Midostaurin
(acute myeloid leukaemia)

Addendum to Project A23-110
(dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AML	acute myeloid leukaemia
DFS	disease-free survival
EFS	event-free survival
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
SGB	Sozialgesetzbuch (Social Code Book)
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1 Background

On 27 March 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-110 (Midostaurin – Benefit assessment according to § 35a Social Code Book V) [1,2].

As part of the commenting procedure for project A23-110, the company submitted several additional analyses for the RATIFY study that go beyond the information contained in the dossier [3,4]. The G-BA's commission comprises the assessment and presentation of the results of the additional analysis presented by the company with its comment [3], in which the patients were censored at the beginning of the maintenance phase of the study (additional analysis 3).

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

In the benefit assessment of midostaurin for the treatment of acute myeloid leukaemia (AML), the randomized controlled trial (RCT) RATIFY was rated as unsuitable for answering the research question. In particular, this is due to the lack of implementation of the ACT in the maintenance phase, as no individualized treatment choosing from azacitidine, sorafenib and watchful waiting took place. A detailed description of the study and the reasons for exclusion of this study can be found in dossier assessment A23-110 [1].

In its comments [3] on the dossier assessment, the company stated that the added benefit of midostaurin already arose in the treatment phases of induction and consolidation, in which, in its view, the ACT was adequately implemented. To substantiate its assessment, the company presented an additional analysis in which all patients had been censored at the beginning of the maintenance phase (additional analysis 3).

In the following, this additional analysis is assessed in accordance with the commission and the results are presented.

2.1 Assessment of the additional analysis presented by the company with censoring of patients at the beginning of the maintenance phase of the RATIFY study

Overall, it should be noted that the additional analysis presented by the company without consideration of the events from the maintenance phase is not meaningful for the derivation of an added benefit of midostaurin. This is due to the fact that the two treatment phases of induction and consolidation in the RATIFY study only cover a period of around 6 months. The approx. 12-month maintenance phase and the subsequent follow-up observation until the final data cut-off after 10 years on 26 March 2022 are not considered in this analysis. The relevance of the maintenance phase is also shown by the fact that after the end of the consolidation phase after approx. 6 months, further events of a relevant extent have demonstrably occurred (see the Kaplan-Meier curves on the outcomes of overall survival and EFS in Appendix B). The conclusion that the effects observed in these two phases of the RATIFY study will persist after adequate implementation of the ACT in the maintenance phase can therefore not be drawn from the sole consideration of the induction and consolidation phase. It is therefore still unclear how an adequate implementation of the ACT in the maintenance phase of the RATIFY study would have affected the effect observed in the study. The data of the additional analysis presented by the company are therefore only presented as supplementary information in Appendix A.

2.2 Analysed outcomes in the company's additional analysis

For the additional analysis with censoring of patients at the beginning of the maintenance phase, the company only presented results on the outcomes of overall survival, event-free

survival (EFS) and disease-free survival (DFS). For the outcome of EFS, the company considered 2 further operationalizations in addition to the one presented in Module 4 of the dossier (referred to in the comments as EFSnew, hereinafter referred to as EFSnew 1 and EFSnew 2). No results on other outcomes (e.g. adverse events) are available for this additional analysis.

Operationalization and assessment of the EFS, EFSnew 1, EFSnew 2 and DFS outcomes

Table 1 shows the operationalizations of the outcomes of EFS, EFSnew 1, EFSnew 2 and DFS.

Table 1: Operationalizations for the outcomes of EFS, EFSnew 1, EFSnew 2 and DFS

	Outcome[a]			
	EFS	**EFSnew 1[b]**	**EFSnew 2[b]**	**DFS**
Definition event	Failure to achieve a complete response within 60 days after start of treatment, relapse or death	Failure to achieve a complete response during the induction or consolidation phase (if this took place), relapse or death	Failure to achieve a complete response throughout follow-up, relapse or death	Relapse or death during the entire follow-up; only patients who achieved a complete response within 60 days after the start of treatment

a. In each case censored at the start of maintenance therapy.
b. The operationalizations designated as EFSnew were additionally submitted by the company with the comments.

DFS: disease-free survival; EFS: event-free survival; EFSnew: operationalizations on disease-free survival from the company's comments [3]

Operationalizations EFS, EFSnew 1 and EFSnew 2

Operationalization EFS

The outcome of EFS represents the failure to achieve a complete response within 60 days of starting treatment, the occurrence of a relapse or death. In the RATIFY study, complete response was defined by both haematological parameters and characteristics of bone marrow aspirates.

