61) Total: Atezolizumab + bevacizumab (N = 375) Sorafenib (N = 183)	Screening: 28 days Treatment: until loss of clinical benefit[e], unacceptable toxicity, revocation of consent, or death. Follow-up[f]: maximum until death	111 centres[g] in Australia, Canada, China, Czech Republic, Germany, France, Hong Kong, Italy, Japan, Poland, Russia, Singapore, South Korea, Spain, Taiwan, United Kingdom, United States 03/2018–ongoing 1st data cut-off: 29/08/2019[h] FDA 3-month safety update: 29/11/2019 2nd data cut-off: 31/08/2020[i]	Co-primary outcomes: Overall survival and PFS Secondary: symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Diagnosis confirmed by histology/cytology or in accordance with AASLD criteria for patients with cirrhosis or by histology in patients without cirrhosis.
c. To support approval in China, patients of Chinese descent who reside in China, Hong Kong, or Taiwan were included.
d. Below, the Chinese cohort is no longer presented separately because, where available, the analyses of the entire population of the IMbrave 150 study were used.
e. Assessed by the investigator in accordance with RECIST Version 1.1.
f. Outcome-specific information is provided in Table 8.
g. Data for the global cohort of the IMbrave150 study.
h. Final/primary analysis of PFS and overall survival.
i. Analysis of efficacy outcomes upon EMA request 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; IRF: independent review facility; N: number of randomized (included) patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characterization of the intervention – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study	Intervention	Comparison
IMbrave150	Atezolizumab, 1200 mg i.v. on Day 1 of the 21-day cycles + Bevacizumab, 15 mg/kg i.v. on Day 1 of the 21-day cycles	Sorafenib, 400 mg, orally, twice daily
	▪ Dose reductions were not permitted. ▪ In case of toxicity, separate dose interruptions for atezolizumab or bevacizumab were permitted.	▪ Dose reductions were permitted as per SPC[a].
	Non-permitted 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 NSAID ▪ ≤ 60 days before the start of the study medication: ▫ Radiotherapy in the abdominal/pelvic region ▫ Abdominal surgery ▪ ≤ 4 weeks before the start of the study medication and during the study: ▫ Major surgical procedures[b] ▫ Other radiotherapy[c] ▫ Local hepatic therapies ▫ Systemic immunostimulants (including interferons or interleukin-2)[d] ▫ Attenuated live vaccines[e] ▪ ≤ 2 weeks before the start of the study medication and during the study: ▫ Strong CYP3A4 inducers[f] ▫ Systemic immunosuppressants[g] ▫ Oral and intravenous antibiotics[h] ▪ ≤ 10 days before the start of the study medication and during the study: ▫ Aspirin (> 325 mg/day) or dipyridamole, ticlopidine, clopidogrel and cilostazol ▫ Therapeutic use of full-dose, oral or parenteral anticoagulants or thrombolytic agents ▪ From the start of study medication: ▫ Herbal therapies / traditional Chinese medicine with demonstrated anti-cancer activity **Permitted concomitant treatment** ▪ Against uncontrolled tumour pain: Pain medication in a stable dosing regimen at study start ▪ Prophylactic anticoagulation if the drug effect leads to an INR < 1.5-fold the upper limit of normal (ULN) and an aPTT in the normal range within 14 days of the study start as well as prophylactic low-molecular-weight heparin ▪ Premedication with antihistamines, antipyretics, and analgesics upon the investigator's discretion in case of infusion-related reactions ▪ Palliative radiotherapy if the target lesion is not locally treated[i]	

Table 7: Characterization of the intervention – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study	Intervention	Comparison
a. Further, the study protocol allows reducing sorafenib to a single 400-mg dose every 2 days if necessary. b. Surgical procedures for diagnostic reasons are permitted. c. Except for palliative radiotherapy of bone lesions ≤ 7 days before the start of the study medication. d. Either ≤ 4 weeks or 5 drug half-lives before study start, whichever was longer. e. Disallowed for 5 months after the last dose of atezolizumab. f. During sorafenib treatment, concomitant treatment was not explicitly disallowed, but a careful approach was recommended for the concomitant use of strong CYP3A4-inducers. g. Before study start, therapy with acute low-dose immunosuppressants or a single high-dose therapy with a systemic immunosuppressant was permitted. Also allowed, even during the study: mineralocorticoids, corticosteroids in COPD or asthma, and low-dose corticosteroids in orthostatic hypotension or adrenal insufficiency. h. The prophylactic use of antibiotics (e.g. for the prevention of urinary tract infections or exacerbations of chronic obstructive pulmonary disease) was permitted. i. During radiotherapy, continuation of atezolizumab treatment was permitted; bevacizumab and sorafenib treatment 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: nonsteroidal anti-inflammatory drugs; RCT: randomized controlled study; SPC: Summary of Product Characteristics; ULN: upper limit of normal		

Study description

IMbrave150 is an open-label, randomized, controlled study comparing atezolizumab + bevacizumab with sorafenib. The study included adults with locally advanced or metastatic and/or unresectable HCC who received no prior systemic therapy. Further inclusion criteria were Child-Pugh class A and general condition rated as an ECOG-PS score of 0 or 1. Hence, no data are available for patients with an ECOG-PS ≥ 2.

In the global cohort, a total of 501 patients were randomly allocated in a 2:1 ratio to treatment with atezolizumab + bevacizumab (N = 336) or sorafenib (N = 165). Randomization was stratified 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), and ECOG-PS (0/1). In addition to this global cohort, there was a Chinese cohort with an identical study protocol (referred to as "Chinese expansion cohort" in the company's dossier). This cohort is described below.

Atezolizumab + bevacizumab treatment was administered in accordance with the SPC [6]. The same largely applies to sorafenib treatment [7]. In the IMbrave150 study, a dose reduction to 400 mg every 2 days was possible in case of adverse drug reactions (the SPC provides for a reduction to 400 mg sorafenib once daily). The available documents do not show how many patients were affected by this discrepancy, but presumably, the latter is of no consequence for the benefit assessment.

Treatment was continued until loss of clinical benefit, unacceptable toxicity, revocation of consent, or death. Patients who met the criteria of disease progression according to Response Evaluation Criteria in Solid Tumours version 1.1 were eligible for continued treatment if they met certain criteria – including evidence of clinical benefit as determined by the investigator and absence of unacceptable toxicity.

Co-primary outcomes of the study were overall survival and PFS. Patient-relevant secondary outcomes were morbidity, health-related quality of life, and AE outcomes.

Subpopulation of the IMbrave150 study (Chinese cohort)

According to the company, about 135 patients from mainland China were to be included in the study for the purposes of obtaining regulatory approval in China. After the end of the global recruitment phase, only 78 patients from mainland China had been included in the IMbrave150 study. According to the company, an expanded inclusion phase in China was therefore carried out, in which additional patients were randomized to the treatment arms in a 2:1 ratio.

The Chinese cohort (N = 194) very strongly overlaps (n = 137) with the global cohort. Only 57 patients were analysed exclusively in the Chinese cohort. The patients of the Chinese cohort were treated using the identical study protocol and statistical analysis plan of the global study population, but according to the company, the data were analysed in a separate study report.

In Module 4 A of the dossier, the company uses exclusively the results of the global cohort of the IMbrave150 study to derive an added benefit. The company reasons that the additional 57 patients in the Chinese expansion cohort are irrelevant for the assessment of medical benefit and added benefit because they were not included in the data package submitted for approval by the European Medicines Agency (EMA).

This approach is inadequate. The patients in the Chinese cohort who are not part of the global cohort (n = 57 [10.2%]) represent a relevant subpopulation of the IMbrave150 study. In Module 4 A (Appendix 4-G) of the dossier, the company presents summary analyses on the basis of individual patient data (IPD) of all patients included in the IMbrave150 study. These analyses are included in this benefit assessment.

