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Daratumumab (newly diagnosed multiple myeloma, unsuitable for stem cell transplantation) –

Addendum to Commission A21-126[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ASCT	autologous stem cell transplantation
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 8 February 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-126 (Daratumumab – 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 pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure [2,3], taking into account the information provided in the dossier [4]:

- Patient-reported outcomes in the categories of morbidity and health-related quality of life (EQ-5D visual analogue scale [VAS], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]):
  - responder analyses of the time to first deterioration (without the inclusion of death due to progression)
  - responder analyses of the time to definitive deterioration

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 (EQ-5D VAS, EORTC QLQ C30)

The open-label, randomized, actively controlled MAIA study was included for the benefit assessment of daratumumab in combination with lenalidomide and dexamethasone (daratumumab + lenalidomide + dexamethasone) in comparison with the appropriate comparator therapy (ACT) in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation (ASCT) [1]. This study compared daratumumab + lenalidomide + dexamethasone with the combination of lenalidomide and dexamethasone (lenalidomide + dexamethasone).

The results presented in the company's dossier [4] included results for the time to deterioration for the patient-reported outcomes on health status, recorded with the EQ-5D VAS, as well as on symptoms and health-related quality of life, each recorded with the EORTC QLQ-C30, for the third data cut-off of the MAIA study (19 February 2021); the dossier contained no clear information on their operationalizations, however [4]. The dossier assessment therefore used results on these outcomes (with a response criterion of ≥ 15 points [EQ-5D VAS] or ≥ 10 points [EORTC QLQ-C30]) under the assumption that the analyses referred to the time to first deterioration. In addition, it remained unclear whether, analogous to the information in the statistical analysis plan, death due to disease progression was included as an event in the assessments.

In the context of the commenting procedure [2,3], the company clarified that the analyses presented in the dossier for patient-reported outcomes referred to the time to first deterioration, and that death due to disease progression was included as an event. Furthermore, the company subsequently submitted additional analyses of the time to first deterioration and the time to definitive deterioration for the outcomes mentioned (data cut-off: 19 February 2021).

2.1.1 Time to first deterioration

The analyses submitted by the company in the commenting procedure for the outcomes of health status (EQ-5D VAS), symptoms and health-related quality of life (both recorded with the EORTC QLQ-C30) are analyses of the time to first deterioration with a response criterion of ≥ 15 points (EQ-5D VAS) or ≥ 10 points (EORTC QLQ-C30). In contrast to the analyses in the dossier, death due to disease progression was not taken into account as an event for deterioration and, besides, the recordings after the start of a subsequent therapy were additionally included in the analyses. However, the subsequently submitted analyses and the analyses in dossier assessment A21-126 show the same results for the added benefit at outcome level in the present data situation (a positive effect with the extent "considerable" for the symptom of pain; positive effects, each with the extent "minor", for 2 of 6 scales for health-related quality of life). Overall, there is therefore no change in comparison with dossier

assessment A21-126 [1]; the analyses presented there are therefore still informative and relevant to the assessment.

2.1.2 Time to "definitive" deterioration (in the company's terminology) (for the benefit assessment to be referred to as: confirmed deterioration under treatment up to 16 weeks after progression)

For the outcomes on symptoms and health-related quality of life (surveyed with the EORTC QLQ-C30 scales and EQ-5D VAS), the company submitted further event time analyses. These were operationalized as time to so-called "definitive deterioration" by 10 points (EORTC) or 7, 10 or 15 points (EQ-5D VAS) without subsequent improvement. The company defined the time to "definitive deterioration" as a deterioration by at least the threshold value compared with baseline, in which the response criterion (the threshold value) is considered to be met in all subsequent observations until the end of the observation. The company presented 2 analyses:

- For the analyses of the time to "definitive deterioration" (in the company's terminology), patients who had deteriorated by at least the threshold value at the time of the last recording were included in the analysis as responders.
- For the analyses of the time to "confirmed definitive deterioration" (in the company's terminology), patients who only showed deterioration by at least the threshold value at the time of the last recording, which was thus a single and unconfirmed event, were censored in the time to "confirmed definitive deterioration" at the time of the last recording.

The recording of patient-reported outcomes was stopped 16 weeks after the onset of disease progression (see dossier assessment A21-126, Table 8 [1]). The data on the median treatment durations as well as on the observation periods for the symptom and health-related quality of life outcomes (see dossier assessment A21-126, Table 10 [1]) show that – especially in the comparator arm – the observation period for these outcomes was shorter than for overall survival. On the one hand, there is thus the problem in the present data situation that the observation period of the patient-reported outcomes does not cover the entire observation period (discontinuation of observation 16 weeks after disease progression). It is therefore not appropriate to speak of a "definitive deterioration" in this situation. Rather, this is only a deterioration confirmed over the shortened observation period.

On the other hand, there are clear differences in the median observation periods between the treatment arms. Although observation periods for the subsequently submitted analyses (outcomes on symptoms and health-related quality of life) are not available in the company's comments and in the information subsequently submitted, similar differences as for the analyses in the dossier can be assumed, i.e. an observation period that was approximately twice as long in the intervention as in the control arm. Kaplan-Meier curves for the analyses subsequently submitted are also not available. Since a sustained deterioration across all subsequent values is potentially more difficult to achieve in the intervention arm (treatment with daratumumab + lenalidomide + dexamethasone) with longer observation than in the comparator arm with

shorter observation, the time to first deterioration continues to be used in the present data situation (see A21-126); a meaningful interpretation of this analysis is possible in the present data situation (clear differences in median observation periods).

2.2 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of daratumumab drawn in dossier assessment A21-126.

The following Table 1 shows the results of the benefit assessment of daratumumab in consideration of dossier assessment A21-126 and the present addendum.

Table 1: Daratumumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation	Daratumumab in combination with bortezomib, melphalan, and prednisone or Bortezomib in combination with melphalan and prednisone or Bortezomib in combination with lenalidomide and dexamethasone or Thalidomide in combination with melphalan and prednisone or **Lenalidomide in combination with dexamethasone**	Hint of considerable added benefit
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 A21-126 are printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Daratumumab (neu diagnostiziertes multiples Myelom, Stammzelltransplantation nicht geeignet) – Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse); Dossierbewertung [online]. 2022 [Accessed: 03.01.2022]. URL: https://www.iqwig.de/download/a21-126_daratumumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Janssen-Cilag GmbH. Stellungnahme zum IQWiG-Bericht Nr. 1266: Daratumumab (neu diagnostiziertes multiples Myelom, Stammzelltransplantation nicht geeignet) - Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse). [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/744/#beschluesse in the document "Zusammenfassende Dokumentation"].

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4. Janssen-Cilag GmbH. Daratumumab (Darzalex); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 13.01.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/744/#dossier.