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Atezolizumab (hepatocellular carcinoma) –

Addendum to Commission A20-97[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AESI	adverse event of special interest
BCLC	Barcelona Clinic Liver Cancer
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	serious adverse event
SMQ	Standardized MedDRA Query
TKI	tyrosine kinase inhibitor
VAS	visual analogue scale

1 Background

On 7 April 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-97 (Atezolizumab – Benefit assessment according to §35a Social Code Book V) [1].

In the dossier assessment [1], the IMbrave150 study, which included adults with locally advanced or metastatic and/or unresectable hepatocellular carcinoma (HCC) who had not received prior systemic therapy, was used for research question 1. The study compared atezolizumab in combination with bevacizumab (hereinafter "atezolizumab + bevacizumab") against sorafenib. For the IMbrave150 study, data are available from a global cohort as well as from a cohort recruited exclusively in China. Where available, the dossier assessment was based on the summary analysis of both cohorts of the IMbrave150 study.

With its comments [2,3], the pharmaceutical company (hereinafter referred to as the "company") presented further data on the IMbrave150 study.

The G-BA commissioned IQWiG with the assessment of the following analyses submitted by the company in the commenting procedure under consideration of the information provided in the dossier:

- analysis of the characteristics of the patients in the summary analysis
- assessment of the data on subsequent therapies subsequently submitted in the commenting procedure
- analysis of overall survival of the summary analysis for the data cut-off of 31 August 2020
- analyses of the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS) with a response threshold of 15 points with the documents subsequently submitted by the company in the commenting procedure
- assessment of the operationalization of the adverse events of special interest (AESIs) submitted in the commenting procedure
- summary assessment of the available data on immune-related adverse events (AEs)

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Characteristics of the study population

In Module 4 A of the dossier, data for the IMbrave150 study were only available separately for the global cohort (N = 501) and the cohort in China (N = 194), and no data were available on the patient characteristics of the entire study population (N = 558). This information was submitted by the company with its comments (Table 1).

Table 1: Characteristics of the study population – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study **Characteristic** **Category**	**Atezolizumab + bevacizumab** **N[a] = 375**	**Sorafenib** **N[a] = 183**
IMbrave150 (total population)		
Age [years], median [min; max]	62 [26; 88]	65 [31; 87]
Sex [F/M], %	16.3/83.7	16.9/83.1
Family origin		
Asian	227 (60.5)	114 (62.3)
Caucasian	123 (32.8)	52 (28.4)
Other	6 (1.6)	5 (2.7)
Unknown	19 (5.1)	12 (6.6)
Region		
Asia (without Japan)	172 (45.9)	86 (47.0)
Rest of the world	203 (54.1)	97 (53.0)
ECOG PS[b], n (%)		
0	234 (62.4)	112 (61.2)
1	141 (37.6)	71 (38.8)
BCLC stage at baseline, n (%)		
Stage A1	6 (1.6)	3 (1.6)
Stage A4	4 (1.1)	3 (1.6)
Stage B	55 (14.7)	26 (14.2)
Stage C	310 (82.7)	151 (82.5)
Extrahepatic spread and macrovascular invasion at baseline, n (%)		
Macrovascular invasion	141 (37.6)	78 (42.6)
Extrahepatic spread	239 (63.7)	106 (57.9)
Macrovascular invasion and/or extrahepatic spread[b]	290 (77.3)	136 (74.3)
Child-Pugh score, n (%)		
A5	268 (71.8)	137 (74.9)
A6	103 (27.6)	46 (25.1)
B7 or B8	2 (0.6)	0 (0.0)

Table 1: Characteristics of the study population – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib (multipage table)