According to the information provided by the company, the specification of a 60-day time window for failure to achieve a complete response is based on the assumption that the induction phase lasts at most 60 days and that the study design requests a complete response in order to start consolidation therapy. This approach is appropriate in the present data situation. It should be noted that, according to the information in the study documents, patients were also included in the consolidation phase if the complete response occurred later than 60 days after the start of treatment. For the operationalization of EFS presented by the company in the additional analysis, patients with a complete response after more than 60 days were nevertheless assessed as an event (failure to achieve a complete response). This applied to 22 patients (6%) in the intervention arm and 16 patients (4.5%) in the comparator

arm. In relation to the number of patients with a complete response within 60 days (212 patients [58.9%] in the intervention arm vs. 191 patients [53.5]), this number is to be classified as low. Therefore, this was not expected to have a relevant influence on the interpretation of the results. Therefore, this was not assumed to have a relevant influence on the results of this outcome.

Operationalization EFSnew 1

According to the company, EFSnew 1 is operationalized as the failure to achieve a complete response during the induction or consolidation phase (if this took place), the occurrence of a relapse or death.

For this operationalization, it is unclear which events were counted as failure to achieve a complete response during the consolidation phase, as according to the study documents, only patients with a complete response in induction therapy were to be included in the consolidation phase.

Operationalization EFSnew 2

According to the company, EFSnew 2 is operationalized as the failure to achieve a complete response during the entire follow-up, the occurrence of a relapse or death.

It is unclear to which period the term “follow-up” refers. Based on the company's comments, it can be assumed that “follow-up” refers to the period until the end of the maintenance phase. However, this contradicts the statement that the patients in the additional analysis to be assessed are censored at the start of the maintenance therapy.

Outcome "DFS"

The outcome of DFS is operationalized as the occurrence of a relapse or death in patients with a complete response within 60 days of starting treatment. Such an operationalization is not meaningful, as only a proportion of patients - those with a complete response in the induction phase - are considered in this outcome. In addition, the events that occurred in the outcome “DFS” are already included in the outcome of EFS via the components of recurrence and death. The outcome “DFS” is therefore not considered in the supplementary presentation of the results in Appendix A.

2.3 Conclusion

With the additional analysis 3, the company presented no relevant data for the derivation of an added benefit of midostaurin in its comments. The analysis is unsuitable because events from the start of maintenance therapy are not included in the analysis and it is therefore unclear how an adequate implementation of the appropriate comparator therapy in the maintenance phase of the RATIFY study would have affected the effect observed in the study.

Irrespective of this, the operationalizations (EFSnew 1 and EFSnew 2) of the outcome "EFS" evaluated specifically for the additional analyses are not sufficiently described. The outcome DFS is not suitable for deriving an added benefit, as not all patients were included in the analysis.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of midostaurin drawn in dossier assessment A23-110.

Table 2 below summarizes the result of the benefit assessment of midostaurin, taking into account dossier assessment A23-110 and the present addendum.

Table 2: Midostaurin – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with newly diagnosed AML and FLT3 mutation, in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and thereafter as midostaurin monotherapy for the maintenance treatment in patients in complete remission	▪ Induction chemotherapyb: ▫ Cytarabine in combination with daunorubicin or idarubicin or mitoxantrone or ▫ daunorubicin/cytarabine (liposomal formulation) (only for patients with t-AML or AML-MRC) ▪ followed by a consolidation therapy[c]: individualized treatment choosing from chemotherapy (cytarabine or daunorubicin/cytarabine [liposomal formulation][d]) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. ▪ followed by maintenance treatment[c]: Individualized therapy choosing from ▫ azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ sorafenib (only for people with FLT3-ITD mutation after an allogeneic stem cell transplantation) ▫ watchful waiting (only for patients without FLT3-ITD mutation after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy as well as the FLT3 mutation status.	Added benefit not proven

Table 2: Midostaurin – 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. Induction chemotherapy: The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be proven versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population. c. For consolidation and maintenance therapy: For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study relating to the treatment phases of consolidation and maintenance is presented, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment. d. According to the Summary of Product Characteristics (SPC), daunorubicin/cytarabine (liposomal formulation) can only be considered as consolidation therapy as part of individualized treatment if patients have already received daunorubicin/cytarabine (liposomal formulation) as part of induction chemotherapy. AML: acute myeloid leukaemia; AML-MRC: AML with myelodysplasia-associated changes; FLT: FMS-like tyrosine kinase; G-BA: Federal Joint Committee; ITD: internal tandem duplication; t-AML: therapy-related AML		

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.