Data cut-offs and available analyses

For the global cohort, analyses are available on the following data cut-offs:

- 1st data cut-off of 29 August 2019: primary analysis of PFS (to occur after approximately 308 events) and final analysis of overall survival since the predefined statistical stopping rule had been reached for overall survival
- 3-month Food and Drug Administration safety update on 29 November 2019: analyses of AEs only
- 2nd data cut-off of 31 August 2020: analysis of overall survival and PFS, among others, upon EMA's request as part of the regulatory approval procedure

For the Chinese cohort, analyses are available on the following data cut-off:

- 1st data cut-off of 29 August 2019: analysis of PFS (to occur at the time of the primary analysis of PFS in the global cohort)

For the benefit assessment, a summary analysis of the entire study population is available on the basis of IPD. For this purpose, the company uses the analyses of the data cut-off of 29 August 2019 for all outcomes except AE outcomes. The summary analysis of AEs is based on different data cut-offs for the two cohorts: the 29 November 2019 data cut-off for the global cohort and the 29 August 2019 data cut-off for patients of the Chinese cohort (57 patients who were analysed exclusively in this cohort).

For the benefit assessment, the most current data cut-off was used in each case. Generally, the benefit assessment is based on the summary analysis of both cohorts of the IMbrave150 study. In the global cohort, the 31 August 2020 data cut-off is used only for the outcome of overall survival because the longer observation period by nearly 1 year offers higher informative value. The number of events is about 75% higher for the 31 August 2020 data cut-off than for the 29 August 2019 data cut-off (161 events in 2019 versus 280 events in 2020). The sample size, in contrast, would increase by only about 10% due to the additional 57 patients from the Chinese cohort if the summary analysis of both cohorts used the 29 August 2019 data cut-off.

Treatment duration and follow-up observation

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

Table 8: Planned follow-up observation – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
IMbrave150	
Mortality	
Overall survival	After progression until death, loss to follow-up, withdrawal of consent, or study discontinuation by the sponsor
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-HCC18) Health status (EQ-5D VAS)	After discontinuation of the study drug or progression, every 3 months for 1 year[a] or until withdrawal of consent or study discontinuation by the sponsor
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-HCC18)	After discontinuation of the study drug or progression, every 3 months for 1 year[a] or until withdrawal of consent or study discontinuation by the sponsor
AEs	
SAEs	Until 90 days after the last dose of study drug or start of a new systemic therapy[b]
Further AEs	Until 30 days after the last dose of study drug or start of a new systemic therapy

a. According to information in the study protocol.
b. Only SAEs related to the study drug are followed up beyond this time period.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HCC: hepatocellular carcinoma; QLQ-C30: Quality of Life Questionnaire Cancer-30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled study; SAE: serious adverse event; VAS: visual analogue scale

In the IMbrave 150 study, only the outcome of overall survival was to be surveyed to the end of study participation.

The follow-up durations for the AE outcomes are systematically shortened since they were surveyed only for the period of treatment with the study drug (plus 90 days for SAEs and plus 30 days for further AEs). While the outcomes on symptoms, health status, and health-related quality of life were surveyed for 1 year beyond the end of treatment, the follow-up periods were cut short here as well. To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire period.

Characterization of the study population

Module 4 A of the dossier does not provide any information on the patient characteristics of the total population (N = 558) of the IMbrave150 study. Table 9 shows the characteristic of the patients of the IMbrave150 study's global cohort.

Table 9: Characterization of the study population – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study **Characteristic** **category**	**Atezolizumab + bevacizumab** **N[a] = 336**	**Sorafenib** **N[a] = 165**
IMbrave150 (global cohort)		
Age [years], median [Q1; Q3]	64 [56; 71]	66 [59; 71]
Sex [f/m], %	18/82	17/83
Ancestry		
Asian	188 (56)	96 (58)
Caucasian	123 (37)	52 (32)
Other	6 (2)	5 (3)
Unknown	19 (6)	12 (7)
Region		
Asia Pacific	176 (52)	95 (58)
Europe	102 (30)	49 (30)
North America	58 (17)	21 (13)
ECOG-PS, n (%)		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
BCLC stage at baseline, n (%)		
Stage A1	5 (1)	3 (2)
Stage A4	3 (1)	3 (2)
Stage B	52 (15)	26 (16)
Stage C	276 (82)	133 (81)
Extrahepatic spread and macrovascular invasion at baseline, n (%)		
Macrovascular invasion	129 (38)	71 (43)
Extrahepatic spread	212 (63)	93 (56)
Macrovascular invasion and/or extrahepatic spread	258 (77)	120 (73)
Child-Pugh class, n %		
A5	239 (72)	121 (73)
A6	94 (28)	44 (27)
B7	1 (0)	0 (0.0)
HCC aetiology		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Non-viral	100 (30)	53 (32)
AFP at screening, n %		
< 400 ng/mL	210 (63)	104 (63)
≥ 400 ng/mL	126 (38)	61 (37)

Table 9: Characterization of the study population – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study Characteristic category	Atezolizumab + bevacizumab N[a] = 336	Sorafenib N[a] = 165
Prior therapy of HCC, n (%)		
Percutaneous ethanol injection (PEI)	12 (4)	3 (2)
Radiofrequency ablation (RFA)	47 (14)	24 (15)
Transarterial embolization (TAE)	12 (4)	8 (5)
Transarterial chemoembolization (TACE)	130 (39)	70 (42)
Drug-eluting bead transarterial chemoembolization (DEB-TACE)	3 (1)	1 (1)
Transarterial infusion of cytostatics (TAI)	3 (1)	2 (1)
Transarterial radioembolization (TARE)	8 (2)	4 (2)
Other	6 (2)	7 (4)
Treatment discontinuation, n (%)	183 (54.5[b])	132 (80.0[b])
Study discontinuation, n (%)	108 (32.1[b])[c]	84 (50.9[b])[c]

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. IQWiG calculations.
c. Study discontinuation due to death affected 95 patients (28.3%) in the atezolizumab + bevacizumab arm and 65 patients (39.4%) in the sorafenib arm.

AFP: alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; f: female; HCC: hepatocellular carcinoma; m: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; Q1, Q3: first quartile, third quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely balanced between the atezolizumab + bevacizumab and sorafenib study arms. Patients were on average 64 and 66 years old, respectively, the majority was male, and about half were of Asian descent. An ECOG-PS of 0 was found in 62% of patients. More than 80% of patients in both study arms were in Barcelona Clinic Liver Cancer stage C. As to aetiology, HCC was due to hepatitis B or C infection in most patients of both study arms. In about 30% of patients, HCC was due to non-viral causes.

The number of treatment discontinuations and study discontinuations in the global cohort differs between the two treatment arms, at about 54% and 32%, respectively, in the atezolizumab + bevacizumab arm and 80% and 51% in the sorafenib arm. The majority of study discontinuations was due to patient death.

Data on the course of the study

For the total population of the IMbrave150 study, Module 4 A of the dossier does not provide any information on treatment or follow-up duration for individual outcomes. Table 10 presents the median patient treatment duration as well as the median duration of follow-up observation

for individual outcomes in the global cohort (29 August 2019 data cut-off). No information is available on the 31 August 2020 data cut-off.

Table 10: Data on the course of the study – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study **Duration of the study phase** **Outcome category**	**Atezolizumab + bevacizumab** **N = 336**	**Sorafenib** **N = 165**
IMbrave150 (global cohort)		
Treatment duration [months]		
Median [Q1; Q3][a]	Atezolizumab: 7.4 [ND] Bevacizumab: 6.8 [ND]	2.8 [ND]
Mean (SD)	ND	ND
Follow-up duration [months]		
Overall survival		
Median [Q1; Q3][a, b]	8.9 [ND]	8.1 [ND]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
AEs	ND	ND

a. Data cut-off: 29/08/2019
b. Referred to by the company as "survival follow-up" without any further explanation.