Study Characteristic Category	Atezolizumab + bevacizumab N[a] = 375	Sorafenib N[a] = 183
HCC aetiology		
Hepatitis B	200 (53.3)	91 (49.7)
Hepatitis C	72 (19.2)	37 (20.2)
Non-viral	103 (27.4)	55 (30.1)
Cause of HCC[c]		
Hepatitis B	200 (53.3)	91 (49.7)
Hepatitis C	81 (21.6)	46 (25.1)
Alcohol	109 (29.1)	55 (30.1)
Unknown	33 (8.8)	18 (9.8)
Other	50 (13.3)	24 (13.1)
AFP at screening, n (%)		
< 400 ng/mL	231 (61.6)	112 (61.2)
≥ 400 ng/mL	144 (38.4)	71 (38.8)
Prior local therapy of HCC, n (%)		
Percutaneous ethanol injection (PEI)	13 (3.5)	3 (1.6)
Radiofrequency ablation (RFA)	55 (14.7)	28 (15.3)
Transarterial embolization (TAE)	13 (3.5)	8 (4.4)
Transarterial chemoembolization (TACE)	155 (41.3)	77 (42.1)
Other	28 (7.5)	17 (9.3)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. According to the information in the eCRF.
c. Multiple answers possible.

AFP: alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; F: female; HCC: hepatocellular carcinoma; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; PEI: percutaneous ethanol injection; RCT: randomized controlled trial; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; TAE: transarterial embolization; vs.: versus

The patient characteristics of the entire study population are largely balanced between the 2 study arms atezolizumab + bevacizumab and sorafenib. The median age of the patients was 62 or 65 years, the majority were male and about 60% were of Asian family origin. A general condition according to Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 was found in 62 and 61% of the patients. More than 80% of patients in both study arms were in Barcelona Clinic Liver Cancer (BCLC) stage C.

As to aetiology, HCC was due to hepatitis B or C infection in most patients of both study arms. In about 27 and 30% of patients, HCC was due to non-viral aetiology. In patients whose HCC was assigned to a non-viral aetiology, no additional viral cause (hepatitis B or C) was present. In addition, the company presented information on the characteristic "cause of HCC" in its documents submitted with the comments; patients could also be counted several times here. However, it is not possible to estimate from these data how many patients had non-viral risk factors in addition to a viral aetiology (hepatitis B or C). There is still no information on treatment and study discontinuations for the entire subpopulation.

2.2 Subsequent therapies

For the dossier assessment, information on which subsequent therapies patients received after discontinuation of the study medication was only available for the global cohort at the 29 August 2019 data cut-off. With its comments, the company provided data on subsequent therapies for the global cohort at the 31 August 2020 data cut-off, both for the entire global cohort and separately by aetiology (Table 2).

