IQWiG Reports – Commission No. A21-138

Venetoclax (acute myeloid leukaemia) –

Addendum to Commission A21-82[1]

Addendum

Commission: A21-138
Version: 1.0
Status: 12 November 2021

[1] Translation of addendum A21-138 *Venetoclax (akute myeloische Leukämie) – Addendum zum Auftrag A21-82* (Version 1.0; Status: 12 November 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Venetoclax (acute myeloid leukaemia) – Addendum to Commission A21-82

Commissioning agency
Federal Joint Committee

Commission awarded on
26 October 2021

Internal Commission No.
A21-138

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

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

IQWiG employees involved in the addendum

- Selver Altin
- Katrin Nink
- Mattea Patt
- Katharina Wölke

Keywords: Venetoclax, Leukemia – Myeloid – Acute, Benefit Assessment, NCT02993523

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List of abbreviations

Abbreviation	Meaning
AML	acute myeloid leukaemia
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

1 Background

On 26 October 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-82 (Venetoclax – benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of venetoclax in combination with a hypomethylating agent (HMA) in adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy, the randomized controlled trial (RCT) Viale-A was included. The study surveyed the predefined outcomes "red blood cell transfusion independence" and "platelet transfusion independence". On the basis of multiple points of criticism, the benefit assessment disregarded the results for these outcomes in the operationalizations presented in the dossier [1]. During the commenting procedure [2], the pharmaceutical company (hereinafter "company") submitted additional analyses for the outcome "transfusion independence".

The G-BA commissioned IQWiG with the assessment of the following analyses submitted by the company in the commenting procedure in consideration of the information provided in the dossier [3]:

- analyses regarding the outcome "transfusion independence" (24 weeks, joint consideration of platelet transfusions and red blood cell transfusions) on the basis of time-to-event analyses.

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

Subsequently submitted analyses on the outcome "transfusion independence"

The outcomes "red blood cell transfusion independence" and "platelet transfusion independence" were predefined in the Viale-A study as the proportion of patients who received no platelet transfusion or no red blood cell transfusion for ≥ 8 weeks. Patients had to have achieved uninterrupted transfusion independence for ≥ 8 weeks between the first dose of study drug and either the last dose of study drug (plus 30 days) or before death or before the initiation of subsequent therapy (whichever was earliest). The company's dossier additionally presented sensitivity analyses for the periods of ≥ 16 weeks and ≥ 24 weeks of transfusion independence [3].

The benefit assessment generally deemed transfusion independence to be patient relevant because in the present therapeutic indication, transfusions are administered based on symptoms, including as supportive therapy of patients with AML [4-7]. However, the event rates on red blood cell and platelet transfusion independence which were presented in Module 4 A of the company's dossier were disregarded for the benefit assessment because of the following points of criticism:

1) The analysis of event rates is inadequate due to the difference in median follow-up durations for the outcome in the intervention arm versus the comparator arm (8.7 months versus 4.9 months [3]).
2) Complete transfusion independence as opposed to a separate analysis of red blood cell independence and platelet transfusion independence is deemed to be the relevant parameter (therefore, the outcome is referred to as "transfusion independence" below).
3) Given the absence of uniform criteria on the administration of transfusions in the Viale-A study, the validity of the outcome cannot be fully assessed [1].

In its comments [2], the company has addressed these aspects.

- Regarding (1): The company submitted analyses on the basis of time-to-event analyses for time to start of initial transfusion independence. Given the substantial differences in median follow-up for the outcome (8.7 months versus 4.9 months [3]), the time-adjusted analysis is preferable over event rates. The risk of bias of results for the outcome of transfusion independence (≥ 24 weeks) is deemed high because follow-up duration differs for this outcome, with incomplete follow-up for potentially informative reasons. Further, the comparator arm's median follow-up duration of 4.9 months is shorter than the 24 weeks (equalling 5.5 months) of transfusion independence to be reached according to the outcome's operationalization. The totality of the time-to-event analyses on transfusion independence for ≥ 8, ≥ 16 and ≥ 24 weeks, as presented in the company's comments, shows a consistent effect in favour of venetoclax + azacitidine, but this effect decreases as

the interval of transfusion independence to be reached increases. Consequently, the longer follow-up interval is not believed to further increase the potential bias of results.

- Regarding (2): For the analysis of complete transfusion independence, the company's subsequently submitted analyses examine red blood cell and platelet transfusion independence overall. This joint analysis is deemed an adequate reflection of complete transfusion independence since recommendations for supportive AML therapy primarily involve the administration of red blood cell and platelet transfusions [5,8,9].
- Regarding (3): The company's comments did not supply any new information on the criteria based on which transfusions were administered in the Viale-A study. Like in the dossier, the company instead points out that transfusions were administered on the basis of a patient-specific assessment upon the physician's discretion in accordance with the applicable local guidelines [2]. The details provided by the company regarding the survey of transfusion independence still do not allow for the validity of the outcome to be adequately assessed because the criteria based on which transfusions were administered (e.g. laboratory parameters and/or symptoms) remain unclear. For the Viale-A study, no information is available regarding the reasons for transfusions. The absence of decision criteria for the administration of transfusions additionally results in an uncertainty regarding the extent to which different study centres administered transfusions under comparable conditions and whether their practices are in line with standard medical practice in Germany.