N: number of analysed patients; ND: no data; Q1, Q3: 25% and 75% quartile, respectively; RCT: randomized controlled trial; SD: standard deviation

On the basis of the global cohort of the IMbrave150 study, the median treatment duration in the intervention arm was 7.4 months for atezolizumab and 6.8 months for bevacizumab. In the comparator arm, the median treatment duration with sorafenib was 2.8 months. The median follow-up duration for the outcome of overall survival was almost identical, at 8.9 versus 8.1 months. No data on follow-up duration are available for the outcome categories of morbidity, health-related quality of life, and AEs. For AEs, the follow-up duration can be estimated on the basis of the median treatment duration because the planned survey time point was 30 days after the last dose of the study drug for AEs and 90 days after the last dose for SAEs.

For the global cohort of the IMbrave150 study, Table 11 presents the follow-up therapies received after discontinuation of the study drug (29 August 2019 data cut-off). No information is available on the 31 August 2020 data cut-off.

Table 11: Information on antineoplastic follow-up therapies – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (IMbrave150 study)

Study	**Patients with follow-up therapy n (%)**	
Therapy	**Atezolizumab + bevacizumab**	**Sorafenib**
Drug	**N = 336**	**N = 165**
IMbrave150 (global cohort)[a]		
Total	ND	ND
Systemic therapy	69 (20.5)	73 (44.2)
Tyrosine kinase inhibitor	63 (18.8)	43 (26.1)
Angiogenesis inhibitor (monoclonal antibody)	2 (0.6)	5 (3.0)
Chemotherapy	4 (1.2)	10 (6.1)
Immunotherapy	4 (1.2)	31 (18.8)
Other	2 (0.6)	5 (3.0)
Local therapy	ND	ND
Radiofrequency ablation (RFA)	1 (0.3)	0
Transarterial embolization (TAE)	2 (0.6)	2 (1.2)
Transarterial chemoembolization (TACE)	4 (1.2)	4 (2.4)
Transcatheter arterial infusion (TAI)	1 (0.3)	2 (1.2)
Transarterial radioembolization (TARE)	1 (0.3)	0
Surgical procedure	5 (1.5)	1 (0.6)
Radiotherapy	9 (2.7)	7 (4.2)

a. Data cut-off: 29/08/2019

n: number of patients with follow-up therapy; N: number of analysed patients; RCT: randomized controlled trial

In the global cohort of the IMbrave150 study, about 20% of patients in the atezolizumab + bevacizumab arm and almost 45% in sorafenib arm received systemic therapy after discontinuation of the study drug. In the sorafenib arm, this was mostly therapy with a tyrosine kinase inhibitor, followed by immunotherapy. Information on the specific drugs used in each case is not available. The study protocol does not provide for a preplanned switch of patients from the sorafenib arm to treatment with atezolizumab + bevacizumab.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
IMbrave150	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the IMbrave150 study. This rating concurs with the company's assessment.

Restrictions resulting from the open-label study design are described in Section 2.3.2.2 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

In Module 4 A, the company argues that the results of the IMbrave150 study are transferable to the German healthcare context because the global study population is reportedly largely equivalent to the population of patients in advanced or unresectable HCC found in the German context of care; to support this assertion, the company cites retrospective analyses conducted by the Mainz and Hannover University Hospitals [8,9] and the Munich Cancer Registry [10]. The company states, for example, that the age structure is comparable overall and the high percentage of male patients is reflected by the IMbrave150 study. It then goes on to discuss the relatively large percentage of IMbrave150 participants from the Asia-Pacific region, whereas only one-third of participants are from Europe. The company asserts that while the higher percentage of patients with hepatitis B in the IMbrave150 study is due to the high proportion of Asian patients and poorly represents the German context of care, the study adequately reflects the considerable percentage of patients with hepatitis C and non-viral risk factors.

The company did not present any further information on the transferability of study results to the German healthcare context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - Overall survival

- Morbidity
  - Symptoms surveyed using the symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-HCC18
  - Health status, recorded with the visual analogue scale (VAS) of the EQ-5D questionnaire
- Health-related quality of life
  - as surveyed with the EORTC QLQ-C30 and EORTC QLQ-HCC18 functioning scales
- AEs
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-mediated AEs (AEs, SAEs, severe AEs)
  - Bleeding (AEs, SAEs, severe AEs)
  - Palmar-plantar erythrodysaesthesia syndrome (severe AEs)
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-HCC18)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-HCC18)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-mediated AEs (AEs, SAEs, severe AEs)	Bleeding (AEs, SAEs, severe AEs)	Palmar-plantar erythrodysaesthesia syndrome[b] (PT, severe AEs[a])	Other specific AEs[c]
IMbrave150	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. MedDRA PT palmar-plantar erythrodysaesthesia syndrome.
c. The following events were assessed (MedDRA coding): "alopecia" (PT, AEs), "diarrhoea (PT, severe AEs [CTCAE grade ≥ 3])", "general disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3])", "blood bilirubin increased (PT, severe AEs [CTCAE grade ≥ 3])", "metabolic and nutritional disorders (SOC, severe AEs [CTCAE grade ≥ 3])", "respiratory, thoracic, and mediastinal disorders (SOC, severe AEs [CTCAE grade ≥ 3])" and "infections and infestations (SOC, SAEs)".
d. No usable data available.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HCC: hepatocellular carcinoma; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; QLQ-C30: Quality of Life Questionnaire Cancer-30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Note on the responder analyses for the outcomes on symptoms and health-related quality of life

- In its dossier, the company presents responder analyses for time to deterioration by 10 points for the EQ-5D VAS. These are not used for the dossier assessment. As discussed in IQWiG General Methods [11], a predefined response criterion should cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change that is perceivable for patients. The responder analysis submitted by the company is presented as supplementary information in Appendix C of the full dossier assessment.
- For EORTC QLQ-C30 and HCC18, the company also presents responder analyses for the time to deterioration by 10 points. Specifically for the EORTC, the analysis with a response

threshold of 10 points is viewed as a sufficient approximation to an analysis with a 15% threshold (15 points) and used for the benefit assessment (see Appendix D of the full dossier assessment).

- For all scales of the instruments EORTC QLQ-C30 and HCC18, the company uses analyses on time to 1st deterioration to derive any added benefit. Furthermore, in the appendix to Module 4 A, the company presents as supplementary information analyses on the time to confirmed deterioration. A deterioration was deemed confirmed if it persisted across 2 consecutive measurements or if death occurred within 3 weeks after initial deterioration. This was a preplanned analysis as per study protocol. Both initial deterioration and confirmed deterioration are generally relevant. However, due to the different follow-up durations and the associated difference in the number of possible follow-up surveys, considerable uncertainties exist regarding confirmed deterioration: In the global cohort, patients in the treatment arm discontinued treatment after approximately 7 months, while those in the comparator arm discontinued after only approximately 3 months. Few follow-up surveys were done after these time points. The present situation is therefore analysed in terms of first deterioration, as was done by the company.

Comments on AEs

No usable data are available on the following patient-relevant outcomes:

- Immune-mediated AEs (each AEs, SAEs, severe AEs): For immune-mediated AEs, the company has not presented a summary analysis of events. Instead, in Module 4 A of the dossier, it merely presents results for individual immune-mediated AEs as part of its analyses of atezolizumab-specific AEs of special interest (AESI). Further, the operationalizations of the individual AESIs are not discussed in Module 4 A of the dossier. Hence, it remains unclear which events (e.g. PTs, Standardized MedDRA Queries [SMQs]) are included in the analyses. It also remains unclear whether the analyses of individual AESIs listed by the company are limited to events which required corticosteroid treatment; after all, this analysis was also preplanned in the IMbrave150 study.

  Therefore, the analysis submitted by the company on individually presented immune-mediated AEs is not usable. A summary analysis of immune-mediated AEs (AEs, SAEs, severe AEs) would have been appropriate.

- Bleeding (AEs, SAEs, severe AEs): Among its analyses on bevacizumab-specific AESIs, the company presents an analysis on bleeding/haemorrhage. However, as described above for immune-mediated AEs, the operationalization of this AESI is not found in Module 4 A. Hence, it remains unclear which events (e.g. PT, SMQ) are included in the company's analysis. The analysis submitted by the company is therefore not usable.