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study Therapy Drug	Patients with subsequent therapy n (%)							
	Total		Hepatitis B aetiology		Hepatitis C aetiology		Non-viral aetiology	
	Atezolizumab + bevacizumab	Sorafenib	Atezolizumab + bevacizumab	Sorafenib	Atezolizumab + bevacizumab	Sorafenib	Atezolizumab + bevacizumab	Sorafenib
IMbrave150 (global cohort)[a]	**N = 336**	**N = 165**	**N = 164**	**N = 76**	**N = 72**	**N = 36**	**N = 100**	**N = 53**
Systemic treatment	120 (35.7)	86 (52.1)	60 (36.6)	39 (51.3)	22 (30.6)	19 (52.8)	38 (38.0)	28 (52.8)
Tyrosine kinase inhibitor	108 (32.1)	54 (32.7)	54 (32.9)	20 (26.3)	19 (26.4)	12 (33.3)	35 (35.0)	22 (41.5)
Angiogenesis inhibitor (monoclonal antibodies)	6 (1.8)	10 (6.1)	2 (1.2)	3 (3.9)	2 (2.8)	4 (11.1)	2 (2.0)	3 (5.7)
Chemotherapy	11 (3.3)	15 (9.1)	6 (3.7)	9 (11.8)	2 (2.8)	2 (5.6)	3 (3.0)	4 (7.5)
Immunotherapy	11 (3.3)	43 (26.1)	8 (4.9)	25 (32.9)	1 (1.4)	9 (25.0)	2 (2.0)	9 (17.0)
Other	6 (1.8)	6 (3.6)	3 (1.8)	4 (5.3)	2 (2.8)	0 (0)	1 (1.0)	2 (3.8)
Local therapy	21 (6.3)	17 (10.3)	13 (7.9)	5 (6.6)	3 (4.2)	6 (16.7)	5 (5.0)	6 (11.3)
Radiofrequency ablation (RFA)	3 (0.9)	4 (2.4)	3 (1.8)	1 (1.3)	0 (0)	1 (2.8)	0 (0)	2 (3.8)
Transarterial embolization (TAE)	4 (1.2)	3 (1.8)	2 (1.2)	1 (1.3)	1 (1.4)	1 (2.8)	1 (1.0)	1 (1.9)
Transarterial chemoembolization (TACE)	12 (3.6)	8 (4.8)	6 (3.7)	2 (2.6)	2 (2.8)	4 (11.1)	4 (4.0)	2 (3.8)
Transcatheter arterial infusion (TAI)	1 (0.3)	4 (2.4)	1 (0.6)	2 (2.6)	ND	ND	0 (0)	2 (3.8)
Transarterial radioembolization (TARE)	1 (0.3)	0 (0)	1 (0.6)	0 (0)	ND	ND	ND	ND
Other	1 (0.3)	2 (1.2)	1 (0.6)	0 (0)	0 (0)	1 (2.8)	0 (0)	1 (1.9)
Surgical procedure	11 (3.3)	1 (0.6)	7 (4.3)	ND	2 (2.8)	1 (2.8)	2 (2.0)	ND
Radiotherapy	17 (5.1)	10 (6.1)	8 (4.9)	2 (2.6)	4 (5.6)	3 (8.3)	5 (5.0)	5 (9.4)

a. Data cut-off: 31 August 2020.

n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

In its comments, the company used the data on subsequent therapies, which were presented separately according to aetiology, among other things to explain the effect modification for the characteristic of aetiology observed for the outcome "overall survival". For example, the company stated in its comments that notably more patients with non-viral cause of HCC who were under sorafenib treatment received another tyrosine kinase inhibitor (TKI) in the second line, which (partly) explained the longer overall survival in the comparator arm. However, this assessment cannot be regarded as an argument against the usability of the subgroup analysis: Different follow-up therapies are part of the respective therapeutic strategy. Regardless of this, neither the use of a follow-up therapy can be reliably attributed to a patient characteristic, such as aetiology, nor is the different distribution of follow-up therapies in the present situation of a magnitude that could explain the observed clear effect modification.

2.3 Results

2.3.1 Overall survival

In dossier assessment A20-97 [1], the analysis of the global cohort at the 31 August 2020 data cut-off was used for the outcome "overall survival", as no analysis for the total study population was available for this data cut-off. In the commenting procedure, the company submitted data on overall survival for the total population of the IMbrave150 study at the 31 August 2020 data cut-off (Table 3). Kaplan-Meier curves for the analyses are not available.

Table 3: Results (mortality) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

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					
Total population (data cut-off: 31 August 2020)	375	19.4 [17.1; 23.7] 196 (52.3)	183	13.4 [11.4; 16.9] 110 (60.1)	0.66 [0.52; 0.83]; < 0.001[a]

a. Effect and CI: Cox proportional hazards model stratified by geographical region (Asia without Japan/rest), extrahepatic spread and/or macrovascular invasion (yes/no) and AFP at screening (< 400 ng/mL/≥ 400 ng/mL); p-value: stratified log-rank test.

AFP: alpha fetoprotein; CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

For the outcome "overall survival", a statistically significant difference between the treatment groups was shown for the total study population at the 31 August 2020 data cut-off.