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4. Novartis Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1721: Midostaurin (akute myeloische Leukämie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Zusatzanalysen der RATIFY Studie. 2024: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1008/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A Data on the outcomes of overall survival and EFS from additional analysis 3 on the RATIFY study

Table 3: Results (mortality, morbidity) – RCT, direct comparison: midostaurin vs. placebo (multipage table)

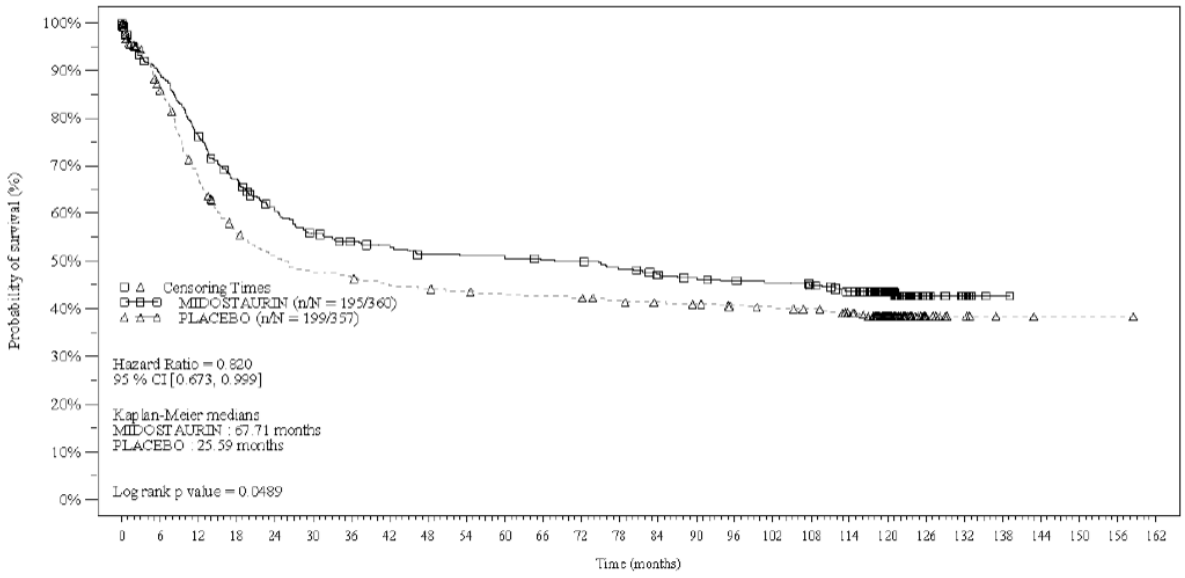
Study outcome category outcome	Midostaurin N	Midostaurin median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Midostaurin vs. placebo HR [95% CI]; p-value
RATIFY (censoring at the time of the maintenance phase)					
Mortality					
Overall survival	360	31.5 [18.6; 84.2] 143 (39.7)	357	19.1 [14.9; 29.5] 162 (45.4)	0.83 [0.66; 1.04]; 0.106
Morbidity					
EFS[a, b]	360	8.1 [5.5; 12.6] 205 (56.9)	357	3.0 [1.9; 5.9] 251 (70.3)	0.74 [0.61; 0.89]; 0.001
Failure to achieve a complete response[c]	360	– 146 (40.6)	357	– 166 (46.5)	–
Relapse	360	– 42 (11.7)	357	– 61 (17.1)	–
Death from any cause	360	– 17 (4.7)	357	– 24 (6.7)	–
EFS for the induction and consolidation phase[a, b] (EFSnew 1)	360	12.7 [8.2; 16.6] 168 (46.7)	357	5.9 [3.6; 7.2] 221 (61.9)	0.68 [0.55; 0.83]; < 0.001
Failure to achieve a complete response[d]	360	– 109 (30.3)	357	– 136 (38.1)	–
Relapse	360	– 42 (11.7)	357	– 61 (17.1)	–
Death from any cause	360	– 17 (4.7)	357	– 24 (6.7)	–
EFS for the entire follow-up[a, b] (EFSnew 2)	360	15.1 [10.1; 26.6] 147 (40.8)	357	6.5 [5.0; 8.5] 207 (58.0)	0.63 [0.51; 0.78]; < 0.001
Failure to achieve a complete response[e]	360	– 88 (24.4)	357	– 122 (34.2)	–
Relapse	360	– 42 (11.7)	357	– 61 (17.1)	–
Death from any cause	360	– 17 (4.7)	357	– 24 (6.7)	–