Overall, no usable data are available for AEs specific to drugs on the intervention side – immune-mediated AEs and bleeding (AEs, SAEs, severe AEs for each). Hence, no final analysis of the specific AEs is possible.

2.3.2.2 Risk of bias

Table 14 presents the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias at study and outcome levels – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study		Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-HCC18)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-HCC18)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-mediated AEs (AEs, SAEs, severe AEs)	Bleeding (AEs, SAEs, severe AEs)	Palmar-plantar erythrodysaesthesia syndrome [b] (PT, severe AEs[a])	Other specific AEs[c]
IMbrave150	L	L	H[d, e]	H[d, e]	H[d, e]	H[d, e]	H[d, e]	H[f]	H[f]	H[d]	-[g]	-[g]	H[f]	H[d, f]

a. Operationalized as CTCAE grade ≥ 3.
b. MedDRA PT palmar-plantar erythrodysaesthesia syndrome.
c. The following events were assessed (MedDRA coding): "alopecia" (PT, AEs), "diarrhoea (PT, severe AEs [CTCAE grade ≥ 3])", "general disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3])", "increased blood bilirubin (PT, severe AEs [CTCAE grade ≥ 3])", "metabolic and nutritional disorders (SOC, severe AEs [CTCAE grade ≥ 3])", "respiratory, thoracic, and mediastinal disorders (SOC, severe AEs [CTCAE grade ≥ 3])" and "infections and infestations (SOC, SAEs)".
d. No blinding in the presence of subjective outcome recording (in specific AEs, only for non-serious/non-severe specific AEs).
e. Strongly decreasing and highly differential returns.
f. Markedly different follow-up duration for treatment arms: potentially informative censoring.
g. No usable data available.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; H: high; HCC: hepatocellular carcinoma; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; QLQ-C30: Quality of Life Questionnaire Cancer-30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias is considered low for the results on the outcome of overall survival. This concurs with the company's assessment.

Due to the increasing percentage of missing values, which also differed between treatment arms, as well as the open study design with subjective recording of outcomes, the risk of bias is rated as high for the results of the outcomes of symptoms (symptom scales of the EORTC QLQ-C30 and EORTC QLQ-HCC18), health status (EQ-5D VAS), and health-related quality

of life (functioning scales of the EORTC QLQ-C30 and EORTC QLQ-HCC18). The company has rated the risk of bias as high as well, but on the basis of only the open study design.

The risk of bias is rated as high for the results of each of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), and specific AEs. The AE outcomes are surveyed only for the period of treatment with the study medication (plus 30 days [AEs] or 90 days [SAEs] or until the start of subsequent antineoplastic therapy, whichever occurred first). For all mentioned outcomes, this results in marked differences in follow-up durations between individual patients, with potentially informative censoring. For non-serious/non-severe AEs, the open study design leads to a high risk of bias as well.

Due to lack of blinding in the presence of subjective recording of outcomes, the risk of bias for the results of the outcome of discontinuation due to AEs is rated as high. This view concurs with the company's assessment.

No usable data are available for the outcomes of immune-mediated AEs (AEs, SAEs, severe AEs) as well as bleeding (AEs, SAEs, severe AEs).

2.3.2.3 Results

Table 15 and Table 16 combine the results of the comparison of atezolizumab + bevacizumab versus sorafenib in patients with advanced or unresectable HCC of Child-Pugh class A or no hepatic cirrhosis who received no prior systemic treatment. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

Kaplan-Meier curves for the entire study population are not available. As an approximation of the results of the study population, the Kaplan-Meier curves for the global cohort of the IMbrave150 study are found in Appendix A of the full dossier assessment. Results on common AEs for the entire study population (summary analysis of global cohort + Chinese cohort) are presented in Appendix B of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, AEs, time to event) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study Outcome category Outcome	Atezolizumab + bevacizumab		Sorafenib		Atezolizumab + bevacizumab vs. sorafenib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
IMbrave150					
Mortality					
Overall survival					
Global cohort[a] (data cut-off: 31/08/2020)	336	19.22 [17.02; 23.66] 180 (53.6)	165	13.4 [11.37; 16.85] 100 (60.6)	0.66 [0.52; 0.85]; < 0.001[b]
Morbidity (data cut-off: 29/08/2019)					
EORTC QLQ-C30 – symptom scales[c]					
Fatigue	375	2.10 [1.48; 2.20] 253 (67.5)	183	1.45 [1.08; 1.51] 129 (70.5)	0.71 [0.57; 0.89]; 0.002[b]
Nausea and vomiting	375	14.29 [8.31; NC] 144 (38.4)	183	4.60 [3.48; 5.62] 88 (48.1)	0.49 [0.37; 0.64]; < 0.001[b]
Pain	375	3.48 [2.79; 4.27] 234 (62.4)	183	1.58 [1.31; 2.33] 119 (65.0)	0.62 [0.49; 0.79]; < 0.001[b]
Dyspnoea	375	9.66 [6.67; 11.93] 162 (43.2)	183	4.17 [2.27; 5.32] 91 (49.7)	0.59 [0.45; 0.78]; < 0.001[b]
Insomnia	375	7.16 [5.55; 9.43] 175 (46.7)	183	4.86 [3.48; 6.97] 80 (43.7)	0.79 [0.60; 1.04]; 0.096[b]
Appetite loss	375	6.28 [4.76; 8.51] 197 (52.5)	183	3.02 [2.14; 3.98] 108 (59.0)	0.57 [0.45; 0.73]; < 0.001[b]
Constipation	375	11.30 [9.69; NC] 140 (37.3)	183	4.17 [2.76; 6.08] 83 (45.4)	0.48 [0.36; 0.64]; < 0.001[b]
Diarrhoea	375	10.71 [7.98; NC] 148 (39.5)	183	2.83 [2.10; 3.52] 103 (56.3)	0.34 [0.26; 0.44]; < 0.001[b]
EORTC QLQ-HCC18 – symptom scales[c]					
Fatigue	375	2.33 [2.07; 3.52] 238 (63.5)	183	1.41 [0.85; 1.58] 126 (68.9)	0.64 [0.51; 0.81]; < 0.001[b]
Icterus	375	4.21 [3.52; 5.55] 203 (54.1)	183	2.14 [1.58; 3.48] 103 (56.3)	0.66 [0.52; 0.85]; 0.001[b]
Pain	375	4.83 [3.84; 5.59] 205 (54.7)	183	3.45 [2.10; 4.86] 98 (53.6)	0.71 [0.55; 0.91]; 0.006[b]
Fever	375	5.55 [3.91; 7.75] 192 (51.2)	183	4.17 [3.02; 7.29] 86 (47.0)	0.87 [0.67; 1.13]; 0.297[b]
Abdominal swelling	375	9.69 [7.62; 11.04] 159 (42.4)	183	5.52 [3.29; NC] 69 (37.7)	0.61 [0.46; 0.82]; 0.001[b]