An effect modification by the characteristic "HCC aetiology" was additionally shown (Table 4). With regard to the individual subgroups, a statistically significant difference in favour of atezolizumab + bevacizumab was only found for patients with viral aetiology (hepatitis B or C). This resulted in an indication of an added benefit of atezolizumab + bevacizumab in comparison with sorafenib. Based on the upper limit of the confidence interval (< 0.85), this is to be assessed as "major". For patients with non-viral aetiology, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of atezolizumab + bevacizumab in comparison with sorafenib; an added benefit is therefore not proven.

The conclusion on the added benefit for the outcome "overall survival" from the dossier assessment A20-97 [1] therefore does not change.

Table 4: 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	200	19.1 [16.3; NC] 100 (50.0)	91	12.7 [7.4; 16.9] 54 (59.3)	0.58 [0.42; 0.81]	0.001
Hepatitis C	72	24.6 [19.8; NC] 31 (43.1)	37	13.1 [7.4; 20.4] 24 (64.9)	0.43 [0.25; 0.73]	0.002
Viral					0.53 [0.40; 0.71][a]	< 0.001[a]
Non-viral	103	17.0 [11.3; 22.8] 65 (63.1)	55	15.7 [11.4; 26.4] 32 (58.2)	1.01 [0.66; 1.54]	0.943[b]
Total					Interaction:	0.035[c]

a. Institute's calculation, meta-analysis with fixed effect.
b. Effect and CI: Cox proportional hazards model, unstratified; p-value: log-rank test.
c. p-value on the interaction test of the company in accordance with the original division of the subgroups.

CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; vs.: versus

2.3.2 Health status (EQ-5D VAS)

The responder analyses for the time to deterioration by 10 points presented by the company in its dossier for the VAS of the EQ-5D were not used for the dossier assessment. As explained in the General Methods of the Institute [4], for a response criterion to reflect with sufficient

certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). With its comments, the company subsequently submitted responder analyses for the time to first deterioration by 15 points for the global cohort of the IMbrave150 study. The subsequently submitted responder analyses met the response threshold of 15% of the scale range and were used for the benefit assessment. The company did not present corresponding analyses for the entire study population.

Risk of bias and determination of the outcome category

The risk of bias for the responder analyses was rated as high due to the open-label study design as well as strongly decreasing and highly differential returns.

The company did not provide any information on the assignment of the severity grade for the outcome "health status" (EQ-5D VAS). Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Results

The results for the responder analyses on health status (EQ-5D VAS) for the global cohort are presented in Table 5. Kaplan-Meier curves for the analysis are not available.

Table 5: Results (health status) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

Study Outcome category	Atezolizumab + bevacizumab		Sorafenib		Atezolizumab + bevacizumab vs. sorafenib
Outcome	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 – global cohort					
Morbidity					
Health status (EQ-5D VAS)[a]					
≥ 15 points	336	9.8 [7.1; NC] 144 (42.9)	165	3.5 [2.8; 5.1] 87 (52.7)	0.53 [0.40; 0.70]; < 0.001[b]

a. Time to first deterioration; defined as a decrease of the score by ≥ 15 points from baseline.
b. Effect and CI: Cox proportional hazards model stratified by geographical region (Asia without Japan/rest), extrahepatic spread and/or macrovascular invasion (yes/no) and AFP at screening (< 400 ng/mL/≥ 400 ng/mL); p-value: stratified log-rank test.

AFP: alpha fetoprotein; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

A statistically significant advantage of atezolizumab + bevacizumab in comparison with sorafenib was shown for the outcome "health status" (EQ-5D VAS). Due to the high risk of bias, this resulted in a hint of an added benefit of atezolizumab + bevacizumab in comparison with sorafenib. Based on the upper limit of the confidence interval (< 0.80) of this non-serious non-severe outcome, the extent is to be assessed as "considerable".

The positive effects described in dossier assessment A20-97 [1] in the category of non-serious/non-severe symptoms/late complications are thus supplemented by another hint of considerable added benefit.

