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Sacituzumab govitecan (breast cancer) –

Addendum to Commission A21-154[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
RCT	randomized controlled trial
TPC	treatment of physician's choice

1 Background

On 12 April 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A21-154 (Sacituzumab govitecan – benefit assessment according to §35a Social Code Book V) [1].

The G-BA commissioned IQWiG with the following assessment of the analyses submitted by the company in the commenting procedure [2,3], taking into account the information provided in the dossier [4]:

- information regarding the inclusion of patients not treated with the study medication and on demographic and clinical patient characteristics of the intention to treat (ITT) population and the safety population
- final results on overall survival from the 25 February 2021 data cut-off
- analyses conducted separately for the individual appropriate comparator therapy (ACT) options
- data on the outcome of hand-foot syndrome

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 Background of the analyses subsequently submitted

The ASCENT study [5] was included to assess the benefit of sacituzumab govitecan monotherapy in comparison with the ACT in adult patients with unresectable or metastatic triple-negative breast cancer (TNBC) who have had 2 or more prior systemic therapies including at least 1 for advanced disease. The ASCENT study is a multicentre, open-label randomized controlled trial (RCT) comparing sacituzumab govitecan with chemotherapy according to physician's choice (TPC) with the options of capecitabine, vinorelbine, eribulin, or gemcitabine, each in the form of monotherapy. Since gemcitabine is not an ACT option, the only subpopulation relevant for the dossier assessment is the subpopulation for whom capecitabine, eribulin, or vinorelbine was the chosen therapy if allocated to the control arm.

A detailed description of the ASCENT study can be found in dossier assessment A21-154 [1].

For the assessment of risk of bias of results on overall survival, it was unclear how the analysis accounted for patients who had received no study medication. The company clarified this issue during the commenting procedure and subsequently submitted data on the percentage of patients censored for this reason at the time of randomization. To address this aspect, the company also subsequently submitted the patient characteristics of the safety population versus the ITT population (see Section 2.2).

The company's dossier presents results on the 11 March 2020 data cut-off for all outcomes. The benefit assessment notes that, according to the information provided in the European Public Assessment Report (EPAR), a later data cut-off of 25 February 2021 is available, and the company should have presented data on all relevant outcomes for said data cut-off. For the morbidity, health-related quality of life, and side effects outcomes, the analyses based on the 11 March 2020 data cut-off were nevertheless deemed usable. For the outcome of overall survival, the analyses of the relevant subpopulation from the 11 March 2020 data cut-off were interpreted together with the available analyses of the total population from 25 February 2021. As part of the commenting procedure, the company subsequently submitted the overall survival analyses of the relevant subpopulation from the 25 February 2021 data cut-off. These analyses are evaluated in Section 2.3.

In the dossier assessment, it was noted that the dossier provides no analyses to determine whether sacituzumab govitecan shows different effects than the individual ACT options. The company subsequently submitted these analyses with its written comments. These analyses are evaluated in Section 2.4.

Furthermore, no usable analyses for the outcome of hand-foot syndrome were available for the benefit assessment. See Section 2.5 for the analyses the company subsequently submitted on this outcome.

2.2 Risk of bias

The dossier assessment derived a high risk of bias for overall survival because it was unclear how patients not treated with the study medication (intervention arm: 3.6%; control arm: 14.3%) were accounted for in the analyses or which percentage of patients was censored at randomization for this reason.

Approach of the company

In its comments, the company explains that between-arm differences in the percentages of patients who did not receive any study medication are indeed to be expected in an open-label study design. In addition, the company argues that the similarity of patient characteristics in the ITT population versus the safety population suggests an absence of systematic bias. Finally, the company notes in its comments that, according to the study protocol, all patients were to receive a survival follow-up every 4 weeks, even after study discontinuation. Survival status was to be surveyed by phone. In addition, it was possible to document survival status using public databases to the extent this was permissible according to local regulations.

In its post hoc submission regarding the written comments [3], the company presented the following information on the patients without study treatment: reason for study discontinuation, follow-up status, follow-up duration, and censoring for overall survival. These data show that no patient in the intervention arm and 8 patients (3.6%) in the control arm were censored at the time of randomization.

Assessment of the company's approach

The low percentage of patients censored for overall survival at the time of randomization eliminates the reason for the high risk of bias cited in the dossier assessment, resulting in a high certainty of results for the outcome. For overall survival, this leads to the derivation of an indication of major added benefit of sacituzumab govitecan in comparison with TPC.

Therefore, low risk of bias can be safely assumed across outcomes as well. For the results of the other outcomes, however, the risk of bias remains unchanged. This is because, for the other outcomes, patients not treated with the study medication were already known at the time of the dossier assessment to have been disregarded in the analyses.

A comparison of the patient characteristics of the ITT population versus the safety population is ill suited for assessing whether patients who were randomized but not treated cause a relevant bias. The two populations largely overlap, and similar characteristics are thus indeed to be expected.

2.3 Final results on overall survival from 25 February 2021 data cut-off

In its written comments [2], the company subsequently submitted results on overall survival for the relevant subpopulation from the 25 February 2021 (see Table 1). These results were relevant for the benefit assessment. Among the relevant subpopulation, 18 intervention-arm

patients and 15 control-arm patients died between the 11 March 2020 data cut-off and the 25 February 2021 data cut-off. The effect estimate and its upper limit of the confidence interval are identical at both data cut-offs. Hence, there is no change in the extent of added benefit of sacituzumab govitecan in comparison with TPC for this outcome. The company did not submit a graphic of the Kaplan-Meier curves.