Table 15: Results (mortality, morbidity, health-related quality of life, AEs, time to event) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study Outcome category Outcome	Atezolizumab + bevacizumab		Sorafenib		Atezolizumab + bevacizumab vs. sorafenib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Health-related quality of life (data cut-off: 29/08/2019)					
EORTC QLQ-C30 – functioning scales[d]					
Global health status	375	3.52 [2.73; 4.21] 222 (59.2)	183	1.48 [1.38; 2.17] 119 (65.0)	0.62 [0.49; 0.78]; < 0.001[b]
Physical functioning	375	4.53 [3.58; 6.24] 212 (56.5)	183	2.10 [1.48; 3.48] 111 (60.7)	0.63 [0.50; 0.81]; < 0.001[b]
Role functioning	375	4.17 [3.12; 4.86] 222 (59.2)	183	1.61 [1.41; 2.14] 126 (68.9)	0.60 [0.47; 0.75]; < 0.001[b]
Emotional functioning	375	NR [11.70; NC] 129 (34.4)	183	4.86 [2.86; 7.06] 90 (49.2)	0.45 [0.34; 0.59]; < 0.001[b]
Cognitive functioning	375	4.57 [3.48; 9.00] 195 (52.0)	183	2.83 [1.87; 4.17] 102 (55.7)	0.66 [0.52; 0.85]; 0.002[b]
Social functioning	375	3.61 [2.79; 4.57] 222 (59.2)	183	2.10 [1.48; 2.83] 116 (63.4)	0.64 [0.50; 0.80]; < 0.001[b]
EORTC QLQ-HCC18 – functioning scales[d]					
Body image	375	3.58 [2.83; 4.90] 227 (60.5)	183	2.53 [1.84; 3.61] 104 (56.8)	0.79 [0.62; 1.00]; 0.0495[b]
Nutrition	375	5.65 [4.21; 7.16] 197 (52.5)	183	2.17 [1.61; 3.02] 117 (63.9)	0.49 [0.39; 0.62]; < 0.001[b]
Sex life	375	NR [10.15; NC] 142 (37.9)	183	6.74 [5.49; NC] 63 (34.4)	0.85 [0.63; 1.15]; 0.286[b]
AEs (data cut-offs: 29/11/2019 [global cohort] and 29/08/2019 [Chinese cohort])					
AEs (supplementary information)	368	ND 361 (98.1)	174	ND 171 (98.3)	-
SAEs	368	ND 146 (39.7)	174	ND 52 (29.9)	1.10 [0.80; 1.51]; 0.570[e]
Severe AEs[f]	368	ND 236 (64.1)	174	ND 104 (59.8)	0.80 [0.63; 1.01]; 0.065[e]
Discontinuation due to AEs[g]	368	ND 62 (16.8)	174	ND 19 (10.9)	1.06 [0.63; 1.79]; 0.815[e]
Immune-mediated AEs (AEs, SAEs, severe AEs)	No usable data[h, i]				
Bleeding (AEs, SAEs, severe AEs)	No usable data[h]				

Table 15: Results (mortality, morbidity, health-related quality of life, AEs, time to event) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study Outcome category Outcome	Atezolizumab + bevacizumab		Sorafenib		Atezolizumab + bevacizumab vs. sorafenib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Palmar-plantar erythrodysaesthesia syndrome [j] (PT, severe AEs[f])	368	ND 0 (0)	174	ND 15 (8.6)	-[k]; < 0.001[e]
Alopecia (PT, AEs)	368	ND 4 (1.1)	174	ND 24 (13.8)	0.06 [0.02; 0.17]; < 0.001[e]
Diarrhoea (PT, severe AEs[f])	368	ND 9 (2.4)	174	ND 9 (5.2)	0.35 [0.14; 0.90]; 0.023[e]
General disorders and administration site conditions (SOC, severe AEs[f])	368	ND 18 (4.9)	174	ND 15 (8.6)	0.42 [0.21; 0.82]; 0.009[e]
Blood bilirubin increased (PT, severe AEs[f])	368	ND 12 (3.3)	174	ND 10 (5.7)	0.42 [0.18; 0.99]; 0.041[e]
Metabolic and nutritional disorders (SOC, severe AEs[f])	368	ND 35 (9.5)	174	ND 21 (12.1)	0.56 [0.33; 0.94]; 0.028[e]
Respiratory, thoracic, and mediastinal disorders (SOC, severe AEs[f])	368	ND 15 (4.1)	174	ND 7 (4.0)	0.44 [0.20; 0.99]; 0.041[e]
Infections and infestations (SOC, SAEs)	368	ND 26 (7.1)	174	ND 3 (1.7)	3.60 [1.10; 11.83]; 0.024[e]

a. This includes 137 patients who are also included in the Chinese cohort.
b. Effect estimation and 95% CI from a Cox proportional-hazards model, stratified by geographic region (Asia excluding Japan / ROW), extrahepatic spread and/or macrovascular invasion (yes/no), and AFP at screening (< 400 ng/mL/ ≥ 400 ng/mL); p-value via stratified log-rank test.
c. Time to first deterioration, defined as a score increase by at least 10 points over baseline.
d. Time to first deterioration, defined as a score decrease by at least 10 points from baseline.
e. Effect estimate and 95% CI calculated using a non-stratified Cox proportional-hazards model; p-value using non-stratified log-rank test.
f. Operationalized as CTCAE grade ≥ 3.
g: AEs which resulted in the discontinuation of at least one drug component were counted as an event.
h. It is unclear how the AESIs presented by the company are operationalized.
i. Instead of any aggregate analyses on immune-mediated AEs, the company merely presented individual immune-mediated AEs which were analysed in the context of AESIs.
j. MedDRA PT palmar-plantar erythrodysaesthesia syndrome.
k. Effect estimate and 95% CI not meaningfully interpretable.

Table 15: Results (mortality, morbidity, health-related quality of life, AEs, time to event) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study **Outcome category** **Outcome**	**Atezolizumab + bevacizumab**		**Sorafenib**		**Atezolizumab + bevacizumab vs. sorafenib**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
AE: adverse event; AESI: adverse events of special interest; AFP: alpha fetoprotein; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HCC: hepatocellular carcinoma; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; ND: no data; NR: not reached; QLQ-C30: Quality of Life Questionnaire Cancer-30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomized controlled trial; ROW: rest of the world; SAE: serious adverse event; SOC: System Organ Class					

Table 16: Results (morbidity, continuous) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study **Outcome category** **Outcome**	**Atezolizumab + bevacizumab**			**Sorafenib**			**Atezolizumab + bevacizumab vs. sorafenib**
	N[a]	**Values at baseline mean (SD)**	**Change by end of study mean[b] (SE)**	**N[a]**	**Values at baseline mean (SD)**	**Change by end of study mean[b] (SE)**	**MD [95% CI]; p-value[b]**
IMbrave150							
Morbidity							
Health status							
EQ-5D VAS[c]	344	77.37 (16.58)	−3.63 (1.11)	158	75.58 (17.47)	−8.90 (1.50)	5.27 [2.39; 8.15]; ND SMD: 0.34 [0.15; 0.53][d]
a. Number of patients included in the analysis for calculating the effect estimator; the figures at baseline (and any other times) may be based on different patient numbers. b. Least squares estimates; MMRM analysis of the mean difference across the course of the study, adjusted by visit, treatment*visit, value at baseline, geographic region (Asia excluding Japan / rest), extrahepatic spread and/or macrovascular invasion (yes/no), and AFP at screening (< 400 ng/mL / ≥ 400 ng/mL). c. Higher values on the scale correspond to better health status; a positive group difference means an advantage for atezolizumab + bevacizumab. d. IQWiG calculations, using the MD estimated from the MMRM analysis, the associated standard error, and the sample sizes. AFP: alpha fetoprotein; CI: confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale						

The available data allow deriving no more than indications, e.g. of an added benefit, for the outcome of overall survival. Due to their high risk of bias, at most a hint, e.g. of added benefit, can be derived for the results of the remaining outcomes. On the outcome level, however, the certainty of results might not be downgraded in some cases (see description of results below).

For deriving an added benefit, the company includes only the results of the global cohort of the IMbrave150 study. This benefit assessment, in contrast, includes the results of the summary analysis of both cohorts of the IMbrave150 study (global cohort + Chinese cohort) – except for the outcome of overall survival, for which only analyses of the global cohort are available at the data cut-off with the longest follow-up duration (31 October 2020).

Mortality

Overall survival

For the outcome of all-cause mortality, a statistically significant difference between treatment groups was found for the global cohort at the 31 August 2020 data cut-off.

In addition, there is an effect modification by the characteristic of HCC aetiology. With regard to the individual subgroups (see Section 2.3.2.4), an indication of added benefit of atezolizumab + bevacizumab in comparison with sorafenib was found only for patients with a viral aetiology (hepatitis B or C). For patients with non-viral aetiology, in contrast, there is no hint of any added benefit of atezolizumab + bevacizumab in comparison with sorafenib; an added benefit is therefore not proven.