2.3.3 Specific AEs

Immune-related AEs and bleeding

In Module 4 A of the dossier [5], the company did not provide usable data for the specific AEs "immune-related AEs" (AEs, serious AEs [SAEs], severe AEs) and "bleeding" (AEs, SAEs, severe AEs). For immune-related AEs (AEs, SAEs, severe AEs), the company did not present a summary analysis of events, but only presented results for individual immune-related AEs as part of its analyses of atezolizumab-specific AESIs. Furthermore, the respective operationalizations of the individual AESIs were not clear from Module 4 A of the dossier. It also remains unclear whether the analyses of individual AESIs listed by the company are limited to events which required corticosteroid treatment, as this was also a preplanned analysis in the IMbrave150 study. The operationalization for the analyses on bleeding/haemorrhage presented by the company as AESI was also not clear from Module 4 A of the dossier.

In the context of the commenting procedure, the company subsequently submitted data on its specific AEs analysed as AESIs, which show which events (e.g. Preferred Terms [PTs], Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries [SMQs]) were behind the AESIs.

Immune-related AEs

No usable data are available for immune-related AEs (AEs, SAEs, severe AEs) despite the subsequently submitted information. For example, the company still presented no summary analysis of the individual immune-related AEs. The company also did not comment on how the AEs it described as "immune-related" (e.g. immune-related hepatitis, immune-related hyperthyroidism, etc.) were operationalized. From the information in the statistical analysis plan [6] of the IMbrave150 study, it can be inferred that only AEs requiring the use of corticosteroids were recorded. This operationalization is not appropriate.

Furthermore, the list of AESIs presented in Module 4 A is obviously not complete. For example, any AESIs listed in the study protocol [6] on neurological complications (Guillain Barre syndrome, myasthenia gravis or meningoencephalitis) were missing. It is unclear whether this is only due to the fact that no events occurred in these AESIs.

Analogous to dossier assessment A20-97 [1], the results for immune-related AEs (AEs, SAEs, severe AEs) are therefore still not usable.

Bleeding

The analyses on bleeding/haemorrhage presented by the company in Module 4 A of the dossier [5], together with the information on the operationalization submitted in the commenting procedure, are usable and were used for the benefit assessment. The events included in the AESI "bleeding/haemorrhage" sufficiently represent the area of "bleeding".

Results

The results on immune-related AEs and bleeding are presented in Table 6.

Table 6: Results (side effects) – RCT, direct comparison: atezolizumab + bevacizumab vs. sorafenib

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					
Side effects (data cut-off: 29 November 2019 [global cohort] and 29 August 2019 [cohort in China])					
Immune-related AEs (AEs, SAEs, severe AEs)	No usable data[a]				
Bleeding (AEs)	368	ND 97 (26.4)	174	ND 32 (18.4)	1.16 [0.78; 1.73]; 0.473[b]
Bleeding (SAEs)	368	ND 36 (9.8)	174	ND 15 (8.6)	0.76 [0.41; 1.40]; 0.382[b]
Bleeding (severe AEs)[c]	368	ND 31 (8.4)	174	ND 12 (6.9)	0.86 [0.44; 1.68]; 0.652[b]

a. Instead of any aggregate analyses on immune-related AEs, the company merely presented individual immune-related AEs which were analysed in the context of AESIs. It can be assumed for these individually analysed immune-related AEs that only those AEs were recorded that required the use of corticosteroids.
b. Effect and CI: Cox proportional hazards model, unstratified; p-value: log-rank test.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; AESI: adverse event of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The data for immune-related AEs (AEs, SAEs, severe AEs) are still not usable. This resulted in no hint of lesser or greater harm from atezolizumab + bevacizumab in comparison with sorafenib for this outcome; lesser or greater harm is therefore not proven.

There was no statistically significant difference between the treatment groups for the outcomes on bleeding (AEs, SAEs, severe AEs). This resulted in no hint of lesser or greater harm from atezolizumab + bevacizumab in comparison with sorafenib for any of these outcomes; lesser or greater harm is therefore not proven.

The conclusion on the added benefit for the specific AEs from the dossier assessment A20-97 [1] therefore does not change.