Appendix A Data on the outcomes of overall survival and EFS from additional analysis 3 on the RATIFY study

Table 3: Results (mortality, morbidity) – RCT, direct comparison: midostaurin vs. placebo (multipage table)

Study outcome category outcome	Midostaurin N	Midostaurin median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Midostaurin vs. placebo HR [95% CI]; p-value
a. Individual components – if available – are shown in the lines below; since only the qualifying events are included in the EFS, the effect estimates of the individual components are not shown. b. An EFS event is defined as failure to achieve a complete response, relapse or death from any cause, whichever occurs first. c. Operationalized as failure to achieve a complete response within 60 days after the start of study treatment. d. Operationalized as failure to achieve a complete response during the induction or consolidation phase of the study. e. Operationalized as failure to achieve a complete response throughout the entire follow-up of the study. CI: confidence interval; EFS: event-free survival; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients (ITT population); NA: not achieved; RCT: randomized controlled trial					

Appendix B Kaplan-Meier curves on the outcomes of overall survival and EFS from the RATIFY study

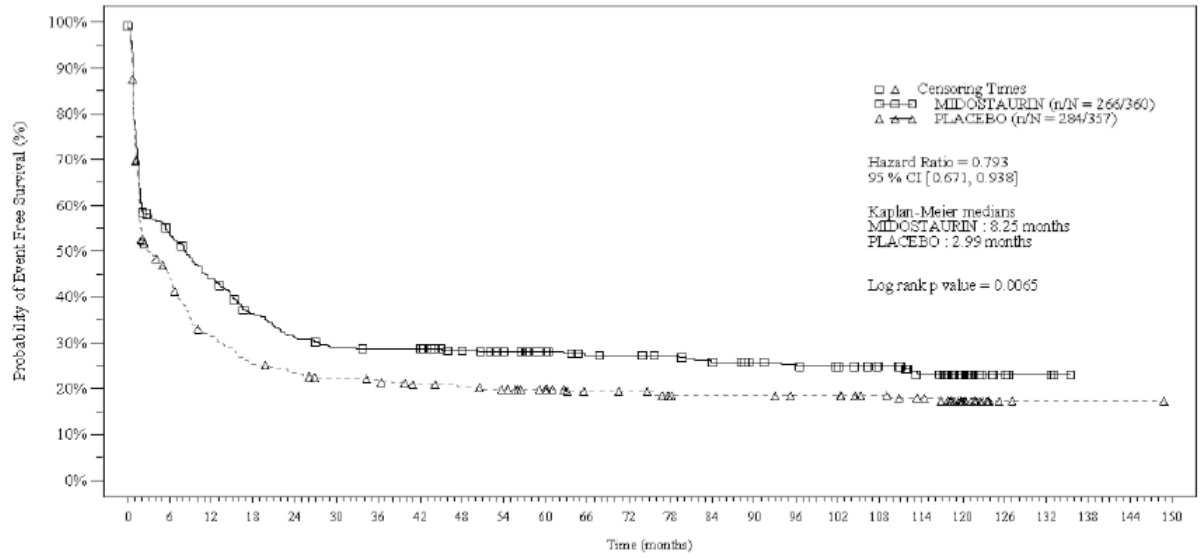


No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162
MIDOSTAURIN	360	314	269	234	208	189	181	177	170	169	169	165	164	158	151	147	144	142	138	130	86	14	6	1	0	0	0	0
PLACEBO	357	284	221	179	163	152	148	142	140	137	135	133	132	127	124	122	118	116	113	106	66	11	5	2	1	1	1	0

Logrank test and Cox regression model stratified for the FLT3 mutation strata used in the randomization.

Figure 1: : Kaplan-Meier curves for the outcome of overall survival, RATIFY study, without censoring after stem cell therapy or start of maintenance therapy; data cut-off: 26 March 2022



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138	144	150
MIDOSTAURIN	360	191	155	125	107	99	97	97	89	83	78	72	71	69	64	59	57	54	49	39	21	5	3	0	0	0
PLACEBO	357	153	106	86	78	73	70	64	62	58	52	45	44	39	38	38	36	36	32	28	16	2	1	1	1	0

Logrank test and Cox regression model stratified for the FLT3 mutation strata used in the randomization.

Figure 2: Kaplan-Meier curves for the outcome of EFS (failure to achieve a complete response within 60 days of treatment initiation, relapse or death), RATIFY study, without censoring after stem cell therapy or start of maintenance therapy; data cut-off: 26 March 2022