Acalabrutinib (mantle cell lymphoma; combination with bendamustine and rituximab)

Addendum to Project A25-89 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
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)
RCT	randomized controlled trial
RR	relative risk
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 11 November 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-89 (Acalabrutinib – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the analyses submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2] and after the oral hearing, taking into account the information provided in the dossier [3]:

- Time points of treatment discontinuations due to coronavirus disease 2019 (COVID-19)
- Censoring reasons for treatment discontinuation due to an adverse event (AE) (time-to-event analysis)

The responsibility for this 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

To assess the added benefit of acalabrutinib in combination with rituximab and bendamustine (hereinafter acalabrutinib + bendamustine + rituximab) in adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant, the company presented the ongoing double-blind, randomized controlled trial (RCT) ECHO, which is described in detail in benefit assessment A25-89 [1].

In accordance with the commission, the analyses of the ECHO study subsequently submitted by the company in the commenting procedure are presented and assessed below, taking into account the information in the dossier.

2.1 Results

Time points of treatment discontinuations due to COVID-19

Table 1 and Table 2 show the treatment discontinuations due to COVID-19, broken down by therapy cycle and by calendar year.

Table 1: Treatment discontinuations due to COVID-19 , broken down by therapy cycle

ECHO study (data cut-off of 15 February 2024)	**Discontinuation of study medication due to COVID-19[a] n (%)**	
	acalabrutinib + bendamustine + rituximab N = 297[b]	**placebo + bendamustine + rituximab N = 297[b]**
Total	26 (8.8)	16 (5.4)
Cycles 1–6	0	3 (1.0)
Cycles 7–30:	16 (5.4)	8 (2.7)
Cycle ≥ 31	10 (3.4)	5 (1.7)

a. The analysis shows the discontinuation of the first component of the study medication.
b. Analysis based on the safety population.

COVID-19: coronavirus disease 2019; n: number of patients in the category; N: number of analysed patients

Table 2: Treatment discontinuations due to COVID-19, presented by calendar year

ECHO study (data cut-off of 15 February 2024)	Discontinuation of study medication due to COVID-19[a] n (%)	
	acalabrutinib + bendamustine + rituximab N = 297[b]	placebo + bendamustine + rituximab N = 297[b]
Total	26 (8.8)	16 (5.4)
2020	4 (1.3)	5 (1.7)
2021	7 (2.4)	6 (2.0)
2022	11 (3.7)	4 (1.3)
2023	4 (1.3)	1 (0.3)

a. The analysis shows the discontinuation of the first component of the study medication.
b. Analysis based on the safety population.

COVID-19: coronavirus disease 2019; n: number of patients in the category; N: number of analysed patients

Overall, treatment discontinuations due to COVID-19 in the ECHO study were slightly more common in the intervention arm than in the comparator arm (26 [8.8%] vs. 16 [5.4%]).

Censoring reasons for treatment discontinuation due to AEs

In the dossier for the benefit assessment, the company presented time-to-event analyses for the outcomes in the side effects category [3]. As part of the commenting procedure, the company additionally presented the censoring reasons for the outcome discontinuation due to AEs [4]. These are presented in Table 3.

Table 3: Censoring reasons for the outcome discontinuation due to AEs

ECHO study (data cut-off of 15 February 2024)	Patients with censoring n (%)[a]	
	acalabrutinib + bendamustine + rituximab N = 297[b]	placebo + bendamustine + rituximab N = 297[b]
Events	150	105
Total censoring	147	192
Reason for censoring:		
Data cut-off	82 (56)	76 (40)
Death	17 (12)	19 (10)
Disease progression	27 (18)	74 (38)
Other	21 (14)	23 (12)

a. The percentages refer to the total number of censorings in the respective treatment arm.
b. Analysis based on the safety population.

n: number of patients in the category; N: number of analysed patients

The most common reason for censoring in the outcome discontinuation due to AEs in both study arms was the time of the data cut-off (56% vs. 40%). There are clear differences between the study arms in terms of censoring due to disease progression (18% vs. 38%).

In its comments, the company argues that treatment discontinuation due to events other than AEs constitute competitive risks that would lead to a strong bias of the results and that this bias would, moreover, be to the disadvantage of the intervention arm.