2.4 Overall conclusion on added benefit

Table 7 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 7: Positive and negative effects from the assessment of atezolizumab + bevacizumab in comparison with sorafenib

Positive effects	**Negative effects**
Mortality ▪ Overall survival: ▫ HCC aetiology (viral [hepatitis B or C]) indication of an added benefit – extent "major"	▪ Serious/severe side effects ▪ Infections and infestations: hint of greater harm – extent "minor"
Non-serious/severe symptoms/late complications: ▪ Pain hint of an added benefit – extent "non-quantifiable" ▪ Fatigue, icterus, abdominal swelling hint of an added benefit – extent "minor" ▪ Nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhoea hint of an added benefit – extent "considerable" ▪ **Health status** **hint of an added benefit – extent "considerable"**	
Health-related quality of life: ▪ Global health status, physical functioning, role functioning, cognitive functioning, social functioning hint of an added benefit – extent "considerable" ▪ Emotional functioning, nutrition hint of an added benefit – extent "major" ▪ Body image hint of an added benefit – extent "minor"	
Serious/severe side effects ▪ Hand-foot syndrome indication of lesser harm – extent "major" ▪ General disorders and administration site conditions hint of lesser harm – extent "considerable" ▪ Diarrhoea, blood bilirubin increased, metabolism and nutrition disorders, respiratory, thoracic and mediastinal disorders in each case hint of lesser harm – extent "minor"	
Non-serious/non-severe side effects ▪ Alopecia indication of lesser harm – extent "considerable"	
Immune-related AEs (AEs, SAEs, severe AEs): no usable data	
The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments. AE: adverse event; HCC: hepatocellular carcinoma; SAE: serious adverse event	

Based on the data analysed for this addendum, there is an additional positive effect of atezolizumab + bevacizumab over sorafenib compared with dossier assessment A20-97. This consists of a hint of an added benefit with the extent "considerable" for the outcome "health status". As already described in dossier assessment A20-97, there are both positive and negative effects of atezolizumab + bevacizumab in comparison with sorafenib. The positive effect in

overall survival was only shown in patients with viral aetiology of HCC. For this reason, positive and negative effects are weighed separately for patients with and without viral aetiology.

Overall, the positive effects continue to clearly outweigh the negative ones. As in dossier assessment A20-97, there is an indication of major added benefit for patients with viral aetiology for research question 1 (patients with advanced or unresectable HCC who have not received prior systemic therapy, with Child-Pugh A or no hepatic cirrhosis). There is hint of considerable added benefit for patients with non-viral aetiology.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of atezolizumab from dossier assessment A20-97.

The following Table 8 shows the result of the benefit assessment of atezolizumab + bevacizumab under consideration of dossier assessment A20-97 and the present addendum.

Table 8: Atezolizumab + bevacizumab – probability and extent of added benefit

Research question	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy: ▪ with Child-Pugh A or no hepatic cirrhosis	**Sorafenib** or lenvatinib	▪ Patients with viral aetiology of HCC: indication of major added benefit[c] ▪ Patients with non-viral aetiology of HCC: hint of considerable added benefit[c]
2	Adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy: ▪ with Child-Pugh B	Best supportive care[d]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed 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. Best supportive care 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; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; TAE: transarterial embolization

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 01.03.2021]. URL: https://www.iqwig.de/download/a20-97_atezolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Roche Pharma AG. Stellungnahme zum IQWiG-Bericht Nr. 1061: Atezolizumab (hepatozelluläres Karzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/613/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Roche Pharma AG. Zusätzliche Analysen der Studie IMbrave150 zur Abgabe einer schriftlichen Stellungnahme zur Nutzenbewertung nach § 35a SGB V und Kosten-Nutzen-Bewertung nach § 35b SGB V. Stand: 22.03.2021; 2021.; study B9991003; Zusatzanalysen [unpublished]. 2021.

4. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

5. Roche Pharma. Atezolizumab (Tecentriq): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2020 [Accessed: 15.04.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/613/#dossier.

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