The time-to-event analysis for the outcome "transfusion independence" (joint analysis of red blood cell and platelet transfusion independence), which was subsequently submitted by the company in the commenting procedure, is presented below.

Results

Table 1 shows the results of the comparison of venetoclax + azacitidine versus placebo + azacitidine in patients with newly diagnosed AML who are ineligible for intensive chemotherapy with regard to the outcome of transfusion independence (≥ 24 weeks). The Kaplan-Meier curves are presented in Appendix A.

Table 1: Results (morbidity) – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation)

Study **Outcome category** **Outcome**	**Venetoclax + azacitidine**		**Placebo + azacitidine**		**Venetoclax + azacitidine vs. placebo + azacitidine**
	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][a]; p-value[b]**
Viale-A					
Morbidity					
Transfusion independence (≥ 24 weeks)[c]	210	ND 74 (35.2)	103	ND 18 (17.5)	1.95 [1.16; 3.27]; 0.010

a. According to the company, effect and CI from stratified Cox proportional hazards model; no information provided on stratification factors.
b. p-value from log rank test.
c. Uninterrupted red blood cell and platelet transfusion independence for ≥ 24 weeks between the first dose of study drug and either the last dose of study drug + 30 days or death or initiation of subsequent therapy (whichever was earliest).

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial

For the outcome of transfusion independence (≥ 24 weeks), a statistically significant effect was found in favour of venetoclax + azacitidine in comparison with placebo + azacitidine.

3 References

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

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Appendix A Kaplan-Meier curves

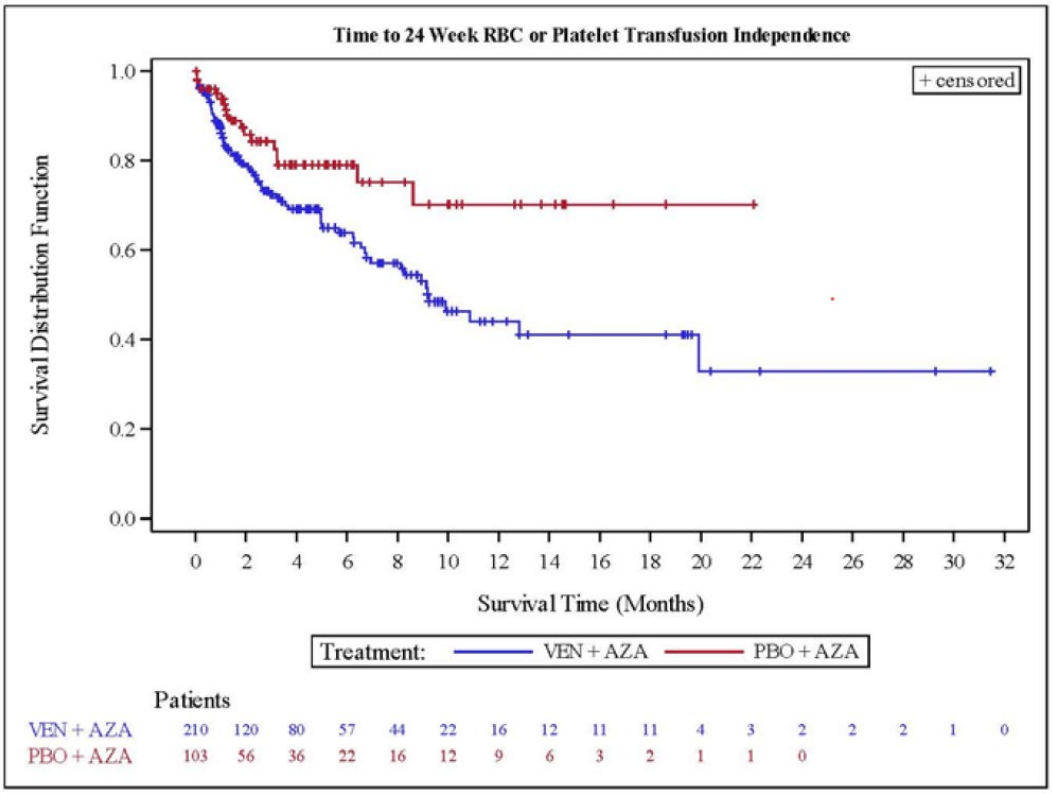

Figure 1: Kaplan-Meier curves on the outcome of transfusion independence (≥ 24 weeks); presented is the time to the start of the first occurrence of transfusion independence (events are counted retroactively to the time point from which a transfusion independence of at least 24-week duration started); Viale-A study, 3rd data cut-off (4 July 2020)