This departs from the company's approach in that, on the basis of the 29 August 2019 data cut-off, the company derives an indication of added benefit for all patients of the global cohort of the IMbrave150 study, regardless of HCC aetiology.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-HCC18 symptom scales)

Nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhoea (EORTC QLQ-C30), icterus, abdominal swelling (EORTC QLQ-HCC18), and fatigue (EORTC QLQ-C30 and EORTC QLQ-HCC18)

A statistically significant difference in favour of atezolizumab + bevacizumab in comparison with sorafenib was found for each of the EORTC QLQ-C30 symptom scales of nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhoea, the EORTC QLQ-HCC18 symptoms scales of icterus and abdominal swelling, and the symptom scale of fatigue of EORTC QLQ-C30 and EORTC QLQ-HCC18. For each of these symptom scales, there is therefore a hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

This deviates from the assessment by the company, which derives indications of added benefit for each of them on the basis of the global cohort.

Pain (EORTC QLQ-C30 and -HCC18)

The pain symptom scale is surveyed using the two questionnaires EORTC QLQ-C30 and -HCC18.

The EORTC QLQ-C30 generally asks about the presence of pain and the associated limitations in daily life. The EORTC QLQ-HCC18, in contrast, asks about pain in certain body regions (abdomen and shoulder). While the two questionnaires cover different aspects of pain, some overlap can be assumed for the pain aspects surveyed by the instruments. The results are therefore interpreted in light of the overall picture. For both symptom scales, there is a statistically significant difference in favour of atezolizumab + bevacizumab in comparison with sorafenib. For the outcome of pain, measured via EORTC QLQ-HCC18, the effect is no more than minor. Nevertheless, the effects are viewed as being in the same direction. In the overall picture, the differences in extent are taken into account when deriving added benefit at outcome level (see Section 2.3.3.1). Overall, for the outcome of pain, there is a hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

This deviates from the assessment by the company, which derives indications of added benefit for each of them on the basis of the global cohort.

Insomnia (EORTC QLQ-C30), fever (EORTC QLQ-HCC18)

No statistically significant difference between treatment groups was found for the EORTC QLQ-C30 insomnia symptom scale or for the EORTC QLQ-HCC18 fever symptom scale. This did not result in any added benefit of atezolizumab + bevacizumab in comparison with sorafenib for these symptom scales; an added benefit is therefore not proven for any of them.

This concurs with the company's assessment, which, based on the results of the global cohort, derived no added benefit for these outcomes either.

Health status (EQ-5D VAS)

For the outcome of health status (as measured with EQ-5D VAS), the difference in mean change from baseline over the course of the study is analysed by means of an MMRM. A statistically significant difference was found in favour of atezolizumab + bevacizumab. However, the 95% confidence interval of the SMD in the form of Hedges' g is not fully outside of the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. Hence, there is no hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib; an added benefit is therefore not proven.

This deviates from the company's approach, which uses the analyses of the operationalization of time to deterioration by ≥ 10 points, deriving an indication of added benefit for the global cohort.

Health-related quality of life

EORTC QLQ-C30 (functioning scales, scale on global health status) and EORTC QLQ-HCC18 (functioning scales)

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (EORTC QLQ-C30), body image, nutrition (EORTC QLQ-HCC18)

Global health status, the EORTC QLQ-C30 functional scales of physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning as well as the EORTC QLQ-HCC18 functional scales of body image and nutrition each show a statistically significant difference in favour of atezolizumab + bevacizumab in comparison with sorafenib. For each of these outcomes, this results in a hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

This deviates from the assessment by the company, which derived indications of added benefit for these outcomes (except for the body image functioning scale) on the basis of the global cohort. For the outcome of body image, the company did not derive any added benefit.

Sex life (EORTC QLQ-HCC18)

For the sex life functional scale of the EORTC QLQ-HCC18, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib for this symptom scale; an added benefit is therefore not proven.

This concurs with the company's assessment, which likewise derived no added benefit for these outcomes on the basis of the global cohort.

AEs

SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, and discontinuation due to AEs. Consequently, there is no hint of greater or lesser harm from atezolizumab + bevacizumab in comparison with sorafenib for these outcomes; greater or lesser harm is therefore not proven for any of them.

This concurs with the company's assessment, which likewise derived no lesser or greater harm for these outcomes on the basis of the global cohort.

Immune-mediated AEs and bleeding (AEs, SAEs, severe AEs for each)

For immune-mediated AEs and bleeding (AEs, SAEs, severe AEs for each), no usable data are available (see Section 2.3.2.1 for the reasoning). Consequently, there is no hint of greater or lesser harm from atezolizumab + bevacizumab in comparison with sorafenib for any of these outcomes; greater or lesser harm is therefore not proven for any of them.

This concurs with the company's assessment in that, on the basis of the global cohort, the company likewise derived no greater or lesser harm for these outcomes.

Palmar-plantar erythrodysaesthesia syndrome (severe AEs)

For the outcome of palmar-plantar erythrodysaesthesia syndrome (severe AEs), a statistically significant difference was found in favour of atezolizumab + bevacizumab in comparison with sorafenib. Despite the high risk of bias of results, this outcome is associated with a high certainty of results due to the size of the effect (also see Section 2.3.3.1) and the fact that despite a longer follow-up duration, no event was observed in the intervention arm. Hence, there is an indication of lesser harm from atezolizumab + bevacizumab in comparison with sorafenib.

This is in line with the company's assessment in that the company derived, on the basis of the global cohort, a hint of added benefit in the overall analysis of the common AEs.

Further specific AEs

Alopecia (PT, AEs)

For the outcome of alopecia (PT, AEs), a statistically significant difference was found in favour of atezolizumab + bevacizumab in comparison with sorafenib. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size. Hence, there is an indication of lesser harm from atezolizumab + bevacizumab in comparison with sorafenib.

This departs from the assessment of the company, which derived a hint of added benefit from the results of the global cohort in the overall analysis of common AEs.

Diarrhoea, blood bilirubin increased (PT, severe AEs for each), general disorders and administration site conditions, metabolic and nutritional disorders, respiratory, thoracic, and mediastinal disorders (SOC, severe AEs for each)

A statistically significant difference was found in favour of atezolizumab + bevacizumab in comparison with sorafenib for each of the outcomes of diarrhoea and blood bilirubin increased (PT, severe AEs for each) and for the outcomes of general disorders and administration site conditions, metabolic and nutritional disorders as well as respiratory, thoracic, and mediastinal disorders (SOC, severe AEs for each). Hence, there is a hint of lesser harm from atezolizumab + bevacizumab in comparison with sorafenib for each of them.

This departs from the assessment of the company, which derived a hint of added benefit from the results of the global cohort in the overall analysis of common AEs.

Infections and infestations (SOC, SAEs)

For the outcome of infections and infestations (SOC, SAEs), a statistically significant difference was found to the disadvantage of atezolizumab + bevacizumab in comparison with sorafenib. Hence, there is a hint of greater harm from atezolizumab + bevacizumab in comparison with sorafenib.

This departs from the company's approach, which derived a hint of added benefit from the overall analysis of common AEs in the global cohort.

2.3.2.4 Subgroups and other effect modifiers

The present benefit assessment accounts for the following potential effect modifiers:

- age (< 65 / ≥ 65 years)
- sex (female/male)
- extrahepatic spread and/or macrovascular invasion at baseline (present/absent)
- HCC aetiology (hepatitis B / hepatitis C / non-viral)

All listed characteristics were prespecified.

Interaction tests were performed if at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 17 shows the results of the subgroup analyses.

Table 17: Subgroups (mortality) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study Outcome Characteristic Subgroup	Atezolizumab + bevacizumab N	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 (%)	Atezolizumab + bevacizumab vs. sorafenib HR [95% CI]	 p-value
IMbrave150						
Overall survival						
HCC aetiology						
Hepatitis B	164	19.02 [16.10; NC] 86 (52.4)	76	12.42 [6.74; 16.85] 46 (60.5)	0.58 [0.40; 0.83]	0.003
Hepatitis C	72	24.57 [19.81; NC] 31 (43.1)	36	12.62 [7.39; 18.43] 24 (66.7)	0.43 [0.25; 0.73]	0.001
Viral					0.53 [0.39; 0.71][a]	< 0.001[a]
Non-viral	100	16.95 [11.73; 22.80] 63 (63.0)	53	18.10 [11.73; 26.35] 30 (56.6)	1.05 [0.68; 1.63]	0.812[b]
Total					Interaction:	0.022[c]

a. IQWiG calculations of the metaanalysis.
b. Effect estimate and 95% CI calculated using a Cox proportional hazards model; p-value via log rank test.
c. p-value for the company's interaction test according to the original subgroup categorization.

CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable ; RCT: randomized controlled trial

Mortality

Overall survival

For the outcome of overall survival, there is an effect modification by the characteristic of HCC aetiology. In paired comparisons, no effect modification was found between the viral aetiologies of hepatitis B versus hepatitis C (interaction p-value of 0.366), but an effect modification exists between viral aetiology (hepatitis B or C) versus non-viral aetiology (interaction p-value of 0.013). For the outcome of overall survival, added benefit is therefore derived separately for viral versus nonviral aetiology.

For the outcome of overall survival, a statistically significant difference in favour of atezolizumab + bevacizumab is found for patients with viral aetiology (hepatitis B or C). This results in an indication of added benefit of atezolizumab + bevacizumab in comparison with sorafenib for patients with HCC of viral aetiology.

In contrast, no statistically significant difference between treatment groups was found for patients with HCC of nonviral aetiology. For patients with HCC of nonviral aetiology, this

results in no hint of added benefit of atezolizumab + bevacizumab in comparison with sorafenib; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.3.2, the extent of the respective added benefit at outcome level was estimated (see Table 18).

Determination of the outcome category for symptom outcomes

Not for all outcomes examined in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Module 4 A of the dossier provides no data suitable for determining the severity of the outcomes of fatigue, pain, nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhoea (EORTC QLQ-C30 scales) or for fatigue, icterus, pain, and abdominal swelling (EORTC QLQ-HCC18 scales). Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 18: Extent of added benefit at outcome level: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab + bevacizumab vs. sorafenib** **Median time to event (months) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival[c]		
HCC aetiology		
Viral (hepatitis B or C)	Median: ND HR: 0.53 [0.39; 0.71][d] p < 0.001[d] Probability: indication	Outcome category: mortality $CI_u < 0.85$ Added benefit; extent: major
Non-viral	Median: 16.95 vs. 18.10 HR: 1.05 [0.68; 1.63] p = 0.812	Lesser/added benefit not proven
Morbidity		
EORTC QLQ-C30 – symptom scales[e]		
Fatigue	Median: 2.10 vs. 1.45 HR: 0.71 [0.57; 0.89]; p = 0.002 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Nausea and vomiting	Median: 14.29 vs. 4.60 HR: 0.49 [0.37; 0.64]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Pain	Median: 3.48 vs. 1.58 HR: 0.62 [0.49; 0.79]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications Added benefit, extent: non-quantifiable[f]
Dyspnoea	Median: 9.66 vs. 4.17 HR: 0.59 [0.45; 0.78]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Insomnia	Median: 7.16 vs. 4.86 HR: 0.79 [0.60; 1.04]; p = 0.096	Lesser/added benefit not proven
Appetite loss	Median: 6.28 vs. 3.02 HR: 0.57 [0.45; 0.73]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable

Table 18: Extent of added benefit at outcome level: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab + bevacizumab vs. sorafenib** **Median time to event (months) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Constipation	Median: 11.30 vs. 4.17 HR: 0.48 [0.36; 0.64]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Diarrhoea	Median: 10.71 vs. 2.83 HR: 0.34 [0.26; 0.44]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
EORTC QLQ-HCC18 – symptom scales[e]		
Fatigue	Median: 2.33 vs. 1.41 HR: 0.64 [0.51; 0.81]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Icterus	Median: 4.21 vs. 2.14 HR: 0.66 [0.52; 0.85]; p = 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Pain	Median: 4.83 vs. 3.45 HR: 0.71 [0.55; 0.91]; p = 0.006	Outcome category: non-serious/non-severe symptoms / late complications Added benefit, extent: non-quantifiable[f]
Fever	Median: 5.55 vs. 4.17 HR: 0.87 [0.67; 1.13]; p = 0.297	Lesser/added benefit not proven
Abdominal swelling	Median: 9.69 vs. 5.52 HR: 0.61 [0.46; 0.82]; p = 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Health status		
EQ-5D VAS	Mean (study end): −3.63 vs. −8.90 MD: 5.27 [2.39; 8.15]; p = ND SMD: 0.34 [0.15; 0.53][g]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – functioning scales[h]		
Global health status	Median: 3.52 vs. 1.48 HR: 0.62 [0.49; 0.78]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable

Table 18: Extent of added benefit at outcome level: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab + bevacizumab vs. sorafenib** **Median time to event (months) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Physical functioning	Median: 4.53 vs. 2.10 HR: 0.63 [0.50; 0.81]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Role functioning	Median: 4.17 vs. 1.61 HR: 0.60 [0.47; 0.75]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Emotional functioning	Median: NR vs. 4.86 HR: 0.45 [0.34; 0.59]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit; extent: major
Cognitive functioning	Median: 4.57 vs. 2.83 HR: 0.66 [0.52; 0.85]; p = 0.002 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Social functioning	Median: 3.61 vs. 2.10 HR: 0.64 [0.50; 0.80]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
EORTC QLQ-HCC18 – functioning scales[e]		
Body image	Median: 3.58 vs. 2.53 HR: 0.79 [0.62; 1.00]; p = 0.0495 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Nutrition	Median: 5.65 vs. 2.17 HR: 0.49 [0.39; 0.62]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit; extent: major
Sex life	Median: NR vs. 6.74 HR: 0.85 [0.63; 1.15]; p = 0.286	Lesser/added benefit not proven
AEs		
SAEs	Median: ND vs. ND HR: 1.10 [0.80; 1.51]; p = 0.570	Greater/lesser harm not proven
Severe AEs[i]	Median: ND vs. ND HR: 0.80 [0.63; 1.01]; p = 0.065	Greater/lesser harm not proven

Table 18: Extent of added benefit at outcome level: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab + bevacizumab vs. sorafenib** **Median time to event (months) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	Median: ND vs. ND HR: 1.06 [0.63; 1.79]; p = 0.815	Greater/lesser harm not proven
Immune-mediated AEs (AEs, SAEs, severe AEs)[i]	No usable data[j,k]	
Bleeding (AEs, SAEs, severe AEs)	No usable data[j]	
Palmar-plantar erythrodysaesthesia syndrome[l] (PT, severe AEs[i])	Median: ND vs. ND HR: -[m]; p < 0.001 Probability: indication	Outcome category: serious/severe AEs Lesser harm; extent: major
Alopecia (PT, AEs)	Median: ND vs. ND HR: 0.06 [0.02; 0.17]; p < 0.001 Probability: indication	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Lesser harm; extent: considerable
Diarrhoea (PT, severe AEs[i])	Median: ND vs. ND HR: 0.35 [0.14; 0.90]; p = 0.023 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
General disorders and administration site conditions (SOC, severe AEs[i])	Median: ND vs. ND HR: 0.42 [0.21; 0.82]; p = 0.009 Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable
Blood bilirubin increased (PT, severe AEs[i])	Median: ND vs. ND HR: 0.42 [0.18; 0.99]; p = 0.041 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Metabolic and nutritional disorders (SOC, severe AEs[i])	Median: ND vs. ND HR: 0.56 [0.33; 0.94]; p = 0.028 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Respiratory, thoracic, and mediastinal disorders (SOC, severe AEs[i])	Median: ND vs. ND HR: 0.44 [0.20; 0.99]; p = 0.041 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Infections and infestations (SOC, SAEs)	Median: ND vs. ND HR: 3.60 [1.10; 11.83]; HR: 0.28 [0.08; 0.91][n]; p = 0.024 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor

Table 18: Extent of added benefit at outcome level: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab + bevacizumab vs. sorafenib** **Median time to event (months) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability is stated whenever a statistically significant and relevant effect is present. b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u). c. Based on the analysis of the global cohort at the 31/08/2020 data cut-off. d. IQWiG calculation of the metaanalysis. e. Time to first deterioration, defined as a score increase by at least 10 points over baseline. f. The joint analysis of the symptom scales of pain (EORTC QLQ-C30 and EORTC QLQ-HCC18) shows a hint of non-quantifiable added benefit due to the effects of different extents in the same direction. g. If the CI for SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be concluded. h. Time to first deterioration, defined as a score decrease by at least 10 points from baseline. i. Operationalized as CTCAE grade ≥ 3. j. It is unclear how the AESIs presented by the company are operationalized. k. The company did not present any aggregate analyses of immune-mediated AEs, but only individual immune-mediated AEs analysed in the context of the AESI. l. MedDRA PT palmar-plantar erythrodysaesthesia syndrome. m. Effect estimate and 95% CI not meaningfully interpretable for HR. Since no events occurred in the intervention arm, the HR cannot be calculated. To determine the extent in the present situation, the RR was asymptotically calculated by IQWiG as an approximation: 0.02 [0.001; 0.254]. n. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of added benefit. AE: adverse event; AESI: adverse events of special interest; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HCC: hepato-cellular carcinoma; HR: hazard ratio; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; ND: no data; NR: not reached; PT: preferred term; QLQ-C30: Quality of Life Questionnaire Cancer-30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; SMD: standardized mean difference; VAS: visual analogue scale		

2.3.3.2 Overall conclusion on added benefit

Table 19 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 19: Favourable and unfavourable effects from the assessment of atezolizumab + bevacizumab in comparison with sorafenib

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival: ▫ HCC aetiology (viral [hepatitis B or C]) Indication of added benefit – extent: major	▪ Serious/severe AEs ▪ Infections and infestations Hint of greater harm – extent: minor
non-serious/non-severe symptoms / late complications: ▪ Pain Hint of added benefit; extent: non-quantifiable ▪ Fatigue, icterus, abdominal swelling Hint of added benefit; extent: minor ▪ Nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhoea Hint of added benefit; extent: considerable	
Health-related quality of life: ▪ global health status, physical functioning, role functioning, cognitive functioning, social functioning Hint of added benefit; extent: considerable ▪ Emotional functioning, nutrition Hint of added benefit; extent: major ▪ Body image Hint of added benefit; extent minor	
Serious/severe AEs ▪ Palmar-plantar erythrodysaesthesia syndrome Indication of lesser harm; extent major ▪ General disorders and administration site conditions Hint of lesser harm; extent: considerable ▪ Diarrhoea, blood bilirubin increased, metabolic and nutritional disorders, respiratory, thoracic, and mediastinal disorders Hint of lesser harm for each; extent: minor	
Non-serious/non-severe AEs ▪ Alopecia Indication of lesser harm; extent: considerable	
Immune-mediated AEs (AEs, SAEs, severe AEs): no usable data Bleeding (AEs, SAEs, severe AEs): no usable data	
AE: adverse event; AESI: adverse events of special interest; EORTC: European Organisation for Research and Treatment of Cancer; HCC: hepatocellular carcinoma; QLQ-C30: Quality of Life Questionnaire Cancer-30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; SAE: serious adverse event	

The overall picture shows several favourable effects, in some cases only for subgroups, and one unfavourable effect; these effects have a probability of a hint or indication and vary in their extents.

The favourable effects in overall survival are found only in patients with HCC of viral aetiology. For this reason, the favourable and unfavourable effects are weighed separately by HCC aetiology below.

Patients with HCC of viral aetiology (hepatitis B or C)

For adult patients with HCC of viral aetiology (hepatitis B or C), there is an indication of major added benefit for the outcome of overall survival. This favourable effect is supported by the hints of added benefit for the symptom and health-related quality of life outcomes, some of major extent. Furthermore, various specific AEs result in hints and indications of lesser harm with an extent up to major. As to the unfavourable effects, a hint of greater harm of minor extent was found in the outcome category of serious/severe AEs. Further, no usable data are available for atezolizumab-specific or bevacizumab-specific AEs, immune-mediated AEs, or bleeding. It is believed that even if unfavourable effects were found concerning these outcomes, the favourable effects would not be called into question. Overall, the extent of added benefit is deemed major in this situation. For adult patients with advanced or unresectable HCC of viral aetiology and Child-Pugh class A or no hepatic cirrhosis who received no prior systemic therapy, this results in an indication of major added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

Patients with HCC of non-viral aetiology

For adult patients with HCC of non-viral aetiology, several favourable effects were found as well. Hints of added benefit, some of them of major extent, were found for the categories of symptoms and health-related quality of life. For various specific AEs, there are hints and indications of lesser harm with an extent of up to major. These favourable effects are offset by a hint of greater harm of an extent of minor in the outcome category of serious/severe AEs (as was the case in patients with HCC of viral aetiology). Further, no usable data are available for atezolizumab-specific or bevacizumab-specific AEs, immune-mediated AEs and bleeding. In this situation as well, it is thought that even if unfavourable effects were found for these outcomes, they would not call the favourable effects into question. Overall, the extent of added benefit in this situation is deemed considerable. For adult patients with advanced or unresectable HCC of non-viral aetiology and Child-Pugh class A or no hepatic cirrhosis who received no prior systemic therapy, this results in a hint of considerable added benefit of atezolizumab + bevacizumab in comparison with sorafenib.

2.4 Research question 2: Patients with Child-Pugh class B

2.4.1 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on atezolizumab (as of 2 October 2020)
- Bibliographic literature search on atezolizumab (most recent search on 2 October 2020)
- Search in trial registries / study results databases on atezolizumab (most recent search on 5 October 2020)
- Search on the G-BA website on atezolizumab (most recent search on 2 October 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on atezolizumab (most recent search on 1 December 2020)

The check of completeness of the study pool revealed no RCT for the direct comparison of atezolizumab + bevacizumab with BSC; this concurs with the company's findings.

2.4.2 Results on added benefit

For adult patients with advanced or unresectable HCC of Child-Pugh class B who received no prior systemic treatment, the company has presented no data for the assessment of added benefit of atezolizumab + bevacizumab in comparison with the ACT. This results in no hint of added benefit of atezolizumab + bevacizumab in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company has not presented any data for the assessment of added benefit of atezolizumab + bevacizumab in adult patients with advanced or unresectable HCC of Child-Pugh class B who received no prior systemic therapy. An added benefit of atezolizumab + bevacizumab in comparison with the ACT is therefore not proven for these patients.

This concurs with the company's assessment, which does not claim any added benefit for this patient group.

2.5 Probability and extent of added benefit – summary

Table 20 presents a summary of the results of the benefit assessment of atezolizumab + bevacizumab in comparison with the ACT.

Table 20: Atezolizumab + bevacizumab – probability and extent of added benefit

Research question	Indication[a]	ACT [b]	Probability and extent of added benefit
1	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class A or no hepatic cirrhosis	**Sorafenib** or lenvatinib	▪ Patients with HCC of viral aetiology: Indication of major added benefit[c] ▪ Patients with HCC of non-viral aetiology: Hint of considerable added benefit[c]
2	Adult patients with advanced or unresectable HCC who received no prior systemic therapy: ▪ with Child-Pugh class B	BSC[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. For this therapeutic indication, it is assumed that neither curative treatment (for BLCL stage 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 treatment with atezolizumab in combination with bevacizumab.
c. Only patients with an ECOG-PS of 0 or 1 were included in the IMbrave150 study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.
d. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

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

For research question 1 (patients with Child-Pugh class A or no hepatic cirrhosis), the above-described assessment departs from that of the company, which derives an indication of major added benefit for all patients with advanced or unresectable hepatocellular carcinoma who received no prior systemic therapy, irrespective of HCC aetiology.

For research question 2 (patients with Child-Pugh class B), the above-described assessment corresponds to the company's assessment, which did not claim any added benefit.

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

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.

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