Table 1: Results (mortality) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study Outcome category Outcome	Sacituzumab govitecan		TPC[a]		Sacituzumab govitecan vs. TPC[a]
	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[b]
ASCENT					
Mortality					
Overall survival, 25 February 2021 data cut-off	221	11.9 [10.2; 14.0] 165 (74.7)	224	6.7 [5.7; 7.5] 190 (84.8)	0.52 [0.42; 0.65]; < 0.001

a. The ASCENT study's TPC options which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Effect, CI, and p-value: Cox proportional hazards model or log rank test, each stratified by region, number of prior chemotherapies, and existing brain metastases at study start.

CI: confidence interval; HR: hazard ratio; n: number of analysed patients with event; N: number of analysed patients; RCT: randomized controlled trial; TPC: treatment of physician's choice

2.4 Analyses conducted separately for the individual ACT options

In the dossier assessment, it was noted that the dossier provided no analyses to determine whether sacituzumab govitecan shows different effects than the individual ACT options, although these analyses would have been desirable. The company presented these analyses in the written comments for all of the outcomes relevant for the benefit assessment except neutropenia.

The analyses subsequently submitted by the company show a statistically significant interaction only for the outcome of severe adverse events (AEs) (see Table 3 in Appendix A). For this outcome, there was a disadvantage of sacituzumab govitecan versus capecitabine as well as an advantage versus vinorelbine. All in all, however, the results of the different treatment options can still presumably be interpreted summarily.

Due to the substantial advantage in overall survival, the statistically significant interaction in the outcome of severe AEs leads to no change in the conclusion on added benefit.

2.5 Data on the outcome of hand-foot syndrome

In the benefit assessment, no time-to-event analyses, which are necessary for a meaningful interpretation of results, were available for the specific AE of hand–foot syndrome. The company did not submit any time-to-event analyses in its written comments either. Hence, there are still no usable data available for this outcome.

The number and percentages of patients with at least 1 event are presented in Table 4 in Appendix B.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion drawn on the added benefit of sacituzumab govitecan in dossier assessment A21-154: For overall survival, the certainty of results is now presumably high, which leads to the overall derivation of an indication of major added benefit of sacituzumab govitecan in comparison with the ACT.

Table 2 below shows the result of the benefit assessment of sacituzumab govitecan, taking into account dossier assessment A21-154 and the present addendum.

Table 2: Sacituzumab govitecan – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
Adult patients with unresectable or metastatic triple-negative breast cancer who have had 2 or more prior systemic therapies including at least 1 of them for advanced disease[c]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline- or taxane-containing therapy[d,e]	**Indication** of major added benefit[f]

a. Presented is the respective 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 of the company is printed in **bold**.
b. Changes in comparison with dossier assessment A21-154 are printed in **bold**.
c. When specifying the ACT, the G-BA assumed that,
- as part of prior therapy, patients typically received taxane-based and/or anthracycline-based chemotherapy.
- in the present therapeutic indication, (secondary) resection or radiotherapy with curative intent is not indicated.
- patients with genomic BRCA1/2 mutation are not candidates for BRCA-specific therapy at the time of therapy with sacituzumab govitecan.

d. The G-BA specifies anthracycline-containing or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline-containing and/or taxane-containing therapy or who are candidates for retreatment with anthracycline-containing or taxane-containing therapy.
e. For patients with a high need for rapid remission, guidelines recommend considering combination therapy.
f. The ASCENT study included only patients with an ECOG PS of 0 or 1. It thus remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; BRCA: breast cancer gene; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

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Appendix A Results of the analyses, separately for the individual ACT options

Table 3: Results of the analyses, separately for the individual ACT options (side effects – RCT, direct comparison: sacituzumab govitecan versus TPC[a])

Study Outcome	Sacituzumab govitecan		TPC[a]		Sacituzumab govitecan vs. TPC[a]	
Characteristic Drug	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][b]	p-value[c]
ASCENT						
Severe AEs[d]						
Treatment option						
Eribulin	110	1.0 [0.7; 2.4] 75 (68.2)	123	1.8 [1.0; 2.8] 77 (62.6)	0.94 [0.68; 1.31]	0.693
Capecitabine	47	0.9 [0.6; 1.6] 36 (76.6)	28	3.5 [1.3; 7.9] 12 (42.9)	2.18 [1.13; 4.23]	0.020
Vinorelbine	56	1.0 [0.8; 1.9] 40 (71.4)	41	0.7 [0.5; 1.0] 33 (80.5)	0.62 [0.39; 0.99]	0.045
Total					Interaction:	0.010[e]

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Effect and CI: Cox proportional hazards model (unstratified).
c. Log rank test (unstratified).
d. Operationalized as CTCAE grade ≥ 3.
e. Interaction of treatment and subgroup from Cox proportional hazards model with the covariates of treatment, subgroup, and the treatment-subgroup interaction term.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; TPC: treatment of physician's choice

Appendix B Results on the specific AE of hand-foot syndrome

Table 4: Results (side effects) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study Outcome category Outcome	Sacituzumab govitecan		TPC[a]		Sacituzumab govitecan vs. TPC[a]
	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
ASCENT					
Side effects					
Hand-foot syndrome[b]	213	ND 4 (1.9)	192	ND 6 (3.1)	ND

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Operationalized as palmoplantar erythrodysesthesia syndrome (PT, AE).

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of analysed patients with (at least 1) event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: system organ class; TPC: treatment of physician's choice