As already outlined in dossier assessment A25-89, the ECHO study showed a statistically significant difference to the disadvantage of the intervention for the outcome discontinuation due to AEs. It also describes that the certainty of results is limited for this outcome. This is explained below: Premature treatment discontinuation for reasons other than AEs (e.g. due to disease progression) represents a competing event for the outcome discontinuation due to AEs that is to be recorded. Patients who have already discontinued treatment due to disease progression may no longer discontinue it due to the occurrence of an AE. Affected patients are excluded from the study; they are censored. Consequently, the outcome criterion discontinuation due to AEs can no longer be recorded for these patients. This means that the company's argument that competing events impair the certainty of results has already been addressed and taken into account in the dossier assessment. A maximum of one hint can be derived for the outcome discontinuation due to AEs [1]. The detailed information provided on the reasons for censoring illustrates this assessment, but does not lead to a deviating assessment.

It should also be noted that, given the current data situation, it is entirely unclear whether patients who discontinued treatment due to disease progression would have been more or less likely to discontinue therapy due to AEs in the respective treatment arms. Even in a Cox proportional hazards model, such as the one used by the company in its analysis, it would not be possible to predict the direction in which the estimation of the hazard ratio would be biased by the occurrence of competing events, as the bias depends not only on the frequency of occurrences of the competing events within the groups, but also, for example, on the connection between the respective competing event and other covariates. Similarly, this also applies to the use of the relative risk (RR). [1].

The results for the outcome discontinuation due to AEs can be found in dossier assessment A25-89 [1].

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of acalabrutinib + bendamustine + rituximab from dossier assessment A25-89.

The following Table 4 shows the result of the benefit assessment of acalabrutinib + bendamustine + rituximab under consideration of dossier assessment A25-89 and the present addendum.

Table 4: Acalabrutinib + bendamustine + rituximab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant	Individualized treatment[d, e] choosing from ▪ rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, predniso[lo]ne)[f] ▪ VRCAP (bortezomib + rituximab + cyclophosphamide, doxorubicin, prednisone) ▪ BR (bendamustine + rituximab)[g] upon achievement of complete or partial remission following induction therapy with R-CHOP or BR, followed by ▪ maintenance therapy with rituximab[h]	▪ Patients for whom bendamustine + rituximab is a suitable individualized treatment: hint of lesser benefit ▪ patients for whom bendamustine + rituximab is not a suitable individualized treatment: added benefit not proven

Table 4: Acalabrutinib + bendamustine + rituximab – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, in this therapeutic indication, it is assumed that patients with mantle cell lymphoma meet the criteria for systemic antineoplastic therapy due to a correspondingly advanced stage of their disease, particularly in terms of a symptomatic course; therefore, a "watchful waiting" strategy, among other options, is not considered. Further, patients are assumed not to be therapeutically indicated for radiotherapy at the time of therapy. c. Furthermore, according to the G-BA, it is assumed that the target population in the therapeutic indication does not include any patients in poor or reduced general health. d. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs). e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). f. Induction therapy with R-CHOP is covered by Part A, Section XXVI of Appendix VI of the AM-RL 'Rituximab for mantle cell lymphoma'. g. Induction therapy with BR is not approved for this therapeutic indication. According to the GBA, data from randomized trials comparing BR with R-CHOP in this therapeutic indication are available [5,6]. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV. h. According to the G-BA, the current guidelines [7,8] recommend maintenance therapy with rituximab following induction with R-CHOP and BR. Rituximab is not approved for use following induction therapy with BR. The off-label use of rituximab following treatment with R-CHOP is eligible for prescription in accordance with Annex VI of the AM-RL. The available guidelines refer to a randomized phase II study and a retrospective cohort study for the use of rituximab as maintenance therapy following induction therapy with BR [9,10]. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of maintenance therapy with BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV. With regard to maintenance therapy with rituximab, the guidelines set out in Appendix VI of the AM-RL must be considered for patients who have previously received R-CHOP therapy. The dosage and treatment regimen should be in line with the generally recognized state of medical knowledge. AM-NutzenV: Regulation on the Evaluation of the Benefits of Medicinal Products; AM-RL: Medicinal Products Directive; BR: Bendamustine + Rituximab; EU: European Union; G-BA: Joint Federal Committee; HTA: Health Technology Assessment; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone		

The G-BA decides on the added benefit.

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